To,

Date: 3rd February, 2015

THE CONTROLLER OF PATENTS,
PATENT OFFICE DELHI,
Boudhik Sampada Bhawan,
Plot No. 32, Sector 14,
Dwarka, New Delhi-110075.

Dear Sir,

Sub: Pre-Grant Opposition
Reg: 9668/DELNP/2007
Title: Diaryhdantoin Compounds
Applicant: The Regents of the University of California
Opponent: Mr. Umesh Shah

I, Mr. Umesh Shah, hereby file a Pre-Grant Opposition by the way of Representaiton under Sec. 25(1) of The Patents Act, 1970, as amended by The Patents (Amendment) Act, 2005 and Rule 55 of The Patent Rules, 2003 as amended by The Patent (Amendment) Rules, 2014. Attached herewith is the Written Statement along with supporting documentary evidence in duplicate.

I am within my Right to file Pre-Grant Opposition since the Patent Application is yet to be granted.

I request you kindly grant an opportunity for personal hearing to me as per the provisions of Sec. 25(1) of The Patents Act, 1970 and Rule 55 of The Patent Rules, 2003.

Kindly acknowledge the receipt of the same

Thanking you in anticipation.

With best regards,

Mr. Umesh Shah
203/B Simla House,
51/B L.J. Marg,
Nepeansea Road,
Mumbai - 400 036
Phone: 982003761
Email id: umesh@sumerikchemi.com

FORM 7A

THE PATENTS ACT, 1970 (39 OF 1970)

AND

THE PATENTS RULES, 2003

REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT

[Rule 55]

I, Mr. Umesh Shah, hereby give representation by way of opposition to the grant of patent in respect of application no. 9668/DELNP/2007 dated 13/12/2007 made by The Regents of the University of California and published on 20/06/2008 on the ground of:

1. Section 25(1)(b) of the Patents Act, 1970: Anticipated by Prior Publication.
2. Section 25(1)(e) of the Patents Act, 1970: Invention is obvious to a person Skilled in Art.
3. Section 25(1)(f) of the Patents Act, 1970: Invention is not an Invention within the meaning of the Act.
4. Section 25(1)(g) of the Patents Act, 1970: Invention is not Clearly and Sufficiently described in the Specification.

My address for service in India is

Mr. Umesh Shah
203/B Simla House,
51/B L.J. Marg,
Nepeansea Road,
Mumbai - 400 036
Phone: 9820003761
Email id: umesh@sumerikchemi.com

Mr. Umesh Shah

To
The Controller of Patents,
The Patent Office,
At Delhi

BEFORE THE CONTROLLER OF PATENTS

PATENT OFFICE, DELHI

In The Matter of Sec 25(1) of the Patents Act, 1970, as amended up to The Patents (Amendment) Act, 2005

AND

In The Matter of Rule 55 of The Patents Rules, 2006 as amended by The Patent (Amendments) Rules, 2014.

AND

In The Matter of Indian Patent Application Number 9668/DELNP/2007 filed on 13th December, 2007 by **The Regents of the University of California** and published on 20th June, 2008.

...**Applicant**

AND

In Matter of Pre-Grant Opposition filed by **Mr. Umesh Shah**

...Opponent

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PRE-GRANT OPPOSITION BY WAY OF REPRESENTAION

Under Sec 25(1) of The Patents Act, 1970 as amended by The Patent (Amendment) Act, 2005

And

In Accordance with Rule 55 of The Patent Rules, 2003 as amended by The Patents (Amendment) Rules, 2014

THE OPPONENT HUMBLY SUBMITS AS FOLLOWS:

I. INTRODUCTION:

1. I, Mr. Umesh Shah (hereinafter referred to as "Opponent") having address at 203/B Simla House, 51/B L.J. Marg, Nepeansea Road, Mumbai - 400 036, Maharashtra, India hereby file a Pre-grant Opposition by way of representation under Sec. 25(1) of The Patents Act, 1970 as amended by The Patents (Amendment) Act, 2005 (hereinafter referred to as "The Patents Act") and in accordance with Rule 55 of The Patents Rule, 2003 as amended by The Patents (Amendment) Rules, 2014 (hereinafter referred to as "The Patents Rules").

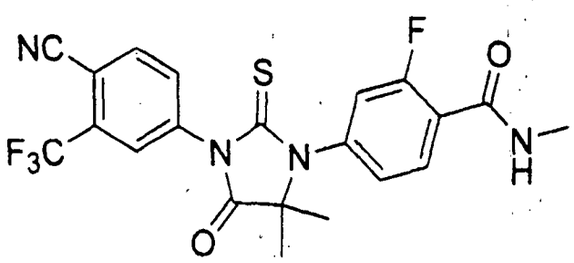
2. The said Opponent, hereby, files a Pre-Grant Opposition by way of Representation against Indian Patent Application Number 9668/DELNP/2007 (herein after referred to as the "Impugned Patent Application") filed by 'The Regents of the University of California' having registered address at 1111 Franklin Street, 12th Floor, Oakland, California 94607-5200, United States of America (hereinafter referred to as "Patent Applicant"), titled "Diaryhdantoin Compounds" dated 13th December, 2007. The impugned application claims a priority date of 13th May, 2005, having US Provisional Application No. 60/680,835. The said Impugned Patent Application has been filed as a National Phase Application of International Patent Application bearing No.

PCT/US2006/011417 dated 23th March, 2006 and published as WO 2006/124118.

3. The said Opponent is entitled to make the present Representation under Sec. 25(1) of the Patents Act, since the Impugned Application is yet to be granted and the same is currently under Prosecution.

4. The said Impugned Patent Application has been filed at the Patent Office, Delhi, therefore, the Hon'ble Controller of Patents has the required Jurisdiction under The Patents Act, 1970.

5. The said Impugned Patent Application relates to Diarylhydantoin Compounds including diarylthiohydantoins, methods for synthesizing them and using them in the treatment of hormone refractory prostate cancer. The said Impugned Patent Application claims a compound of formula



and the pharmaceutical salts thereof.

6. Although the representation can be made by 'any person' in writing under Sec. 25(1) of The Patents Act, 1970; however, the interest of the Opponents in opposing the application is substantial and real. The said Opponents, therefore, have the required *locus standi* in opposing the said Impugned Patent Application.

7. The said Opponents are filing the present opposition to Patent Application no. 9668/DELNP/2007 alongwith the requisite documentary evidence to support their grounds.

8. It is submitted that the said Impugned Patent Application having number 9668/DELNP/2007 along with the original claims and the bibliographic page (as available online on the Official Site the Indian Patent Office) is annexed hereto as **Annexure I.** The corresponding International Patent Publication Number WO 2006/124118 with original claims is annexed hereto as **Annexure II**.

9. It is further submitted that the said Impugned Patent Application has been under opposition since 2012. Subsequently, the said Patent Applicant has amended the Claims and the amended claims whereof are annexed hereto as **Annexure III**, as available online on the Official Site of the Indian Patent Office.

II. GROUNDS OF OPPOSITION:

In this representation by way of opposition, the following grounds enumerated in Section 25 (1) of The Patents Act, 1970 are relied upon by the Opponent:

Section 25(1)((b):

that the invention so far as claimed in any claim of complete specification has been published before the priority date of the claim -

i) in any specification filed in pursuance of an application for a patent made in India on or after the 1st day of January, 1912; or

ii) in India or elsewhere, in any other document provided that the ground specified in sub-clause (ii) shall not be available where such publication

does not constitute an anticipation of the invention by virtue of sub-section (2) or sub-section (3) of section 29;

Section 25(1)(e):

That the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step having regard to the matter published as mentioned in clause (b) or having regard what was used in India before the priority date of the applicant's claim;

Section 25(1)(f):

that the subject matter of any claim of the complete specification is not invention within the meaning of this Act, or is not patentable under this Act; and

Section 25(1)(g):

that the complete specification does not sufficiently and clearly describe the invention or the method by which if is to be performed.

III. DOCUMENTS RELIED UPON:

1. The opponent humbly relies upon the following documents to support his contentions against the said Impugned Patent Application:
   i. **US5411981 (US '981) [Annexure IV] – Priority Date: 9th January, 1991, titled** ***"Phenylimidazolidines having antiandrogenic activity"***
   ii. **2440/DEL/1996 [Annexure V] – Priority Date: 16th November, 1995, titled:** ***"New Preparation Process for Phenylimidazolidine Derivatives"***
   iii. **US5627201 (US '201) [Annexure VI] – Priority Date: 9th January, 1991, titled** ***"Phenylimidazolidines having antiandrogenic activity"***
   iv. **US5434176 (US '176) [Annexure VII] – Priority Date: 8th July, 1992, titled** ***"Phenylimidazolidines"***

v. **US5589497 (US '497) [Annexure VIII] – Priority Date: 8th July, 1992, titled** ***"Antiandrogens"***

vi. **USRE35956 (US '956) [Annexure IX] – Priority Date: 9th January, 1991, titled** ***"Phenylimidazolidines having antiandrogenic activity"***

vii. **US5656651 (US '651) [Annexure X] – Priority Date: 16th June, 1995, titled** ***"Androgenic directed compositions"***

viii. **Decision of Ld. Controller in the Matter of Patent Application No. 6087/DELNP/2005 [Annexure XI]**

IV. OPPOSITION TO CLAIMS

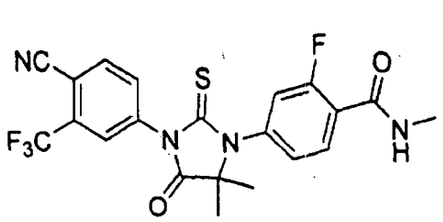
1. The said Opponent opposes the Claims of said Impugned Patent Application by relying upon the abovestated grounds of The Patents Act, 1970, by way of submissions and contentions to draw up his Pre-Grant Opposition Representation as under:

2. The said Opponent states that it is pertinent to note that, the said Impugned Patent Application originally laid out 42 Claims **(Annexure I)** which were subsequently narrowed down drastically to just 15 Claims **(Annexure III)**. This impetuous and pre-meditated move apparently was made in order to get a hasty Patent grant and to mow down any further opportunities of opposition.

3. **<u>Opposition to Claim 1</u>**

Claim 1:

"A compound having the formula



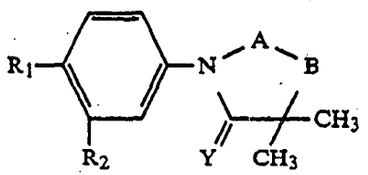
or a pharmaceutically acceptable salt thereof."

A. <u>Lack of Novelty:</u>

The Claim 1 as claimed in the said Impugned Patent Application is not novel in view of disclosures apparent in the following Patents:

i. <u>With respect to US Patent No. US5411981 [Annexure IV]</u>

(a) The Applicant hereby submits that the product as claimed in Claim 1, is anticipated by US '981 filed on 18th May, 1993 assigned to Roussel Uclaf having an earliest priority date of 9th January, 1991. The said Patent claims compounds of formula (I) -



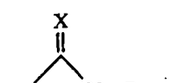
Formula (I)

Wherein, according to Claim 1,

R_1 is —**CN**, —NO_2 or halogen;

R_2 is —**CF_3** or halogen

Y is **Oxygen** or Sulphur or —NH—

—A–B— is 

,

wherein X is Oxygen or **Sulphur**

R_3 is selected from the group consisting of a) hydrogen, b) alkyl, alkenyl and alkynyl of up to 12 carbon atoms, c) **phenyl** and phenylalkyl unsubstituted or **substituted with at least one member** of the group consisting of --OH, **halogen**, --OCH3, --CN and haloalkyl, d) acyl of an organic carboxylic acid of up to 7 carbon atoms, e) free or salified carboxy, carboxy esterified with alkyl and **amidified carboxy**, f) amino and mono and dialkylamino of 1 to 4 carbon atoms and g) --S--phenyl

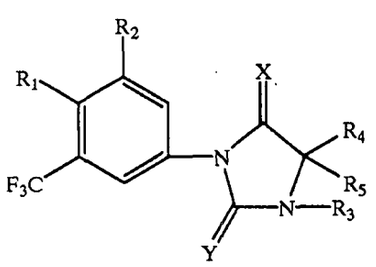
unsubstituted or substituted with at least one member of the group consisting of--CF3 and alkyl, alkenyl, alkoxy, alkenyloxy, alkynyl and alkynyloxy of up to 12 carbon atoms with the sulfur unoxidized or oxidized to sulfone or sulfoxide, the alkyl, alkenyl and alkynyl being uninterrupted or interrupted with oxygen, sulfur or nitrogen.

(b) It is indeed, noteworthy, from the above description of the compound that the compound as claimed in Claim 1 of the said impugned Patent Application is **CLEARLY ANTICIPATED and hence, grossly lacks novelty**.

(c) Therefore, the said Claim 1, is strongly opposed under Sec. 25(1)(b)(ii) read with Sec. 25(1)(e) as being published before the priority date of the Claim and hence, is obvious and clearly does not involve an inventive step. It is thus, prayed that the said Claim 1, be outrightly rejected *in toto*.

ii. *With respect to Indian Patent Application No. 2440/DEL/1996 [Annexure VI]:*

(a) The Applicant hereby, submits, that the product as claimed in Claim 1, is anticipated by 2440/DEL/1996 filed on 6th November, 1996 assigned to Hoechst Marion Roussel having earliest priority date of 16th November, 1995. The said Patent application claims a process for preparation of compounds of formula (II)



Formula II

Wherein, R_1 and R_2, identical or different, are chosen from the **hydrogen** atom, halogen atoms and the following radicals alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, phenyl, phenoxy, nitro, trifluoro-methyl, acyl, **cyano**, amino, monoalkylamino, dialkylamino, free, esterified, **amidified** or salified **carboxy**,

(b) R_3 is chosen from the hydrogen atom and alkyl, alkenyl, alkynyl, **aryl** and arylalkyl radicals, all these radicals being **optionally substituted by one or more substituents** chosen from **halogen** atoms, the following radicals: optionally esterified, etherified or protected hydroxyl, alkoxy, alkenyloxy, alkynyloxy, trifluoromethyl, mercapto, **cyano**, acyl, acyloxy, free, esterified, **amidified** or salified **carboxy**, amino, mono- and dialkylamino, arylthio and cyclic radicals containing 3 to 6 members, the alkyl, alkenyl or alkynyl radicals being moreover optionally interrupted by one or more oxygen, nitrogen or sulphur atoms, all the sulphur atoms being optionally oxidized in the form of the sulphoxide or sulphone, the aryl and aralkyl radicals being moreover, optionally substituted by an alkyl, alkenyl or alkynyl radical;

R_4 and R_5: either are identical or different and represent a hydrogen atom or an **alkyl radical**, optionally substituted by one or more substituents chosen from halogen atoms, the optionally esterified, etherified or protected hydroxyl radical and phenylthio and alkylthio radicals, in which the sulphur atom can be oxidized into the sulphoxide or sulphone and being optionally substituted by one or more radicals chosen from halogen atoms and optionally esterified, etherified or protected hydroxyl radicals, free, esterified, amidified or salified carboxy radicals, amino, mono- and dialkylamino radicals, or form together a heterocyclic

radical with 4 to 6 members containing an oxygen or sulphur atom,

X and Y, identical or different, represent an **oxygen or sulphur** atom,

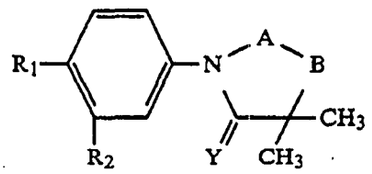
(c) It is therefore, pertinent to note, that the compound as claimed in said Claim 1, is clearly and unequivocally **ANTICIPATED** by Indian Patent Application No. 2440/DEL/1996. Hence, said Claim 1 is opposed under Sec. 25(1)(b)(i) read with Sec. 25(1)(e).

B. <u>Lack of Inventive Step:</u>

The Claim 1 of the Impugned Patent Application clearly lacks an inventive step with regard to the disclosures apparent in the following Patents/Patent Applications.

i. <u>With respect to US Patent No. US5411981 [Annexure IV]</u>

(a) The Applicant hereby submits that the product as claimed in Claim 1, does not involve an inventive step in view of US '981 filed on 18th May, 1993 assigned to Roussel Uclaf having an earliest priority date of 9th January, 1991. The said Patent claims compounds of formula (I) -



Formula (I)

Wherein, according to Claim 1,

R_1 is —**CN**, —NO_2 or halogen;

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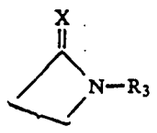
—A–B— is 

,

wherein X is Oxygen or **Sulphur**

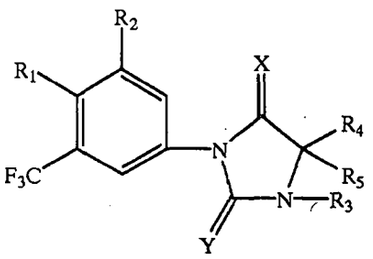
R_3 is selected from the group consisting of a) hydrogen, b) alkyl, alkenyl and alkynyl of up to 12 carbon atoms, c) **phenyl** and phenylalkyl unsubstituted or **substituted with at least one member** of the group consisting of --OH, **halogen**, --OCH3, --CN and haloalkyl, d) acyl of an organic carboxylic acid of up to 7 carbon atoms, e) free or salified carboxy, carboxy esterified with alkyl and **amidified carboxy**, f) amino and mono and dialkylamino of 1 to 4 carbon atoms and g) --S--phenyl unsubstituted or substituted with at least one member of the group consisting of--CF3 and alkyl, alkenyl, alkoxy, alkenyloxy, alkynyl and alkynyloxy of up to 12 carbon atoms with the sulfur unoxidized or oxidized to sulfone or sulfoxide, the alkyl, alkenyl and alkynyl being uninterrupted or interrupted with oxygen, sulfur or nitrogen.

(b) It is obvious from the above description of the compound that the compound as claimed in Claim 1 of the said impugned Patent Application does not involve an inventive step **and hence, is obvious to any person skilled in the art**.

(c) Therefore, the said Claim 1, is strongly opposed under Sec. 25(1)(e) as being obvious and clearly does not involve an inventive step. It is thus, prayed that the said Claim 1, be outrightly rejected *in toto*.

ii. *With respect to Indian Patent Application No. 2440/DEL/1996 [Annexure V]:*

(a) The Applicant further submits that, the Claim 1 of said impugned patent application does not involve any inventive step in view of 2440/DEL/1996 filed on 6th November, 1996, assigned to Hoechst Marion Roussel having earliest priority date of 16th November, 1995. The said Patent application claims a process for preparation of compounds of formula (II)



Formula II

Wherein, R_1 and R_2, identical or different, are chosen from the **hydrogen** atom, halogen atoms and the following radicals alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, phenyl, phenoxy, nitro, trifluoro-methyl, acyl, **cyano**, amino, monoalkylamino, dialkylamino, free, esterified, **amidified** or salified **carboxy**;

R_3 is chosen from the hydrogen atom and alkyl, alkenyl, alkynyl, **aryl** and arylalkyl radicals, all these radicals being **optionally substituted by one or more substituents** chosen from **halogen** atoms, the following radicals: optionally esterified, etherified or protected hydroxyl, alkoxy, alkenyloxy, alkynyloxy, trifluoromethyl, mercapto, **cyano**, acyl, acyloxy, free, esterified, **amidified** or salified **carboxy**, amino, mono- and dialkylamino, arylthio and cyclic radicals containing 3 to 6 members, the alkyl, alkenyl or alkynyl radicals being moreover optionally interrupted by one or more oxygen, nitrogen or sulphur atoms, all the sulphur atoms being optionally oxidized in the form of the sulphoxide

or sulphone, the aryl and aralkyl radicals being moreover, optionally substituted by an alkyl, alkenyl or alkynyl radical;

R_4 and R_5: either are identical or different and represent a hydrogen atom or an **alkyl radical**, optionally substituted by one or more substituents chosen from halogen atoms, the optionally esterified, etherified or protected hydroxyl radical and phenylthio and alkylthio radicals, in which the sulphur atom can be oxidized into the sulphoxide or sulphone and being optionally substituted by one or more radicals chosen from halogen atoms and optionally esterified, etherified or protected hydroxyl radicals, free, esterified, **amidified** or salified **carboxy radicals**, amino, mono- and dialkylamino radicals, or form together a heterocyclic radical with 4 to 6 members containing an oxygen or sulphur atom,

X and Y, identical or different, represent an **oxygen or sulphur** atom,

(b) It is therefore, pertinent to note, that the compound as claimed in said Claim 1, is clearly obvious and devoid of any inventive step in view of Indian Patent Application No. 2440/DEL/1996. Hence, said Claim 1 is opposed under Sec. 25(1)(e) of The Patent Act, 1970.

iii. *With respect to -*

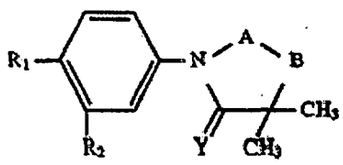
US5627201 (US '201) [Annexure VI];

US5434176 (US '176) [Annexure VII];

US5589497 (US '497), [Annexure VIII] and

USRE35956 (US '956) [Annexure IX].

(a) The abovementioned US Patents are assigned to Roussel Uclaf. The said Patents relate to an invention that claim compounds of general formula,



The compounds disclosed therein, describe various options for substitutions, such that, the substitutions as made in the claims of the said Patents clearly make the Claim 1 of said Impugned Patent Application obvious to any person skilled in the art. The compounds therein, exhibit a substantial structural and functional similarity with the compound, as claimed in Claim 1 of the said Impugned Patent Application. Hence, the Claim 1 of the said Impugned Patent Application does not contain any inventive step as defined under sec. 2(1)(ja), and is thus, is opposed under Sec. 25(1)(e) of The Patents Act, 1970.

(b) Further, it is humbly submitted that the abovementioned Patents have priority dates prior to the Priority Date of the said Impugned Patent Application, that is, 13th May, 2005. Therefore, the compound, as claimed in Claim 1 of the said Impugned Patent Application has been formerly claimed in the claims of the complete specifications published prior to the priority date of the said Impugned Patent Application. Hence, Claim 1 is also hereby, opposed under Sec. 25(1)(b)(ii) of the Patents Act.

iii. *With respect to US5656651 (US '651) – [Annexure X]*

(a) The abovementioned US Patent is assigned to Biophysica Inc. The said Patents relates to substituted phenylthiohydantoins, for use in detecting the presence of tumor cells having androgenic receptors and providing for cytostatic and cytotoxic activity toward such cells. The subject compounds provide for vehicles for

specific targeting to the androgenic receptor containing cells of cytostatic and/or cytotoxic agents, heavy or light radioactive or radioopaque atoms, and the like for detection and treatment of cancer cells involving androgenic receptors or blocking androgenic receptors.

(b) The Claim 1 of US '651 claims a list of compounds which are **derivatives of 4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile**. The compounds claimed in claims of US '651 merely differ from each other by varying side chains. Therefore, in view of US '651 read along with US '981, US '201, US '176, US '497 and US '956 the present Claim 1 of the said Impugned Patent Application is rendered obvious to any person skilled in the art and it clearly does not involve any inventive step as defined under Sec. 2(1)(ja). Therefore, the Claim 1, is hereby, vehemently also opposed under Sec. 25(1)(e) of The Patents Act.

C. **Under Sec 3(d):**

(a) The compound as claimed in Claim 1 is a mere derivative of known substance in view of US '981, US '201, US '176, US '497 and US '956. Therefore, it is considered to be the same substance, since it does not differs significantly in properties with regard to efficacy.

(b) The Applicant has failed to provide the requisite data under Sec. 3(d) of the Patents Act, 1970 which could show that the compound as Claimed in Claim 1 of said Impugned Patent Application exhibits any substantial enhancement in efficacy for treatment of prostate cancer or any similar hyperproliferative disorders as claimed.

(c) Therefore, Claim 1 of said Impugned Patent Application, is fervently opposed under Sec. 25(1)(f) read with Sec. 3(d). In support of his contentions the Opponent also relies up on the decision of the Ld. Controller in the matter of Pre-Grant Opposition in Indian Patent Application No. 6087/DELNP/2005 filed in India on 27/12/2005 by Gilead Pharmasset, Inc, USA **[Annexure XI]**.

4. <u>Opposition to Claim 2</u>

Claim 2:

"A compound as claimed in claim 1, for treatment of a hyperproliferative disorder."

A. <u>Lack of Novelty and/or Inventive Step:</u>

(a) Claim 2 of the said Impugned Patent Application states, that, the compound claimed in claim 1, is used for treatment of hyperproliferative disorder. However, this Claim is not novel in the light of US '981, US '201, US '176, US '497, US '956 and US '651 wherein structurally similar compounds have already been shown to exhibit same functional properties viz. anti-androgenic.

(b) It is further stated, that, the compounds claimed in the Claims of US '981, US '201, US '176, US '497 and US '956, wherein, it is pertinent to note that, the hyperproliferative effect of compounds having structural similarity with the compound claimed in the abovementioned claims of the said Impugned Patent Application is **grossly obvious**. The same, therefore, is opposed under Sec. 25(1)(b)(ii) of the Patents Act, 1970.

(c) Hence, the claim is not a novel invention as per Sec. 2(1)(l) of The Patents Act, 1970. Therefore, the present Claim 2, is opposed under Sec. 25(1)(e) of The Patent Act, 1970.

B. <u>Insufficient Disclosure:</u>

(a) The Opponent submits that the Claim 2 pertaining to function/activity of the compound claimed in Claim 1, is not supported by any concrete and/or significant data in the Complete Specification. The Opponent further submits that the Claims relating to function/activity/efficacy of the compound claimed in Claim 1 are mere extrapolations of the other similar compounds, which have been deliberately disclaimed in the amended claims [Annexure III] of the said Impugned Patent Application.

(b) More particularly, it may be added that the molecule claimed in Claim 1, appears to have been advertently/ intentionally suppressed in the intrinsic data set forth in the Complete Specification of the said Impugned Patent Application in order to hide the factual data as the same, perhaps, does not support the claimed activity/efficacy of the claimed compound.

(c) Further, the Claim 2 is also thwarted by the admittance of the Patent Applicant in Para [00175] of the complete specification, (*"Judgment was applied in ranking compounds relative to each other for their utility in treating prostate cancer..."*).

(d) Furthermore, the Patent Applicant by his own candid admission accepts that - ***"...what might appear to be a small change in the structure of hydantoin compounds may result in a large change in that compound's performance in treating prostate cancer"***, which clearly

contradicts their extrapolated claims relating to the function and efficacy of the compound and hence, do not hold any water.

(e) Therefore, the Claim 2 of the said Impugned Patent Application is in contravention of Sec 10(4)(a) & (c) and hence, opposed under section 25(1)(g).

C. <u>Under Sec 3(a):</u>

(a) Claim 2 of the said Impugned Patent Application claims that the molecule claimed in Claim 1, has anti-hyperproliferative effect. However, the data relied upon by the Patent Applicant for exhibiting any marked activity does not support the claim and is grossly silent on the subject with respect to the claimed molecule. Therefore, the said Claim 2 is frivolous, with regard to disclosed data and is grossly thwarted in the light of Sec 3(a) and hence, is opposed under Sec. 25(1)(f) of The Patents Act.

5. <u>Opposition to Claims 3 – 7:</u>

Claim 3:

"A pharmaceutical composition comprising a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent."

Claim 4:

"A phannaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.001 mg per kg body weight per day to about 100 mg per kg body weight per day for treatment of a hyperproliferative disorder."

Claim 5:

"A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.01 mg per kg body weight per day to about 1 00 mg per kg body weight per day for treatment of a hyperproliferative disorder."

Claim 6:

"A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.1 mg per kg body weight per day to about I 0 mg per kg body weight per day for treatment of a hyperproliferative disorder."

Claim 7:

"A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of about 1 mg per kg body weight per day for treatment of a hyperproliferative disorder."

A. <u>Lack of Novelty and/or Inventive Step:</u>

(a) The Opponents submits that, the composition as claimed in Claim 3 does not involve any inventive step in view of Claims contained in US '201.

(b) Therefore said claim 3 of the Impugned Patent Application lacks inventiveness and hence is opposed under Sec. 25(1)(b)(ii) read with Sec. 2(1)(ja).

B. <u>Under Sec 3(e):</u>

(a) Claims 3 – 7 of the said Impugned Patent Application claim pharmaceutical compositions comprising of the compound as claimed in Claim 1 in varying concentrations along with pharmaceutically acceptable carrier or diluents. Further, no data

has been provided to establish any increase in efficacy of the claimed composition.

(b) Moreover, it is unclear if the pharmaceutical compositions as claimed in claims 3 – 7, severally, act together to provide an efficacious effect which is greater than just the sum of two or more agent acting alone, or, whether the combination is in fact, a mere juxtaposition with no interaction of agents at all.

(c) Therefore, the said Claim is severely thwarted in the light of Sec. 3 (e) as being mere admixtures and not resulting in any substantial increase in efficacy or effect. Therefore, Claim 3 is opposed under Sec 25(1)(f).

6. <u>Opposition to Claims 8 – 12:</u>

Claim 8:

"The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is prostate cancer."

Claim 9:

"The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is hormone refractory prostate cancer."

Claim 10:

"The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is hormone sensitive prostate cancer."

Claim 11:

"The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is breast cancer."

Claim 12:

"The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is ovarian cancer."

A. <u>Lack of Novelty and/or Inventive Step:</u>

(a) The said Opponent submits that the Claims 8 – 12 of the said Impugned Patent Application enumerate that the pharmaceutical compositions as claimed in Claims 2 – 7 are effective in the treatment of hyperproliferative disorder such as prostate cancer, hormone refractory prostate cancer, hormone sensitive prostate cancer, breast cancer and ovarian cancer.

(b) **However, these claims appear to be mere extrapolation of a functionally known activity, viz., anti-androgenic activity, of structurally similar compounds already known and disclosed in prior art**, viz., US '981, US '201, US '176, US '497 and US '956.

(c) Further, the applicant has failed to provide any concrete supporting evidence showing increased efficacy of the claimed compound, as claimed in Claim 1, as against the abovementioned prior art. Since, the compound as claimed in Claim 1 is structurally similar to compounds known in prior art, the anti-androgenic activity is **anticipated and obvious.** Moreover, there is no evidence exhibiting enhanced efficacy of the compound as against the compounds found in prior art.

(d) The Opponent further submits that, it is noteworthy, that the Patent Applicant has advertently avoided the use of the word "anti-androgenic" to describe the activity of the claimed compound, in order to create an impression that the claimed compound is novel in its activity. However, it is pertinent to note,

that on a general glance of the Complete Specification, it becomes amply clear that the cause of the anti-hyperproliferative activity as claimed is the result of substantial androgen receptor antagonist activity, that is, anti-androgenic activity. This shows that the anti-hyperproliferative activity/androgen receptor antagonist activity/anti-androgenic activity is clearly obvious due to the structural similarity with the compounds found in prior art.

(e) Therefore, these Claims are opposed under Sec. 25(1)(e) for being obvious to the person skilled in art as against prior art. Further, the activity claimed is also thwarted under Sec. 25(b)(i) in the light of Indian Patent Application No. 2440/DEL/1996.

7. **Opposition to Claims 13 – 14:**

Claim 13:

"The pharmaceutical composition as claimed in claim 3, wherein the compound is in a form that can be administered as an intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally."

Claim 14:

"The pharmaceutical composition as claimed in claim 3, wherein the composition has a form selected from the group consisting of a solution, dispersion, suspension, powder, capsule, tablet, pill, time release capsule, time release tablet, and time release pill."

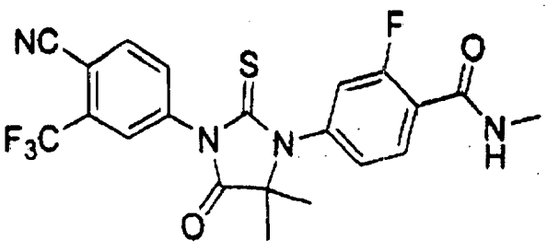
A. Lack of Novelty and/or Inventive Step:

(a) The Opponents submits that, the Claims 13 and 14 of the said Impugned Patent Application are not novel or innovative and hence, the same are opposed under Sec. 25(1)(b)(ii), and 25(1)(e) read with Sec. 2(1)(ja).

8. **Opposition to Claim 15:**

Claim 15:

"A method of synthesizing the compound comprising:



mixing N-Methyl-2-tluoro-4-(1, 1-d imethyl-cyanomethyl)-aminobenzamide and 4-Isothiocyanato-2-tritluoromethylbenzonitrile in DMF and heating to form a firstmixture;

adding an alcohol and an acid to the first mixture to fonn a second mixture;

retluxing the second mixture; and

cooling the second mixture, combining the second mixture with water and extracting an organic layer;

isolating the compound from the organic layer."

A. **Insufficient Disclosure:**

(a) The Opponents submits that, the Claim 15 pertaining to synthesis of the compound as claimed in Claim 1 is not sufficiently and clearly described. Therefore the claim is opposed under Sec. 25(1)(g) read with Sec 10(4)(a) & (b), for insufficiently and vaguely describing the method of synthesis as claimed.

B. **Lack of Inventive Step:**

(a) Moreover, the method of synthesis is comparable to the synthesis of similar compounds is discussed in US '201, US '981 and US '956. Therefore, the Opponents states that the method of synthesis is obvious to a person skilled in the art and clearly does not involve any inventive step as defined under Sec. 2(1)(ja) of The

Patent Act. Therefore, the said Claim is further opposed under Sec. 25(1)(e) read with 2(1)(ja).

V. RELIEFS PRAYED:

In the light of the abovestated submissions and averments, the Opponent humbly prays as follows:

(a) that the Indian Patent Application No. 9668/DELNP/2007 be dismissed *in toto*;

(b) that a copy of Applicant's Reply Statement be given to the Opponent

(c) any other relief, as the Hon'ble Ld. Controller may deem fit in favour of the Opponents.

As a matter of precaution, we request the Learned Controller to grant us an oral hearing before disposing off this application/opposition.

Dated this 3rd day of February, 2015

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Annexure I

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Filing Date :29/03/2006
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Filing Date :NA
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(57) Abstract :
The present invention relates to diarylhydantoin compounds, including diarylthiohydantoins, and methods for syntheszing them and using them in the treatment of hormone refractory prostate cancer.

No. of Pages : 162 No. of Claims : 46

THE PATENTS ACT, 1970 9668 DELNP 2007

13 DEC 2007

COMPLETE SPECIFICATION

Section 10

"DIARYLHYDANTOIN COMPOUNDS"

The Regents of the University of California, a corporation organized and existing under the laws of USA, of 1111 Franklin Street, 12th Floor, Oakland, California 94607-5200 USA..

ORIGINAL

The following specification particularly describes the invention and the manner in which it is to be performed:

27

DIARYLHYDANTOIN COMPOUNDS

FIELD OF THE INVENTION

[0001] The present invention relates to diarylhydantoin compounds including diarylthiohydantoins, and methods for synthesizing them and using them in the treatment of hormone refractory prostate cancer. This application claims priority from U.S. provisional applications bearing serial numbers 60/756,552, 60/750,351, and 60/680,835, the specifications of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] Prostate cancer is the most common incidence of cancer and the second leading cause of cancer death in Western men. When the cancer is confined locally, the disease can be cured by surgery or radiation. However, 30% of such cancer relapses with distant metastatic disease and others have advanced disease at diagnoses. Advanced disease is treated by castration and/or administration of antiandrogens, the so-called androgen deprivation therapy. Castration lowers the circulating levels of androgens and reduces the activity of androgen receptor (AR). Administration of antiandrogens blocks AR function by competing away androgen binding, therefore, reducing the AR activity. Although initially effective, these treatments quickly fail and the cancer becomes hormone refractory.

[0003] Recently, overexpression of AR has been identified and validated as a cause of hormone refractory prostate cancer. See Chen, C.D., Welsbie, D.S., Tran, C., Baek, S.H., Chen, R., Vessella, R., Rosenfeld, M.G., and Sawyers, C.L., Molecular determinants of resistance to antiandrogen therapy, Nat. Med., 10: 33-39, 2004, which is hereby incorporated by reference. Overexpression of AR is sufficient to cause progression from hormone sensitive to hormone refractory prostate cancer, suggesting that better AR inhibitors than the current drugs can slow the progression of prostate cancer. It was demonstrated that AR and its ligand binding are necessary for growth of hormone refractory prostate cancer, indicating that AR is still a target for this disease. It was also demonstrated that overexpression of AR converts anti-androgens from antagonists to agonists in hormone refractory prostate cancer (an AR antagonist inhibits AR activity and an AR agonist stimulates AR activity). Data from this work explains why castration and anti-androgens fail to prevent prostate cancer progression and reveals unrecognized properties of hormone refractory prostate cancer.

[0004] Bicalutamide (brand name: Casodex) is the most commonly used anti-androgen. While it has an inhibitory effect on AR in hormone sensitive prostate cancer, it fails to suppress AR when

cancer becomes hormone refractory. Two weaknesses of current antiandrogens are blamed for the failure to prevent prostate cancer progression from the hormone sensitive stage to the hormone refractory disease and to effectively treat hormone refractory prostate cancer. One is their weak antagonistic activities and the other is their strong agonistic activities when AR is overexpressed in hormone refractory prostate cancer. Therefore, better AR inhibitors with more potent antagonistic activities and minimal agonistic activities are needed to delay disease progression and to treat the fatal hormone refractory prostate cancer.

[0005] Nonsteroidal anti-androgens, such as bicalutamide, have been preferred over steroidal compounds for prostate cancer because they are more selective and have fewer side effects. This class of compounds has been described in many patents such as U.S. Patent Number 4,097,578, U.S. Pat. No. 5,411,981, U.S. Pat. No. 5,705,654, PCT International Applications WO 97/00071 and WO 00/17163, and U.S. Published Patent Application Number 2004/0009969, all of which are hereby incorporated by reference.

[0006] U.S. Patent No. 5,434,176 includes broad claims which encompass a very large number of compounds, but synthetic routes are only presented for a small fraction of these compounds and pharmacological data are only presented for two of them, and one skilled in the art could not readily envision other specific compounds.

[0007] Because the mechanism of hormone refractory prostate cancer was not known, there was no biological system to test these compounds described in these patents for their effect on hormone refractory prostate cancer. Particularly, the ability of AR overexpression in hormone refractory prostate cancer to switch inhibitors from antagonists to agonists was not recognized. Some new properties of hormone refractory prostate cancer are reported in PCT applications US04/42221 and US05/05529, which are hereby incorporated by reference. PCT International Application US05/05529 presented a methodology for identifying androgen receptor antagonist and agonist characteristics of compounds. However, for each compound produced, the time consuming process of determining the antagonist and agonist characteristics of a compound must be determined. That is, there is no method to accurately predict characteristics relevant to treating prostate cancer from the chemical structure of a compound alone.

[0008] There is a need for new thiohydantoin compounds having desirable pharmacological properties, and synthetic pathways for preparing them. Because activities are sensitive to small structural changes, one compound may be effective in treating prostate cancer, whereas a second compound may be

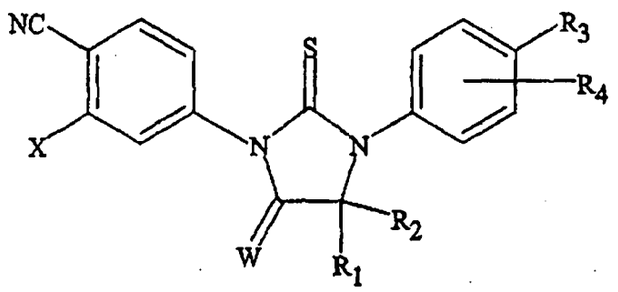
ineffective, even if it differs from the first compound only slightly, say by the replacement of a single substituent.

[0009] Identification of compounds which have high potency to antagonize the androgen activity, and which have minimal agonistic activity should overcome hormone refractory prostate cancer (HRPC) and avoid or slow down the progression of hormone sensitive prostate cancer (HSPC). Therefore, there is a need in the art for the identification of selective modulators of the androgen receptor, such as modulators which are non-steroidal, non-toxic, and tissue selective.

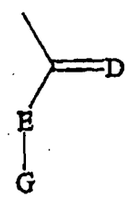
SUMMARY OF THE INVENTION

[0010] The invention provides a series of compounds having strong antagonistic activities with minimal agonistic activities against AR. These compounds inhibit the growth of hormone refractory prostate cancer.

[0011] The invention includes a compound having the formula



wherein X is selected from the group consisting of trifluoromethyl and iodo, wherein W is selected from the group consisting of O and NR5, wherein R5 is selected from the group consisting of H, methyl, and



wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or D is S or O and E-G together are C1-C4 lower alkyl,

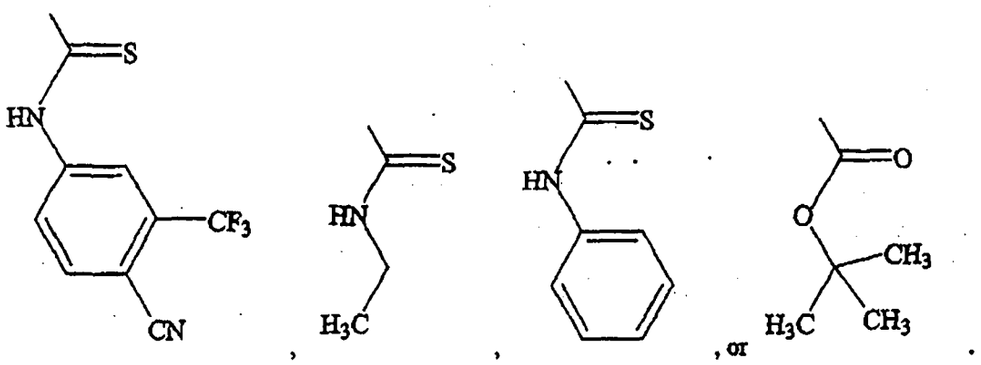
[0012] wherein R1 and R2 together comprise eight or fewer carbon atoms and are selected from the group consisting of alkyl, substituted alkyl including haloalkyl, and, together with the carbon to which they are linked, a cycloalkyl or substituted cycloalkyl group,

[0013] wherein R3 is selected from the group consisting of hydrogen, halogen, methyl, C1-C4 alkoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methoxycarbonyl, acetamido, methanesulfonamino, methanesulfonyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, and C1-C6 alkyl or alkenyl optionally substituted with hydroxyl, methoxycarbonyl, cyano, amino, amido, nitro, carbamoyl, or substituted carbamoyl including methylcarbamoyl, dimethylcarbamoyl, and hydroxyethylcarbamoyl,

[0014] wherein R4 is selected from the group consisting of hydrogen, halogen, alkyl, and haloalkyl, and

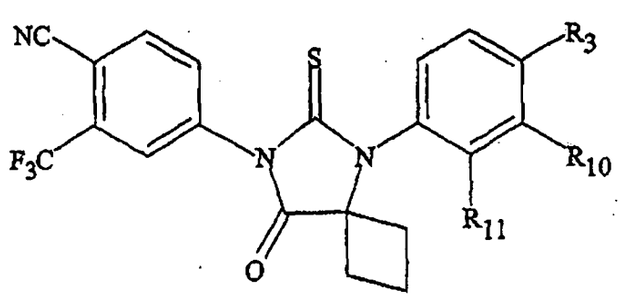
[0015] wherein R3 is not methylaminomethyl or dimethylaminomethyl.

[0016] R5 may be



, , , or .

[0017] The compound may have the formula



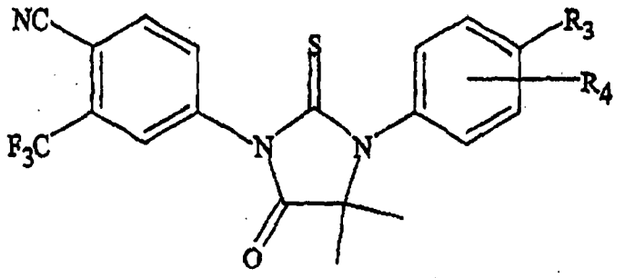
wherein R3 is selected from the group consisting of hydroxy, methylcarbamoyl, methylcarbamoylpropyl, methylcarbamoylethyl, methylcarbamoylmethyl, methylsulfonecarbamoylpropyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, carbamoylmethyl, carbamoylethyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoylpropyl, carboxypropyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, methoxycarbonyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, hydroxyethylcarbamoylethyl, and hydroxyethoxycarbonylethyl, and

[0018] wherein R10 and R11 are both H or, respectively, F and H, or H and F. In certain embodiments, R10 and R11 may both be H or, respectively, F and H. R3 may be methylcarbamoyl.

[0019] In some embodiments, R1 and R2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms, and R3 is selected from the group consisting of carbamoyl, alkylcarbamoyl, carbamoylalkyl, and alkylcarbamoylalkyl, and R4 is H or F or R4 is 3-fluoro.

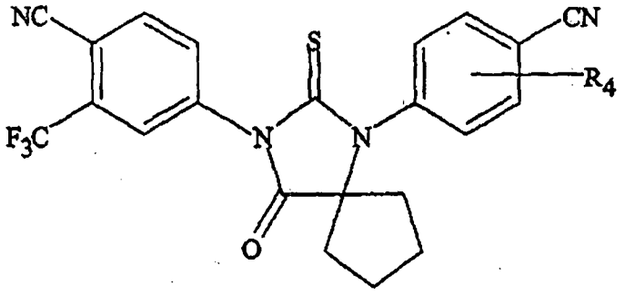
[0020] In other embodiments, R1 and R2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms, R3 is selected from the group consisting of cyano, hydroxy, methylcarbamoyl, methylcarbamoyl-substituted alkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, acetamido, methanesulfonamido, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-(1,1-dimethylethoxy)carbonyl)-1-piperazinyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyethoxycarbonyl-substituted alkyl, and 3-cyano-4-trifluoromethylphenylcarbamoyl, and R4 is F.

[0021] Compounds of the invention may have the formula



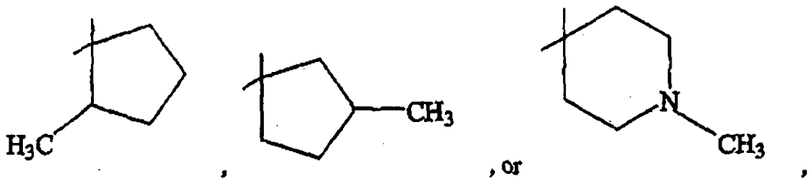
wherein R3 is selected from the group consisting of methylcarbonyl, methoxycarbonyl, acetamido, and methanesulfonamido, and R4 is selected from the group consisting of F and H.

[0022] Compounds of the invention may have the formula

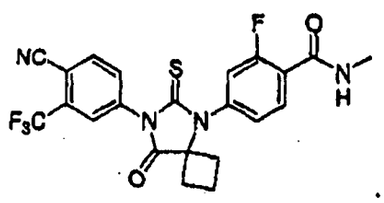


wherein R4 is selected from the group consisting of F and H.

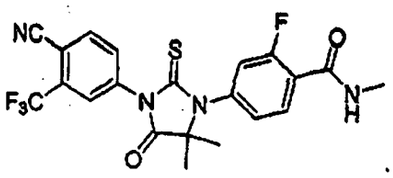
[0023] In embodiments of the invention, wherein R1 and R2 together with the carbon to which they are linked are



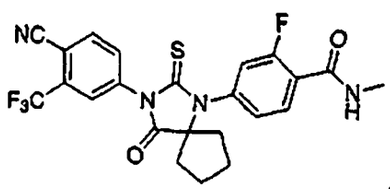
[0024] Compounds of the invention may be those listed in Tier 1, Tier 2, Tier 3, and/or Tier 4, below. Particular compounds of the invention include



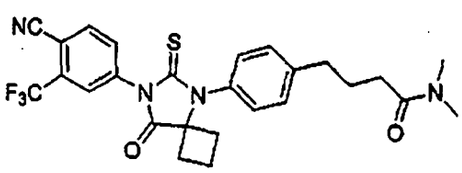
[RD162]



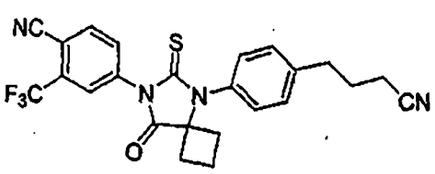
[RD162']



[RD162"]



[RD169]



[RD170]

[0025] The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of the preceding compounds or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

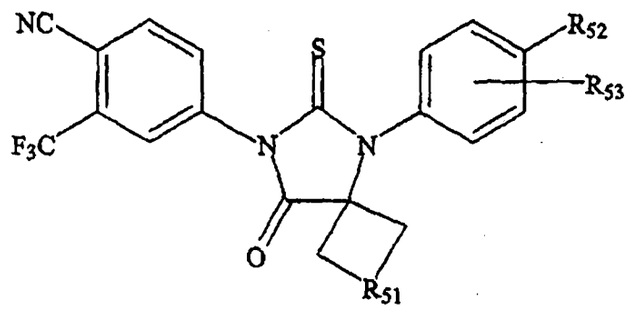
[0026] The invention encompasses a method for treating a hyperproliferative disorder

comprising administering such a pharmaceutical composition to a subject in need of such treatment, thereby treating the hyperproliferative disorder. The hyperproliferative disorder may be hormone refractory prostate cancer. The dosage may be in the range of from about 0.001 mg per kg body weight per day to about 100 mg per kg body weight per day, about 0.01 mg per kg body weight per day to about 100 mg per kg body weight per day, about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day, or about 1 mg per kg body weight per day.

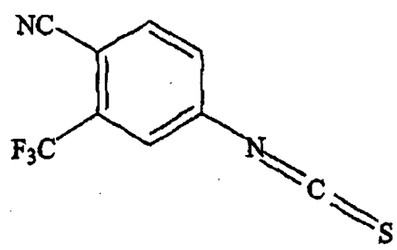
[0027] The compound may be administered by intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally. The composition may have a form selected from the group consisting of a solution, dispersion, suspension, powder, capsule, tablet, pill, time release capsule, time release tablet, and time release pill.

[0028] The administered compound may be selected from the group consisting of RD162', RD162", RD 169, or RD170, or a pharmaceutically acceptable salt thereof. The administered compound may be RD162 or a pharmaceutically acceptable salt thereof.

[0029] The invention provides a method of synthesizing a diaryl compound of formula:

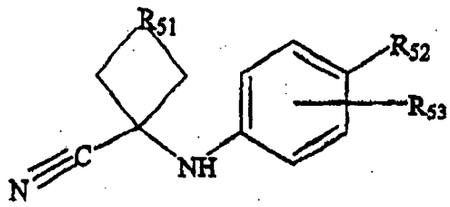


comprising mixing Compound I



Compound I

with Compound II

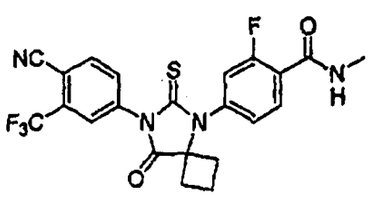


Compound II

in a first polar solvent to form a mixture, heating the mixture, adding a second polar solvent, the same as or different from the first polar solvent, and an aqueous acid to the mixture, refluxing the mixture, cooling the mixture and combining with water, and separating the diaryl compound from the mixture, wherein R51 comprises an alkyl chain of from 1 to 4 carbon atoms, R52 is selected from the group consisting of cyano, hydroxy, methylcarbamoyl, methylcarbamoyl-substituted alkyl, *methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl,* methylsulfonyloxymethyl, methoxycarbonyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, and hydroxyethoxycarbonyl-substituted alkyl, and R53 is selected from the group consisting of F and H.

[0030] R51 may comprise an alkyl chain of from 1 to 2 carbon atoms, R52 may be selected from the group consisting of carbamoyl and methylcarbamoyl, and R53 may be F.

[0031] *The invention provides methods of synthesizing a compound of formula:*



[RD162]

comprising mixing 4-isothiocyanato-2-trifluoromethylbenzonitrile and *N*-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide in dimethylformamide to form a first mixture, heating the

first mixture to form a second mixture, adding alcohol and acid to the second mixture to form a third mixture, refluxing the third mixture to form a fourth mixture, cooling the fourth mixture, combining the fourth mixture with water and extracting an organic layer; isolating the compound from the organic layer.

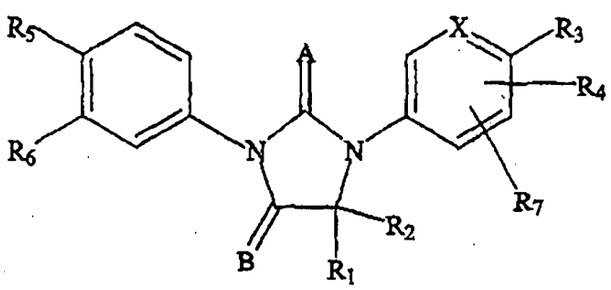
[0032] Likewise, the invention provides a method of synthesizing RD162' comprising mixing *N*-Methyl-2-fluoro-4-(1,1-dimethyl-cyanomethyl)-aminobenzamide. and 4-Isothiocyanato-2-trifluoromethylbenzonitrile in DMF and heating to form a first mixture, and processing as above.

[0033] The invention also provides a method of synthesizing RD162", comprising mixing *N*-Methyl-2-fluoro-4-(1-cyanocyclopentyl)aminobenzamide, 4-isothiocyanato-2-trifluoromethyl benzonitrile, and DMF and heating under reflux to form a first mixture, and processing as above.

[0034] The invention further provides a method of synthesizing RD169, comprising mixing *N,N*-Dimethyl 4-[4-(1-cyanocyclobutylamino)phenyl]butanamide, 4-isothiocyanato-2-trifluoromethyl benzonitrile, and DMF and heating under reflux to form a first mixture; and processing as above.

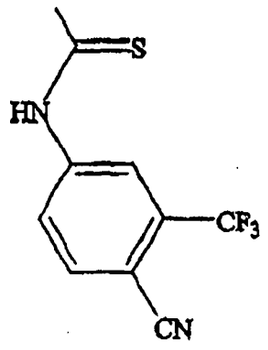
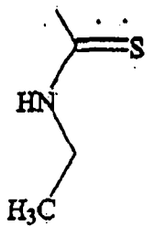
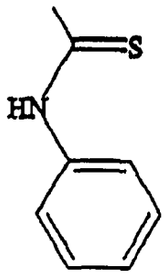
[0035] The invention provides a method of synthesizing RD170, comprising mixing DMSO, dichloromethane, and oxalyl chloride to form a first mixture, adding 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)butanamide to the first mixture to form a second mixture; adding triethylamine to the second mixture to form a third mixture; warming the third mixture and quenching with aqueous NH_4Cl to form a fourth mixture; extracting an organic layer from the fourth mixture; and isolating the compound from the organic layer.

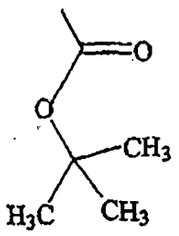
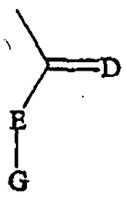
[0036] Further compounds according to the invention have the formula



wherein R5 is CN or NO2 or SO2R11, wherein R6 is CF3, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated akynyl, halogen, wherein A is sulfur (S) or oxygen (O), wherein B is O or S or NR8, wherein R8 is selected from the group consisting of H, methyl, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, SO2R11,

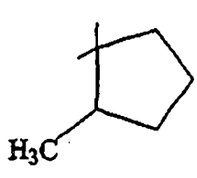
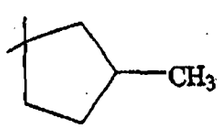
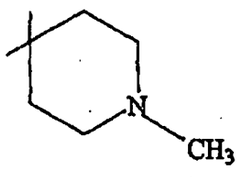
NR11R12, (CO)OR11, (CO)NR11R12, (CO)R11, (CS)R11, (CS)NR11R12, (CS)OR11,

[0037]  ,  ,  , and

 , and 

wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or D is S or O and E-G together are C1-C4 lower alkyl,

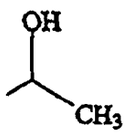
[0038] wherein R1 and R2 are independently alkyl, haloalkyl, hydrogen, aryl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkenyl, halogenated akynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocylic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, or R1 and R2 are connected to form a cycle which can be heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl,

[0039]  ,  , or  ,

[0040] wherein X is carbon or nitrogen and can be at any position in the ring, and

[0041] wherein R3, R4, and R7 are independently selected from the group consisting of hydrogen, halogen, methyl, methoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methylcarbamoyl-substituted alkyl, dimethylcarbamoyl-substituted

alkyl, methoxycarbonyl, acetamido, methanesulfonamino, carbamoyl-substituted alkyl, methanesulfonyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyl-substituted alkyl, hydroxyl-substituted alkenyl, carbamoyl-substituted alkenyl, methoxycarbonyl-



substituted alkyl, cyano-substituted alkyl, , aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkenyl, halogenated alkynyl, SO2R11, NR11R12, NR12(CO)OR11, NH(CO)NR11R12, NR12 (CO)R11, O(CO)R11, O(CO)OR11, O(CS)R11, NR12 (CS)R11, NH(CS)NR11R12, NR12 (CS)OR11, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, haloalkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, acetamido, methanesulfonamido, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-(1,1-dimethylethoxy)carbonyl)-1-piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyethoxycarbonyl-substituted alkyl, 3-cyano-4-trifluoromethylphenylcarbamoyl,

[0042] wherein R11 and R12 are independently hydrogen, aryl, aralkyl, substituted aralkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, or substituted cycloalkyl, or R11 and R12 can be connected to form a cycle which can be heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic, cycloalkyl, or substituted cycloalkyl.

[0043] Such compounds have substantial androgen receptor antagonist activity and no substantial agonist activity on hormone refractory prostate cancer cells.

[0044] The invention encompasses a method comprising providing at least one such compound, measuring inhibition of androgen receptor activity for the compound and determining if the inhibition is above a first predetermined level, measuring stimulation of androgen receptor activity in hormone refractory cancer cells for the compound and determining if the stimulation is below a second predetermined level, and selecting the compound if the inhibition is above the first predetermined level and the stimulation is below the second predetermined level. The predetermined levels may be those of bicalutamide. The step of measuring inhibition may comprise measuring inhibitory concentration (IC50) in an AR response reporter system or a prostate specific antigen secreting system. The step of measuring

stimulation may comprise measuring fold induction by increasing concentrations in an AR response reporter system or a prostate specific antigen secreting system. The method of measuring inhibition and/or stimulation may comprise measuring an effect of the compound on tumor growth in an animal.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] The following Figures present the results of pharmacological examination of certain compounds.

[0046] Figure 1 is a graph depicting that bicalutamide displays an agonistic effect on LNCaP-AR. Agonistic activities of bicalutamide in AR-overexpressed hormone refractory prostate cancer. LNCaP cells with overexpressed AR were treated with increasing concentrations of DMSO as vehicle or bicalutamide in the absence of R1881. Activities of AR response reporter were measured.

[0047] Figure 2 is a graph depicting an antagonistic assay of bicalutamide on LNCaP-AR. Agonistic activities of bicalutamide in hormone sensitive prostate cancer. LNCaP cells were treated with increasing concentrations of DMSO as vehicle or bicalutamide in the absence of R1881. Activities of AR response reporter were measured.

[0048] Figure 3 is a graph depicting the effect of compounds on LNCaP-AR.

[0049] Figure 4 is a graph depicting the effect of compounds on LNCaP-AR.

[0050] Figure 5 is a graph depicting the inhibition effect on LNCaP-AR.

[0051] In Figures 6-10, example 5-3b is RD7 and example 7-3b is RD37.

[0052] Figure 6. Inhibition on growth of AR-overexpressed LNCaP cells. Androgen starved LNCaP cells with overexpressed AR were treated with increasing concentrations of DMSO as vehicle or test substances in the presence of 100 pM of R1881. After 4 days of incubation, cell growth was measured by MTS assay.

[0053] Figure 7. Inhibitory effect on growth of AR-overexpressed LNCaP xenograft model. Mice with established LN-AR xenograft tumors were randomized and treated with indicated compounds orally once daily. Tumor size was measured by caliber. (A), mice were treated with 1 mg per kg of bicalutamide, example 7-3b, or vehicle for 44 days. (B), mice were treated with vehicle, 0.1, 1, or 10 mg per kg of example 7-3b for 44 days.

[0054] Figure 8. Inhibitory effect on PSA expression of AR-overexpressed LNCaP xenograft model. Mice were treated with vehicle, 0.1, 1, or 10 mg per kg of example 7-3b for 44 days orally once daily. The tumors were taken out from the mice after 44 days of treatment, tumor lysate was extracted, and PSA level in tissue lysate was determined by ELISA.

[0055] Figure 9. Inhibitory effect on growth and PSA of hormone refractory LAPC4 xenograft model. Mice with established tumors were randomized and treated with 1 mg per kg of bicalutamide, example 7-3b, or vehicle for 17 days orally once daily. (A), tumor size was measured by caliber. (B), the tumors were taken out from the mice after 17 days of treatment, tumor lysate was extracted, and PSA level in tissue lysate was determined by ELISA.

[0056] Figure 10. Inhibitory effect on growth of hormone sensitive prostate cancer cells. Androgen starved LNCaP cells were treated with increasing concentrations of DMSO as vehicle or test substances in the presence of 1 pM of R1881. After 4 days of incubation, cell growth was measured by MTS assay.

[0057] Figure 11 is a graph of tumor size. AR overexpressing LNCaP cells were injected in the flanks of castrated SCID mice, subcutaneously. When tumors reached about 100 cubic mm, they were randomized into five groups. Each group had nine animals. After they reached this tumor volume, they were given orally with either vehicle, bicalutamide or RD162 at 10 or 50 mg/kg everyday. The tumors were measured three-dimensionally, width, length and depth, using a caliper.

[0058] Figure 12 depicts experimental results of tumor size. At day 18, the animals were imaged via an optical CCD camera, 3 hours after last dose of treatment. A ROI was drawn over the tumor for luciferase activity measurement in photon/second. The right panels is a representation of the ROIs measurements.

[0059] Figure 13 is a graph depicting the pharmacokinetic curves of RD162 from intravenous (upper curve) and oral administration (lower curve).

[0060] Figure 14 is a graph depicting PSA absorbance measured for LN-AR cells after treatment with various doses of several compounds.

[0061] Figure 15 presents a table providing several characteristics of compounds. Figure 15 also presents a graph providing the pharmacokinetic characteristics of several compounds in terms of compound serum concentration as a function of time.

[0062] Figure 16 is a chart depicting prostate weight after treatment with various compounds.

10, 25, or 50 mg of compound per kilogram body weight were administered per day, as indicated by the label of a bar. The compounds were administered to healthy FVB mice. After treatment with compound for 14 days, the urogenital tract weight was determined by removing and weighing the semi-vesicles, prostate, and bladder. Three mice were administered a given compound to obtain the data presented by a bar in the chart. A set of mice was not treated with a compound: data are presented in the bar labeled "untreated". Another set of mice was treated only with vehicle solution: data are presented in the bar labeled "vehicle".

[0063] Figure 17 is a graph presenting a PSA assay performed along with the experimental protocol presented in Fig. 6.

[0064] Figure 18 is a graph presenting the effect of various dose regimens of RD162 on tumor volume.

[0065] Figure 19 is a graph presenting the rate of photon emission associated with luciferase activity at day 17 relative to the rate at day 0 after treatment with RD162 at doses of 0.1, 1, and 10 mg per kilogram body weight per day and without treatment with RD162.

[0066] Figure 20 presents the results of an experiment in which SCID mice were injected with the LN-AR (*HR*) cell line to induce tumor growth. One set of mice were treated with the compound RD162 at a dose of 10 mg per kilogram body weight per day; the other set of mice were treated only with vehicle solution. (A) The relative tumor volume as a function of time shown for each set of mice. (B) Images of each set of mice with photon emission associated with luciferase activity at day 31 shown as color contours. (C) Rate of photon emission associated with luciferase activity shown at several times for each set of mice.

[0067] Figure 21 is a graph presenting PSA absorbance associated with LN-AR cells treated with various concentrations of RD162, RD162', RD162", and RD170 and vehicle solution.

[0068] Figure 22 is a graph presenting PSA absorbance associated with LN-CaP cells treated with various concentrations of RD37, RD131, RD162, bicalutamide, and DMSO.

[0069] Figure 23 presents results of an experiment conducted with wild type nontransgenic mice (WT), castrated luciferase transgenic mice (Cast), and non-castrated luciferase transgenic mice (Intact). Data are shown for castrated luciferase transgenic mice treated with an implanted testosterone pellet yielding 12.5 mg per kilogram body weight with a 90 day release period (T/Cast), and data are shown for non-castrated luciferase transgenic mice treated with an implanted testosterone pellet yielding 12.5 mg per kilogram body weight with a 90 day release period (Intact+T). Data are shown for castrated

luciferase transgenic mice treated with the implanted testosterone pellet and with bicalutamide (BIC+T/Cast) or with RD162 (RD162+T/Cast) at 10 mg per kilogram body weight per day. (A) Urogenital tract weight at 14 days. (B) Photon emission rate at 14 days. In all cases, a hormone refractory disease state was not induced.

[0070] Figure 24 is a graph of luciferase activity of the L1AR cell line dosed with various compounds administered at concentrations ranging from 125 nmol to 1000 nmol.

[0071] Figure 25 is a graph of luciferase activity for the LN/AR cell line for various compounds administered at concentrations ranging from 1.25 to 10 μmol.

[0072] Figure 26 is a graph of luciferase activity for the 4AR cell line for various compounds administered at concentrations ranging from 1.25 to 10 μmol.

[0073] Figure 27 is a graph of PSA levels for the 1AR cell line for various compounds administered at concentrations ranging from 1.25 to 10 μmol.

[0074] Figure 28 is a graph of PSA levels for the LN/AR cell line for various compounds administered at concentrations ranging from 125 nmol to 1000 nmol.

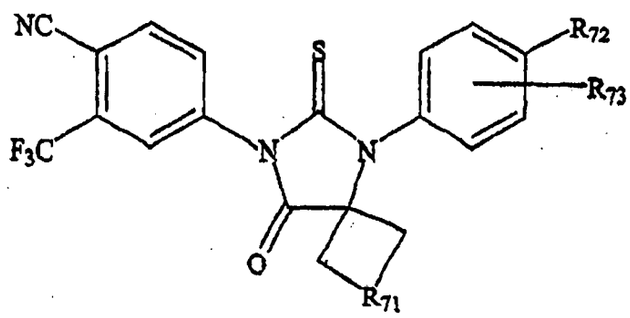
[0075] Figure 29 is a graph of luciferase activity for various compounds administered at concentrations ranging from 125 nmol to 1000 nmol.

DETAILED DESCRIPTION

[0076] Embodiments of the invention are discussed in detail below. In describing embodiments, specific terminology is employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology so selected. A person skilled in the relevant art will recognize that other equivalent parts can be employed and other methods developed without parting from the spirit and scope of the invention. All references cited herein are incorporated by reference as if each had been individually incorporated.

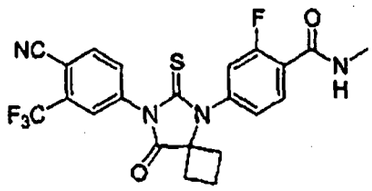
Synthesis of Diarylhydantoin Compounds

[0077] The invention provides for synthesis of diarylthiohydantoin compound having the formula



with R71 including an alkyl chain of from 1 to 4 carbon atoms. For example, R72 can be carbamoyl, e.g., -(CO)NH_2, or methylcarbamoyl, e.g., -(CO)$NHCH_3$. An amide group bonded at the carbon atom of the carbonyl to another structure is termed a carbamoyl substituent. For example, R73 can be a fluorine or a hydrogen atom. That is, a fluorine atom can be attached to any one of the carbons of the right-hand aryl ring which are not bonded to the R72 substituent or the nitrogen atom. Alternatively, no fluorine atom can be attached to the carbons of the right-hand aryl ring which are not bonded to the R72 substituent or the nitrogen atom. For example, a hydrogen atom can be attached to each of the carbons of the right-hand aryl ring which are not bonded to the R72 substituent or the nitrogen atom.

[0078] For example, as further presented below (see, for example, Figs. 3, 5, 11-13), the compound having the formula



[RD162]

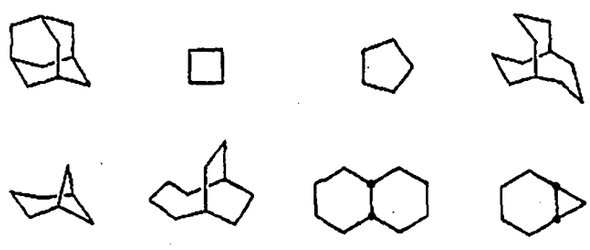
exhibited surprisingly potent antagonistic activities with minimal agonistic activities for overexpressed AR in hormone refractory prostate cancer.

[0079] A list of several compounds according to this invention is presented in Tables 5 - 11. The compounds are grouped into tiers, with Tier 1 to Tier 3 compounds being expected to be superior to bicalutamide for the treatment of prostate cancer, Tier 4 compounds being comparable to bicalutamide in effectiveness, and Tier 5 and Tier 6 compounds being worse than bicalutamide for the treatment of prostate cancer. A more detailed description of the protocol used to rank the compounds into tiers is presented below.

Definitions

[0080] As used herein, the term "alkyl" denotes branched or unbranched hydrocarbon chains, preferably having about 1 to about 8 carbons, such as, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, 2-methylpentyl pentyl, hexyl, isohexyl, heptyl, 4,4-dimethyl pentyl, octyl, 2,2,4-trimethylpentyl and the like. "Substituted alkyl" includes an alkyl group optionally substituted with one or more functional groups which may be attached to such chains, such as, hydroxyl, bromo, fluoro, chloro, iodo, mercapto or thio, cyano, alkylthio, heterocyclyl, aryl, heteroaryl, carboxyl, carbalkoyl, alkyl, alkenyl, nitro, amino, alkoxyl, amido, and the like to form alkyl groups such as trifluoro methyl, 3-hydroxyhexyl, 2-carboxypropyl, 2-fluoroethyl, carboxymethyl, cyanobutyl and the like.

[0081] Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or more double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl. "Substituted cycloalkyl" includes a cycloalkyl group optionally substituted with 1 or more substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the substituents included in the definition of "substituted alkyl." For example,



and the like.

[0082] Unless otherwise indicated, the term "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 2 to 8 carbons in the normal chain, which include one or more double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-

hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like. "Substituted alkenyl" includes an alkenyl group optionally substituted with one or more substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl."

[0083] Unless otherwise indicated, the term "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one or more triple bonds in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like. "Substituted alkynyl" includes an alkynyl group optionally substituted with one or more substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl."

[0084] The terms "arylalkyl", "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkyl, alkenyl and alkynyl groups as described above having an aryl substituent. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, phenethyl, benzhydryl and naphthylmethyl and the like. "Substituted arylalkyl" includes arylalkyl groups wherein the aryl portion is optionally substituted with one or more substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl."

[0085] The terms "arylalkyl", "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkyl, alkenyl and alkynyl groups as described above having an aryl substituent. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, phenethyl, benzhydryl and naphthylmethyl and the like. "Substituted arylalkyl" includes arylalkyl groups wherein the aryl portion is optionally substituted with one or more substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl."

[0086] The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine.

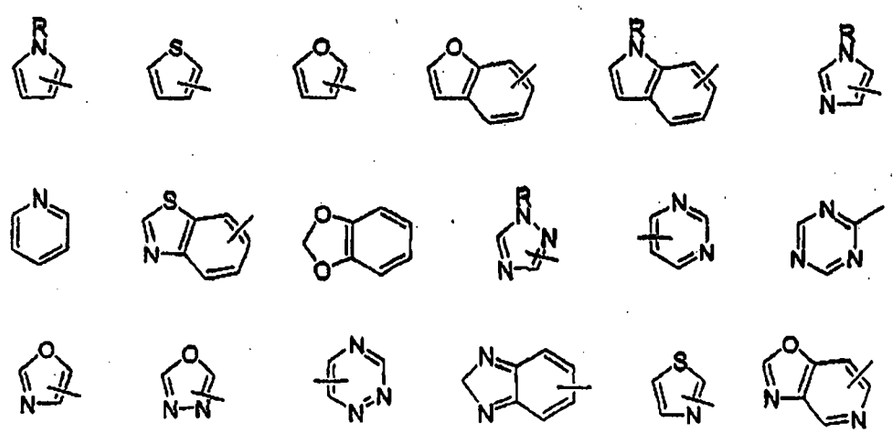
[0087] The terms "halogenated alkyl", "halogenated alkenyl" and "alkynyl" as used herein alone or as part of another group refers to "alkyl", "alkenyl" and "alkynyl" which are substituted by one or more atoms selected from fluorine, chlorine, bromine, fluorine, and iodine.

[0088] Unless otherwise indicated, the term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and polycyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include

one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings).

[0089] "Substituted aryl" includes an aryl group optionally substituted with one or more functional groups, such as halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, alkoxycarbonyl, arylcarbonyl, arylalkenyl, aminocarbonylaryl, arylthio, arylsulfinyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl and/or any of the alkyl substituents set out herein.

[0090] Unless otherwise indicated,, the term "heterocyclic" or "heterocycle", as used herein, represents an unsubstituted or substituted stable 5- to 10-membered monocyclic ring system which may be saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from N, O or S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but is not limited to, piperidinyl, piperazinyl, oxopiperazinyl, oxopiperidinyl, oxopyrrolidinyl, oxoazepinyl, azepinyl, pyrrolyl, pyrrolidinyl, furanyl, thienyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isooxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, thiadiazolyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. The term "heterocyclic aromatic" as used here in alone or as part of another group refers to a 5- or 7-membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur and such rings fused to an aryl, cycloalkyl, heteroaryl or heterocycloalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. "Substituted heteroaryl" includes a heteroaryl group optionally substituted with 1 to 4 substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl." Examples of heteroaryl groups include the following:



and the like.

Example 1

4-isothiocyanato-2-trifluoromethylbenzonitrile, (1a)

[0091] 4-Amino-2-trifluoromethylbenzonitrile, (2.23 g, 12 mmol) was added portionwise over 15 minutes into the well-stirred heterogeneous mixture of thiophosgene (1 ml, 13 mmol) in water (22 ml) at room temperature. Stirring was continued for an additional 1 h. The reaction medium was extracted with chloroform (3 × 15 ml). The combined organic phase was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to yield desired product, 4-isothiocyanato-2-trifluoromethylbenzonitrile, (1a), as brownish solid and was used as such for the next step (2.72 g, 11.9 mmol, 99%).

Example 2

2-1). (4-aminophenyl)carbamic acid *tert*-butyl ester, (2a)

[0092] An aqueous solution of potassium carbonate (1.52 g, 11 mmol in 5 ml of water) was added to a solution of 1,4-diaminobenzene (3.24 g, 30 mmol) in THF (30 ml) and DMF (10 ml). To this mixture was added di-*tert*-butyl pyrocarbonate, Boc_2O (2.18 g, 10 mmol), dropwise over 0.5 h. The reaction mixture was stirred for an additional 4 h at room temperature. The mixture was then poured into cold water (40 ml) and extracted with chloroform (3 × 50 ml). The combined organic phase was dried over $MgSO_4$ and concentrated to yield a brown residue which was subjected to flash chromatography (dichloromethane/acetone, 4:1) to afford (4-aminophenyl)carbamic acid *tert*-butyl ester, (2a) as a yellow solid (1.98 g, 9.5 mmol, 95%) (yield based on Boc_2O).

2-2). {4-[(1-cyano-1-methylethyl)amino]phenyl}carbamic acid *tert*-butyl ester, 2b

[0093] The mixture of 2a (0.83 g, 4 mmol), acetone cyanohydrin (4 ml) and $MgSO_4$ (2 g) was

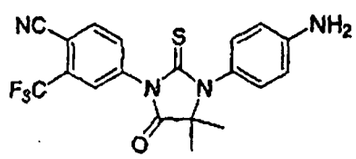
heated to 80 °C and stirred over 2.5 h. After cooling down to room temperature, compound **2b** was crystallized into water (30 ml). The solid was filtered and dried to yield {4-[(1-cyano-1-methylethyl)amino]phenyl}carbamic acid *tert*-butyl ester, **2b** (1.08 g, 3.9 mmol, 98%).

2-3). {4-[3-(4-cyano-3-trifluoromethylphenyl)-4-imino-5,5-dimethyl-2-thioxo-imidazolidin-1-yl]phenyl}carbamic acid *tert*-butyl ester, (2c)

[0094] Triethylamine (0.202 g, 2 mmol) was added to a solution of **1a** (0.456 g, 2 mmol) and **2b** (0.57 g, 2 mmol) in dry THF (5 ml). The reaction mixture was stirred at room temperature for 15 h and then concentrated to yield a dark residue which was subjected to flash chromatography (ethyl ether/acetone, 97:3) to afford {4-[3-(4-cyano-3-trifluoromethylphenyl)-4-imino-5,5-dimethyl-2-thioxo-imidazolidin-1-yl]phenyl}carbamic acid *tert*-butyl ester, (2c) (0.15 g, 0.3 mmol, 15%).

2-4). 4-[3-(4-aminophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 2d, [RD9]

[0095] The mixture of **2c** (0.15 g, 0.3 mmol) in HCl aq, 3N. (1 ml) and methanol (4 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (5 ml) and extracted with dichloromethane (8 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane/acetone, 9:1) to yield 4-[3-(4-aminophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, **2d**, [RD9] (0.118 g, 0.29 mmol, 97%) as a yellow solid.

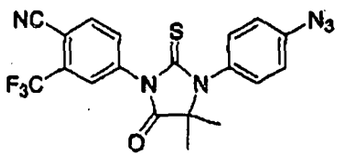


^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 6H), 6.73-6.75 (m, 2H), 7.00-7.03 (m, 2H), 8.02 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 66.2, 109.1, 114.3, 114.9, 120.4, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 130.4, 132.5 (q, J = 33.0 Hz), 133.4, 135.6, 138.5, 149.2, 175.3, 180.4.

2-5). 4-[3-(4-azidophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 2e, [RD10]

[0096] An aqueous solution of sulfuric acid (25% wt, 1 ml) was added to a solution of **2d** (0.10

g, 0.25 mmol) in acetone (1 ml) at -5 °C. An aqueous solution of $NaNO_2$ (0.024 g, 0.35 mmol, in 0.5 ml of water) was added slowly the above mixture over 0.1 h. The reaction mixture was allowed to stir at -5 °C for an additional 1 h and then an aqueous solution of NaN_3 (0.02 g, 0.3 mmol in 0.3 ml of water) was added dropwise. Upon completion of the addition, the reaction medium was warmed to room temperature and stirred for an additional 3 h. The product was extracted with dichloromethane (3 × 5 ml). The combined organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-[3-(4-azidophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 2e, [RD10] (0.08 g, 0.18 mmol, 72%) as a yellowish solid.



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 6H), 7.17-7.20 (m, 2H), 7.27-7.30 (m, 2H), 7.84 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 66.4, 110.1, 114.8, 120.4, 122.1 (q, J = 272.5 Hz), 127.0 (q, J = 4.7 Hz), 131.1, 131.5, 132.3, 133.3 (q, J = 33.0 Hz), 135.3, 137.1, 141.7, 174.8, 180.1. MS for $C_{19}H_{13}F_3N_6OS$, calculated 430.4, found 430.1.

Example 3

3-1). 2-(4-hydroxyphenylamino)-2-methylpropanenitrile, 3a

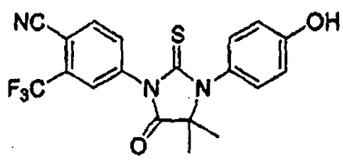
[0097] A mixture of 4-aminophenol (1.09 g, 10 mmol), acetone cyanohydrin (10 ml) and MgSO4 (2 g) was heated to 80 °C and stirred for 4 h. After concentration of the medium under vacuum, compound 3a was crystallized from water (20 ml). The solid was filtered and dried to yield 2-(4-hydroxyphenylamino)-2-methylpropanenitrile, 3a (1.69 g, 9.6 mmol, 96%).

3-2). 4-[3-(4-hydroxyphenyl)-5-imino-4,4-dimethyl-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 3b

[0098] Triethylamine (0.101 g, 1 mmol) was added to a solution of 1a (0.456 g, 2 mmol) and 3a (0.352 g, 2 mmol) in dry THF (5 ml). The reaction mixture was stirred at 0 °C for 48 h and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 85:15) to afford 4-[3-(4-hydroxyphenyl)-5-imino-4,4-dimethyl-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 3b (0.274 g, 0.68 mmol, 34%).

3-3). 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 3c, [RD8]

A mixture of 3b (0.202 g, 0.5 mmol) in HCl aq., 2N (2 ml) and methanol (5 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane/acetone, 9:1) to yield 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 3c, [RD8] (0.198 g, 0.49 mmol, 98%) as a white powder.

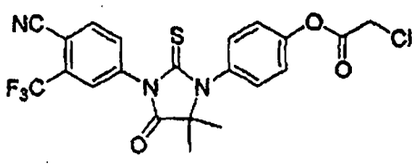


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57 (s, 6H), 6.26 (s, OH), 6.90-6.93 (m, 2H), 7.11-7.14 (m, 2H), 7.84 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 23.6, 66.5, 109.9, 114.9, 115.7, 116.8, 121.9 (q, J = 272.7 Hz), 127.2 (q, J = 4.7 Hz), 130.6, 132.3, 133.5 (q, J = 33.2 Hz), 135.3, 137.2, 157.0, 175.3, 180.2.

Example 4

Chloroacetic acid 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]phenyl ester, 4a, [RD13]

Chloroacetyl chloride (0.045 g, 0.4 mmol) was added to a mixture of 3c (0.101g, 0.25 mmol) and triethylamine (0.041g, 0.41 mmol) in dry THF (1.5 ml). The mixture was stirred at room temperature for 4 h. Triethylamine hydrochloride was filtered off. The filtrate was concentrated and chromatographed (dichloromethane/acetone, 95:5) to yield 84% of Chloroacetic acid 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]phenyl ester, 4a, [RD13] (0.101 g, 0.21 mmol) as white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58 (s, 6H), 4.32 (s, 2H), 7.33 (s, 4H), 7.83 (dd, J_1 = 8.3 Hz, J_2 = 1.9 Hz, 1H), 7.95-7.97 (m, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 23.7, 40.8, 66.5, 110.1, 114.8, 121.9 (q, J = 272.5 Hz), 122.7, 127.1 (q, J = 4.7 Hz), 130.9, 132.3, 132.9, 133.5 (q, J = 33.2 Hz), 135.3, 137.1, 150.9, 165.5, 174.8, 180.0.

Example 5

5-1a). 2-methyl-2-(4-methylphenyl)aminopropanenitrile, 5a

A mixture of *p*-toluidine (1.07 g, 10 mmol) and acetone cyanohydrin (10 ml) was heated to 80 °C and stirred for 4 h. The medium was concentrated and dried under vacuum to yield 2-methyl-2-(4-methylphenyl)aminopropanenitrile, **5a** (1.72g, 9.9 mmol, 99%) as brown solid.

5-1b). 2-methyl-2-(4-methylphenyl)aminopropanenitrile, 5a

Sodium cyanide (0.735g, 15 mmol) was added to a mixture of *p*-toluidine (1.07 g, 10 mmol) and acetone (1.16 g, 20 mmol) in 90% acetic acid (10 ml). The reaction mixture was stirred at room temperature for 12 h and then ethyl acetate (50 ml) was added. The organic layer was washed with water (4 × 30 ml), dried over magnesium sulfate and concentrated under vacuum to dryness to yield 2-methyl-2-(4-methylphenyl)aminopropanenitrile, **5a** (1.65g, 9.5 mmol, 95%) as a brown solid.

5-2). 4-[3-(4-methylphenyl)-5-imino-4,4-dimethyl-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 5b

Triethylamine (0.101 g, 1 mmol) was added to a solution of **1a** (0.456 g, 2 mmol) and **5a** (0.348 g, 2 mmol) in dry THF (3 ml). The reaction mixture was stirred at 0 °C for 2 days and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 95:5) to afford 4-[3-(4-methylphenyl)-5-imino-4,4-dimethyl-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, **5b** (0.136 g, 0.34 mmol, 17%).

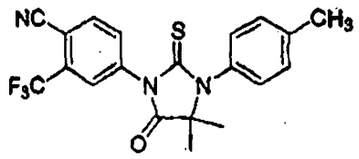
5-3a). 4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 5c

A mixture of **5b** (0.121 g, 0.3 mmol) in HCl aq., 2N (2 ml) and methanol (5 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, **5c** (0.118 g, 0.294 mmol, 98%) as a white powder.

5-3b). 4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile, 5c , [RD7]

A mixture of **1a** (0.547 g, 2.4 mmol) and **5a** (0.348 g, 2 mmol) in dry DMF (0.6 ml) was stirred for 36 h. To this mixture were added methanol (20 ml) and 2N HCl (5 ml). The second mixture was refluxed for 6

h. After being cooled to room temperature, the reaction mixture was poured into cold water (30 ml) and extracted with ethyl acetate (40 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile, 5c, [RD7] (0.596 g, 1.48 mmol, 74%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 6H), 2.44 (s, 3H), 7.17-7.20 (m, 2H), 7.33-7.36 (m, 2H), 7.86 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 23.6, 66.4, 110.0, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.2, 130.6, 132.2, 132.3, 133.4 (q, J = 33.2 Hz), 135.2, 137.2, 140.1, 175.1, 179.9.

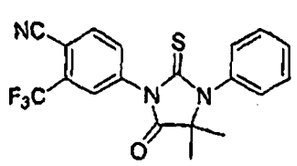
Example 6

6-1). 2-methyl-2-phenylaminopropanenitrile, 6a

A mixture of aminobenzene (0.931 g, 10 mmol) and acetone cyanohydrin (2 ml) was heated to reflux and stirred for 20 h. After being cold to room temperature, the reaction mixture was poured into ethyl acetate (40 ml) and washed with cold water (2 × 30 ml). The organic layer was dried over $MgSO_4$, concentrated under vacuum to dryness to yield 2-methyl-2-phenylaminopropanenitrile, 6a (1.51g, 9.4 mmol, 94%) as slurry brown liquid.

6-2). 4-[3-phenyl-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 6b, [RD10]

A mixture of 1a (0.274 g, 1.2 mmol) and 6a (0.160 g, 1 mmol) in dry DMF (0.2 ml) was stirred for 48 h. To this mixture were added methanol (10 ml) and 2N HCl (3 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (20 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-[3-phenyl-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 6b, [RD10] (0.276 g, 0.71 mmol, 71%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60 (s, 6H), 7.28-7.31 (m, 2H), 7.50-7.58 (m, 3H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96-7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 66.4, 110.2, 114.8, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.5, 129.8, 129.9, 132.2, 133.4 (q, J = 33.2 Hz), 135.1, 135.2, 137.2, 175.0, 179.9.

Example 7

7-1a). 1-(4-methylphenyl)aminocyclobutanenitrile, 7a

Sodium cyanide (0.147g, 3 mmol) was added to a mixture of *p*-toluidine (0.214 g, 2 mmol) and cyclobutanone (0.21 g, 3 mmol) in 90% acetic acid (3 ml). The reaction mixture was stirred at room temperature for 12 h and then 20 ml of ethyl acetate was added. The organic layer was washed with water (3 × 10 ml), dried over magnesium sulfate and concentrated under vacuum to dryness to yield 1-(4-methylphenyl)aminocyclobutanenitrile, 7a (0.343 g, 1.84 mmol, 92%) as a brown solid.

7-1b). 1-(4-methylphenyl)aminocyclobutanenitrile, 7a

Trimethylsilyl cyanide (0.93 ml, 7 mmol) was added dropwise to a mixture of *p*-toluidine (0.535 g, 5 mmol) and cyclobutanone (0.42 g, 6 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield 1-(4-methylphenyl)aminocyclobutanenitrile, 7a (0.912 g, 4.9 mmol, 98%) as a yellowish solid.

7-2). 4-(8-imino-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 7b

To a solution of 1a (2.28 g, 10 mmol) in dry DMF (3 ml) was added progressively, over 20 hours, a solution of 7a (1.764 g, 9 mmol) in dry DMF (3 ml) at room temperature. The medium was stirred for an additional 4 h. After DMF being evaporated, the residue was chromatographed (dichloromethane/acetone, 95:5) to afford 4-(8-imino-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 7b (1.937 g, 4.68 mmol, 52%).

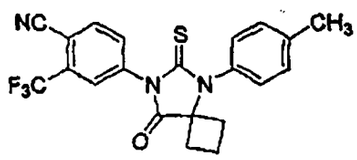
7-3a). 4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 7c [RD37]

A mixture of 7b (0.041 g, 0.1 mmol) in HCl aq., 2N (3 ml) and methanol (1 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (5 ml) and extracted with ethyl acetate (6 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-

diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 7c (0.04 g, 0.096 mmol, 96%) as a white powder.

7-3b). 4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 7c, [RD37]

A mixture of **1a** (0.912 g, 4 mmol) and **7a** (0.558 g, 3 mmol) in dry DMF (0.5 ml) was stirred at room temperature for 24 h. To this mixture were added methanol (30 ml) and HCl aq. 2N (6 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 ml) and extracted with ethyl acetate (60 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, **7c** (0.959 g, 2.31 mmol, 77%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62-1.69 (m, 1H), 2.16-2.22 (m, 1H), 2.46 (s, 3H), 2.55-2.66 (m, 4H), 7.19-7.26 (m, 2H), 7.36-7.42 (m, 2H), 7.86 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 21.3, 31.4, 67.4, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.5, 130.8, 132.2, 132.4, 133.3 (q, J = 33.2 Hz), 135.2, 137.3, 140.1, 175.0, 180.0.

Example 8

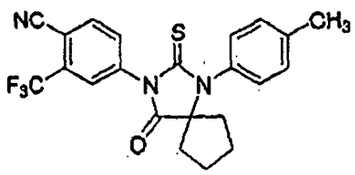
8-1). 1-(4-methylphenyl)aminocyclopentanenitrile, 8a

Trimethylsilyl cyanide (0.865 ml, 7 mmol) was added dropwise to a mixture of *p*-toluidine (0.535 g, 5 mmol) and cyclopentanone (0.589 g, 7 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield 1-(4-methylphenyl)aminocyclopentanenitrile, **8a** (0.981 g, 4.9 mmol, 98%) as a yellowish solid.

8-2). 4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 8b, [RD35]

A mixture of **1a** (0.296 g, 1.3 mmol) and **8a** (0.2 g, 1 mmol) in dry DMF (0.2 ml) was stirred for 48 h. To this mixture were added methanol (10 ml) and HCl aq. 2N (3 ml). The second mixture was refluxed for 6

h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 8b, [RD35] (0.3 g, 0.7 mmol, 70%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47-1.57 (m, 2H), 1.81-1.92 (m, 2H), 2.20-2.24 (m, 2H), 2.27-2.34 (m, 2H), 2.43 (s, 3H), 7.18-7.22 (m, 2H), 7.33-7.36 (m, 2H), 7.86 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 25.2, 36.3, 75.1, 110.0, 114.9, 121.9 (q, J = 272.5 Hz), 127.1 (q, J = 4.7 Hz), 129.5, 130.7, 123.2, 133.0, 133.4 (q, J = 33.2 Hz), 135.1, 137.4, 140.0, 176.3, 180.2.

Example 9

9-1). 1-(4-methylphenyl)aminocyclohexanenitrile, 9a

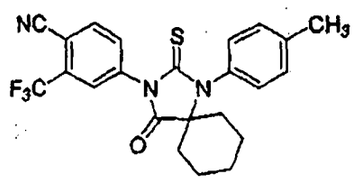
Sodium cyanide (0.147g, 3 mmol) was added to a mixture of *p*-toluidine (0.214 g, 2 mmol) and cyclohexanone (0.294 g, 3 mmol) in acetic acid 90% (3 ml). The reaction mixture was stirred at room temperature for 12 h and then 20 ml of ethyl acetate was added. The organic layer was washed with water (3 × 10 ml), dried over magnesium sulfate and concentrated under vacuum to dryness to yield 1-(4-methylphenyl)aminocyclohexanenitrile, 9a (0.398 g, 1.86 mmol, 93%) as a brown solid.

9-2). 4-(4-imino-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 9b

Triethylamine (0.05 g, 0.5 mmol) was added to a solution of **1a** (0.228 g, 1 mmol) and **9a** (0.214 g, 1 mmol) in dry THF (2 ml). The reaction mixture was stirred at room temperature for 2 days and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 95:5) to afford 4-(4-imino-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 9b (0.035 g, 0.08 mmol, 8%).

9-3). 4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 9c, [RD48]

A mixture of **9b** (0.035 g, 0.08 mmol) in HCl aq., 2N (1 ml) and methanol (3 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (5 ml) and extracted with ethyl acetate (6 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 9c, [RD48] (0.034 g, 0.076 mmol, 95%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02-1.05 (m, 1H), 1.64-1.76 (m, 4H), 2.03-2.12 (m, 5H), 2.44 (s, 3H), 7.12-7.15 (m, 2H), 7.33-7.36 (m, 2H), 7.85 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 21.3, 24.0, 32.6, 67.4, 109.9, 114.9, 122.0 (q, J = 272.5 Hz), 127.3 (q, J = 4.6 Hz), 130.0, 130.5, 132.0, 132.5, 133.3 (q, J = 33.2 Hz), 135.2, 137.3, 140.1, 174.1, 180.1.

Example 10

10-1). 1-(4-methylphenyl)aminocyclohexanenitrile, 10a

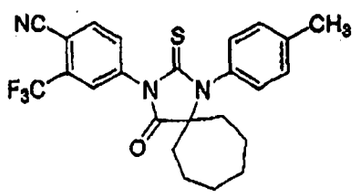
Sodium cyanide (0.147g, 3 mmol) was added to a mixture of *p*-toluidine (0.214 g, 2 mmol) and cycloheptanone (0.337 g, 3 mmol) in acetic acid 90% (3 ml). The reaction mixture was stirred at room temperature for 12 h and then 20 ml of ethyl acetate was added. The organic layer was washed with water (3 × 10 ml), dried over magnesium sulfate and concentrated under vacuum to dryness to yield 1-(4-methylphenyl)aminocyclohexanenitrile, **10a** (0.438 g, 1.92 mmol, 96%) as a brown solid.

10-2). 4-(4-imino-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]undec-3-yl)-2-trifluoromethylbenzonitrile, 10b

Triethylamine (0.05 g, 0.5 mmol) was added to a solution of **1a** (0.228 g, 1 mmol) and **9a** (0.228 g, 1 mmol) in dry THF (2 ml). The reaction mixture was stirred at room temperature for 2 days and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 95:5) to afford 4-(4-imino-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]undec-3-yl)-2-trifluoromethylbenzonitrile, **10b** (0.036 g, 0.08 mmol, 8%).

10-3). 4-(4-oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]undec-3-yl)-2-trifluoromethylbenzonitrile, 10c, [RD49]

A mixture of **9b** (0.036 g, 0.08 mmol) in HCl aq., 2N (1 ml) and methanol (3 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (5 ml) and extracted with ethyl acetate (6 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **10c** (0.034 g, 0.075 mmol, 94%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24-134 (m, 2H), 1.37-1.43 (m, 2H), 1.53-1.60 (m, 2H), 1.74-1.82 (m, 2H), 2.19-2.25 (m, 4H), 2.44 (s, 3H), 7.16-7.19 (m, 2H), 7.32-7.35 (m, 2H), 7.83 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.95-7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 22.2, 30.9, 36.3, 71.1, 110.0, 114.9, 121.9 (q, J = 272.5 Hz), 127.2 (q, J = 4.6 Hz), 129.6, 130.5, 132.3, 133.0, 133.2 (q, J = 33.2 Hz), 135.1, 137.4, 140.0, 175.9, 179.7.

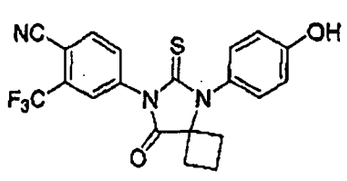
Example 11

11-1). 1-(4-hydroxyphenyl)aminocyclobutanenitrile, 11a

Trimethylsilyl cyanide (0.93 ml, 7 mmol) was added dropwise to a mixture of 4-hydroxyaniline (0.545 g, 5 mmol) and cyclobutanone (0.42 g, 6 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane:acetone, 98:2) to yield **11a** (0.903 g, 4.8 mmol, 96%) as a yellowish solid.

11-2). 4-(8-oxo-6-thioxo-5-(4-hydroxyphenyl)-5,7-diazaspiro[3,4]oct-7-yl)-2-trifluoromethylbenzonitrile, 11b , [RD58]

A mixture of **1a** (0.57 g, 2.5 mmol) and **7a** (0.376 g, 2 mmol) in dry DMF (0.5 ml) was stirred at room temperature for 40 h. To this mixture were added methanol (30 ml) and HCl aq. (5 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (40 ml) and extracted with ethyl acetate (50 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 98:2) to yield **11b** (0.659 g, 1.58 mmol, 79%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55-1.63 (m, 1H), 2.01-2.09 (m, 1H), 2.50-2.65 (m, 4H), 6.97-7.01 (m, 2H), 7.20-7.24 (m, 2H), 8.02 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 13.4, 31.3, 67.5, 108.9, 114.8, 116.1, 123.5 (q, J = 271.5 Hz), 127.4 (q, J = 4.9 Hz), 131.3, 131.8 (q, J = 32.7 Hz), 133.3, 135.5, 136.2, 138.5, 158.1, 175.1, 180.7.

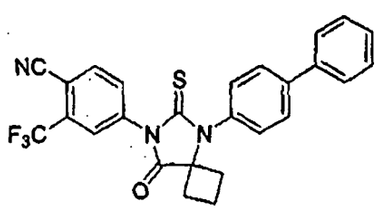
Example 12

12-1). 1-(4-biphenylamino)cyclobutanecarbonitrile, 12a

Trimethylsilyl cyanide (0.2 ml, 1.5 mmol) was added dropwise to a mixture of 4-biphenylamine (0.169 g, 1 mmol) and cyclobutanone (0.098 g, 1.4 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **12a** (0.24 g, 0.97 mmol, 97%) as a white solid.

12-2). 4-(8-oxo-6-thioxo-5-(4-biphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 12b [RD57]

A mixture of **1a** (0.137 g, 0.6 mmol) and **12a** (0.124 g, 0.5 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 3 days. To this mixture were added methanol (5 ml) and HCl aq. 2N (1 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (15 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **12b** (0.162 g, 0.34 mmol, 68%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67-1.76 (m, 1H), 2.19-2.31 (m, 1H), 2.59-2.74 (m, 4H), 7.40-7.44 (m, 3H), 7.47-7.53 (m, 2H), 7.64-7.67 (m, 2H), 7.79-7.82 (m, 2H), 7.88 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 67.5, 110.0, 114.9, 122.0 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 127.3, 128.1, 128.7, 129.0, 130.2, 132.3, 133.5 (q, J = 33.2 Hz), 134.2, 135.2, 137.2, 139.6, 142.8, 174.9, 179.9.

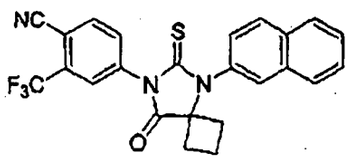
Example 13

13-1). 1-(2-naphthylamino)cyclobutanecarbonitrile, 13a

Trimethylsilyl cyanide (0.27 ml, 2 mmol) was added dropwise to a mixture of 2-aminonaphthalene (0.143 g, 1 mmol) and cyclobutanone (0.098 g, 1.4 mmol). The reaction mixture was stirred at room temperature for 12 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **13a** (0.209 g, 0.94 mmol, 94%) as a yellow solid.

13-2). 4-(8-oxo-6-thioxo-5-(4-biphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 12b, [RD85]

A mixture of **1a** (0.137 g, 0.6 mmol) and **13a** (0.111 g, 0.5 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 3 days. To this mixture were added methanol (5 ml) and HCl aq. (1 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (15 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **12b** (0.146 g, 0.325 mmol, 65%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 158-1.68 (m, 1H), 2.17-2.29 (m, 1H), 2.61-2.75 (m, 4H), 7.40 (dd, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 1H), 7.58-7.65 (m, 2H), 7.86-8.00 (m, 5H), 8.04 (J = 1.8 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.6, 67.7, 110.0, 114.9, 122.0 (q, J = 272.6 Hz), 126.8, 127.1 (q, J = 4.8 Hz), 127.2, 127.7, 128.0, 128.3, 129.1, 130.2, 132.2, 132.5, 133.4, 133.5 (q, J = 33.1 Hz), 133.6, 135.2, 137.2, 175.0, 180.1.

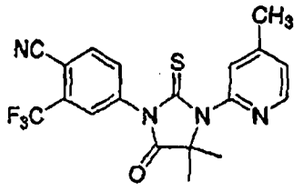
Example 14

14-1). 2-(4-methyl-2-pyridinamino)-2-methylpropanenitrile, 14a

Trimethylsilyl cyanide (0.27 ml, 2 mmol) was added dropwise to a mixture of 2-amino-4-methylpyridine (0.108 g, 1 mmol) and acetone (0.58 g, 10 mmol). The reaction mixture was stirred at room temperature for 6 days and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane: acetone, 60:40) to yield **14a** (0.133 g, 0.76 mmol, 76%) as a white solid.

14-2). 4-[4,4-dimethyl-3-(4-methylpyridin-2-yl)-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 14b, [RD83]

A mixture of **1a** (0.91 g, 0.4 mmol) and **14a** (0.053 g, 0.3 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 6 days. To this mixture were added methanol (5 ml) and HCl aq. (1ml). The second mixture was refluxed for 5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (15 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **14b** (0.07 g, 0.174 mmol, 58%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (s, 6H), 2.44 (s, 3H), 7.19 (d, J = 4.4 Hz, 1H), 7.45 (t, J = 0.6 Hz, 1H), 7.82 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 8.47 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 24.1, 67.1, 110.2, 114.8, 121.9 (q, J = 272.6 Hz), 124.4, 125.1, 127.3 (q, J = 4.8 Hz), 132.4, 133.5 (q, J = 33.2 Hz), 135.3, 137.1, 149.2, 149.5, 150.0, 175.2, 179.0.

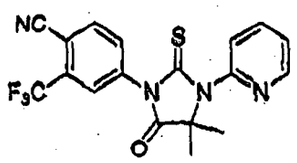
Example 15

15-1). 2-(2-pyridinamino)-2-methylpropanenitrile, 15a

Trimethylsilyl cyanide (0.27 ml, 2 mmol) was added dropwise to a mixture of 2-aminopyridine (0.094 g, 1 mmol) and acetone (0.58 g, 10 mmol). The reaction mixture was stirred at room temperature for 6 days and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane: acetone, 60:40) to yield **15a** (0.131 g, 0.81 mmol, 81%) as a white solid.

15-2). 4-[4,4-dimethyl-3-(4-pyridin-2-yl)-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 15b, [RD82]

A mixture of **1a** (0.91 g, 0.4 mmol) and **15a** (0.048 g, 0.3 mmol) in dry DMF (0.3 ml) was stirred at room temperature for 10 days. To this mixture were added methanol (5 ml) and of HCl aq. (1 ml). The second mixture was refluxed for 5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (15 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **15b** (0.059 g, 0.153 mmol, 51%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (s, 6H), 7.38 (dd, J_1 = 7.3 Hz, J_2 = 5.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.87 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.95 (td, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 1.3 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 8.62 (dd, J_1 = 4.7 Hz, J_2 = 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 67.1, 110.3, 114.8, 121.9 (q, J = 272.6 Hz), 123.7, 123.8, 127.3 (q, J = 4.8 Hz), 132.4, 133.6 (q, J = 33.2 Hz), 135.3, 137.1, 138.2, 149.5, 149.6, 175.1, 179.0.

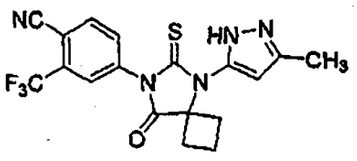
Example 16

16-1). 1-(5-methyl-2H-pyrazol-3-ylamino)-cyclobutanecarbonitrile, 16a

Trimethylsilyl cyanide (0.532 ml, 4.0 mmol) was added dropwise to the mixture of 3-amino-5-methylpyrazole (0.194 g, 2.0 mmol) and cyclobutanone (0.154 g, 2.2 mmol). The reaction mixture was stirred at room temperature for 40 h and then concentrated under vacuum to obtain a dark liquid which was subjected to chromatography (dichloromethane) to yield **16a** (0.267 g, 1.52 mmol, 76%) as a off-white powder.

16-2). 4-[5-(5-methyl-2H-pyrazol-3-yl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-7-yl]-2-trifluoromethyl-benzonitrile, 16b, [RD84]

A mixture of **1a** (0.0684 g, 0.3 mmol) and **16a** (0.053 g, 0.3 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 4 days. To this mixture were added methanol (10 ml) and HCl aq. 2N (2 ml). The second mixture was refluxed for 5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (30 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 97:3) to yield **16b** (0.0826 g, 0.2 mmol, 67%) as a white powder.

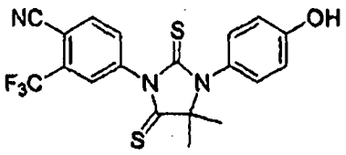


^{1}H NMR (acetone d_6, 400 MHz) δ δ 1.66-1.76 (m, 1H), 2.00-2.07 (m, 1H), 3.35 (s, 3H), 2.56-2.63 (m, 2H), 2.85-2.93 (m, 2H), 8.04 (dd, J_1 = 8.2 Hz, J_2 = 1.6 Hz, 1H), 8.18 (d, J = 1.6 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 11.99 (s, 1H); ^{13}C NMR (acetone d_6, 100 MHz) δ 10.2, 13.1, 31.1, 67.4, 102.5, 109.1, 114.8, 122.5 (q, J = 271.4 Hz), 127.8 (q, J = 4.8 Hz), 131.9 (q, J = 33.6 Hz), 133.6, 135.6, 138.4, 139.9, 145.0, 175.0, 179.6.

Example 17

4-[3-(4-hydroxyphenyl)-4,4-dimethyl-2,5-dithioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 17a, [RD59]

A mixture of 3c (0.081 g, 0.2 mmol) and Lawesson reagent (0.097 g, 0.24 mmol) in toluene (3 ml) was heated to reflux for 15 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:pentane, 9:1) to yield 17a (0.0185 g, 0.044 mmol, 22%) as a white powder.

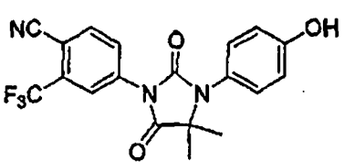


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65 (s, 6H), 6.95-6.97 (m, 2H), 7.15-7.18 (m, 2H), 7.75 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H), 7.98 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 77.8, 110.9, 114.7, 116.7, 121.9 (q, J = 272.6 Hz), 128.1 (q, J = 4.8 Hz), 129.1, 130.7, 133.3, 133.5 (q, J = 33.2 Hz), 135.5, 140.3, 156.8, 179.9, 207.9.

Example 18

4-[3-(4-hydroxyphenyl)-4,4-dimethyl-2,5-dioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 18a, [RD60]

Hydrogen peroxide, 30% (3 ml, 26 mmol) was added dropwise to a solution of of 3c (0.121 g, 0.4 mmol) in glacial acetic acid (3 ml). The mixture was stirred at room temperature for 12 h and then 20 ml of ethyl acetate was added. The organic layer was washed with water (3 × 15 ml), dried over magnesium sulfate, concentrated and chromatographed (dichloromethane) to yield 18a (0.102 g, 0.261 mmol, 87%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52 (s, 6H), 6.70-6.73 (m, 2H), 7.01-7.04 (m, 2H), 7.92 (d, J = 8.4 Hz, 1H), 8.00 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1H), 8.15 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 63.7, 108.4, 115.0, 116.7, 121.9 (q, J = 272.6 Hz), 123.5 (q, J = 4.8 Hz), 124.0, 128.5, 130.5, 133.6 (q, J = 33.2 Hz), 135.5, 136.2, 153.4, 157.2, 174.5.

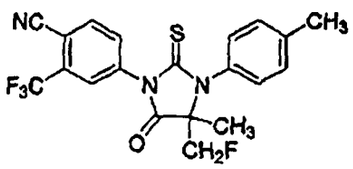
Example 19

19-1). 3-fluoro-2-methyl-2-(4-methylphenyl)aminopropionitrile, 19a

Trimethylsilyl cyanide (0.146 ml, 1.1 mmol) was added dropwise to the mixture of *p*-toluidine (0.107 g, 1 mmol) and fluoroacetone (0.082 g, 1.1 mmol). The reaction mixture was stirred at room temperature for 12 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **19a** (0.179 g, 0.93 mmol, 93%) as a yellowish solid.

19-2). 4-(4-fluoromethyl-4-methyl-5-oxo-2-thioxo-3-(4-methylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile, 19b, [RD68]

A mixture of **1a** (0.16 g, 0.7 mmol) and **19a** (0.096 g, 0.5 mmol) in dry DMF (0.3 ml) was stirred at room temperature for 48 h. To this mixture were added methanol (10 ml) and HCl aq. 2N (2 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (30 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **19b** (0.168 g, 0.4 mmol, 80%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 3H), 2.44 (s, 3H), 4.35 (dd, J_1 = 47.2 Hz, J_2 = 10.0 Hz, 1H), 4.71 (dd, J_1 = 45.2 Hz, J_2 = 10 Hz, 1H), 7.22-7.26 (m, 2H), 7.35-7.39 (m, 2H), 7.82 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.93 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.0 (d, J = 4.6 Hz), 21.3, 69.3 (d, J = 18.3 Hz), 81.9 (d, J = 179.5 Hz), 109.9, 114.8, 121.8 (q, J = 272.6 Hz), 127.2 (q, J = 4.7 Hz), 129.3, 130.9, 131.6, 132.3, 133.3 (q, J = 33.2 Hz), 135.3, 137.0, 140.5, 174.1, 181.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -62.5, 110.9.

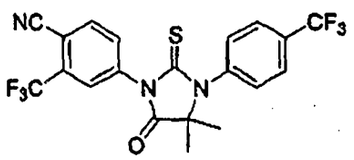
Example 20

20-1). 2-methyl-2-(4-trifluoromethylphenyl)aminopropanenitrile, 20a

A mixture of 4-trifluoromethylaniline (1.61 g, 10 mmol), acetone cyanohydrin (5 ml) and magnesium sulfate (2 g) was heated to 80 °C and stirred for 12 h. To the medium was added ethyl acetate (50 ml) and then washed with water (3 × 30 ml). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to dryness to yield **20a** (2.166 g, 9.5 mmol, 95%) as brown solid.

20-2). 4-(4,4-dimethyl-5-oxo-2-thioxo-3-(4-trifluoromethylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile, 20b, [RD66]

A mixture of **1a** (0.114 g, 0.5 mmol) and **20a** (0.092 g, 0.4 mmol) in dry DMF (0.3 ml) was stirred at room temperature for 48 h. To this mixture were added methanol (10 ml) and HCl aq. (3 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (20 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **20b** (0.117 g, 0.256 mmol, 64%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 6H), 7.45-7.49 (m, 2H), 7.80-7.83 (m, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 66.6, 110.3, 114.8, 121.8 (q, J = 272.6 Hz), 123.5 (q, J = 271.1 Hz), 127.0 (q, J = 4.6 Hz), 127.1 (q, J = 4.7 Hz), 130.3, 131.9 (q, J = 32.9 Hz),, 132.2, 133.5 (q, J = 33.3 Hz), 135.3, 136.9, 138.4, 174.6, 179.9.

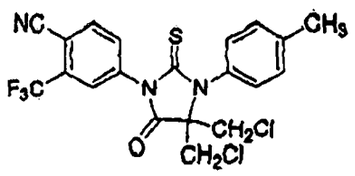
Example 21

21-1). 3-chloro-2-chloromethyl-2-(4-methylphenyl)aminopropanenitrile, 21a

Trimethylsilyl cyanide (0.27 ml, 2 mmol) was added dropwise to a mixture of *p*-toluidine (0.107 g, 1 mmol) and 1,3-dichloroacetone (0.254 g, 2 mmol). The reaction mixture was heat to 80 °C and stirred for 6 h. To the mixture was added 20 ml of ethyl acetate and then wash with water (2 × 20 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **21a** (0.192 g, 0.79 mmol, 79%) as a brown powder.

21-2). 4-(4,4-bischloromethyl-5-oxo-2-thioxo-3-(4-methylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile, 21b, [RD67]

A mixture of **1a** (0.16 g, 0.7 mmol) and **21a** (0.122 g, 0.5 mmol) in dry DMF (0.5 ml) was stirred at room temperature for 10 days. To this mixture were added methanol (10 ml) and of HCl aq. 2N (2 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **21b** (0.09 g, 0.19 mmol, 38%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.44 (s, 3H), 3.54 (d, J = 11.8 Hz, 2H), 3.93 (d, J = 11.8 Hz, 2H), 7.37-7.40 (m, 2H), 7.48-7.51 (m, 2H), 7.79 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 42.8, 74.3, 110.7, 114.7, 121.7 (q, J = 272.6 Hz), 127.2 (q, J = 4.7 Hz), 128.8, 131.0, 131.1, 132.4, 133.8 (q, J = 33.2 Hz), 135.5, 136.9, 140.9, 169.5, 182.5.

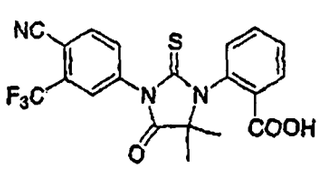
Example 22

22-1). 1-(4-methylphenyl)aminocyclohexanenitrile, 22a

Sodium cyanide (0.245g, 5 mmol) was added to a mixture of anthranilic acid (0.411 g, 3 mmol) and acetone (1 ml, 13.6 mmol) in acetic acid 90% (3 ml). The reaction mixture was stirred at room temperature for 12 h and then 50 ml of ethyl acetate was added. The organic layer was washed with brine (3 × 30 ml). The organic layer was dried over magnesium sulfate, concentrated and chromatographed (dichloromethane:acetone, 90:10) to yield **22a** (0.551 g, 2.7 mmol, 90%) as a brown solid.

22-2). 2-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]benzoic acid, 22b, [RD65]

A mixture of **1a** (0.114 g, 0. mmol) and **22a** (0.103 g, 0.5 mmol) in dry DMF (0.5 ml) was stirred at room temperature for 3 days. To this mixture were added methanol (10 ml) and HCl aq. 2N, (3 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (ethyl acetate:pentane, 2:1) to yield **22b** (0.143 g, 0.33 mmol, 66%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 3H), 1.78 (s, 3H), 7.39 (d, J = 7.7 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H) 7.76-7.82 (m, 2H), 7.90-7.98 (m, 2H), 8.22 (d, J = 6.8 Hz, 1H), 8.96 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 26.2, 67.6, 110.1, 114.8, 121.9 (q, J = 272.6 Hz), 127.2 (q, J = 4.7 Hz), 128.9, 131.0, 130.2, 132.5, 133.2 (q, J = 33.3 Hz), 133.7, 134.7, 135.4, 135.8, 137.3, 169.8, 175.3, 180.7.

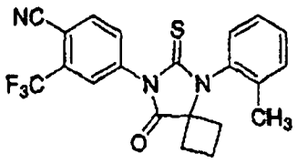
Example 23

23-1). 1-(2-methylphenyl)aminocyclobutanenitrile, 23a

Trimethylsilyl cyanide (0.66 ml, 5 mmol) was added dropwise to the mixture of *p*-toluidine (0.321 g, 3 mmol) and cyclobutanone (0.28 g, 4 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **23a** (0.541 g, 2.91 mmol, 97%) as a yellowish solid.

23-2). 4-(8-oxo-6-thioxo-5-(2-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 23b, [RD71]

A mixture of **1a** (0.114 g, 0.5 mmol) and **23a** (0.093 g, 0.5 mmol) in dry DMF (0.3 ml) was stirred at room temperature for 3 days. To this mixture were added methanol (10 ml) and HCl aq. 2N, (3 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **23b** (0.116 g, 0.28 mmol, 56%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63-1.69 (m, 1H), 2.26 (s, 3H), 2.28-2.41 (m, 2H), 2.58-2.76 (m, 3H), 7.21 (d, J = 7.6 Hz, 1H), 7.39-7.49 (m, 3H), 7.89 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 18.0, 30.7, 32.2, 67.6, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 127.5, 129.8, 130.2, 131.9, 132.3, 133.4, 133.5 (q, J = 34.3 Hz), 135.2, 135.8, 137.1, 138.0, 175.3, 178.7.

Example 24

24-1). 1-aminocyclopentanecarbonitrile, 24a

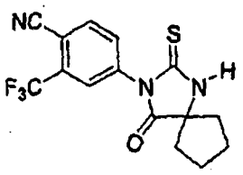
Ammonia anhydrous was bubble into a mixture of cyclopentanone (0.452 g) and trimethylsilyl cyanide (0.66 ml, 5 mmol). The excess of ammonia was refluxed by a dry ice-acetone condenser. After 1 h of reflux, the ammonia was allowed to degas form the medium and then the remaining mixture was concentrated under vacuum to yield **24a** (0.522 g, 4.75 mmol, 95%) as a colorless liquid.

24-2). 4-(4-imino-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 24b

Triethylamine (0.101 g, 0.1 mmol) was added to a solution of **1a** (0.684 g, 3 mmol) and **24a** (0.33 g, 3 mmol) in dry THF (5 ml). The reaction mixture was stirred at room temperature for 5 h and then concentrated to yield a brown residue which was subjected to flash chromatography (dichloromethane/acetone, 93:7) to afford **24b** (0.741 g, 2.19 mmol, 73%).

24-3). 4-(4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 24c, [RD77]

A mixture of **24b** (0.741 g, 2.19 mmol) in HCl aq., 2N (4 ml) and methanol (20 ml) was heated to reflux for 1 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (40 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **24c** (0.72 g, 2.12 mmol, 97%) as a white powder.

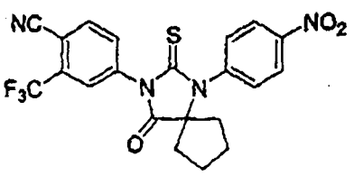


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.86-190 (m, 2H), 1.96-2.05 (m, 4H), 2.26-2.30 (m, 2H), 7.80 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H) 8.20 (bs, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3, 38.1, 71.0, 110.1, 114.8, 121.8 (q, J = 272.7 Hz), 126.8 (q, J = 4.7 Hz), 131.9, 133.6 (q, J = 34.3 Hz), 135.3, 136.7, 176.1, 179.8.

Example 25

25). 4-[1-(4-nitrophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl]-2-trifluoromethylbenzonitrile, 25a, [RD55]

A mixture of **25c** (0.0678 g, 0.2 mmol), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.05 g, 0.33 mmol) and 4-fluoronitrobenzene (0.056 g, 0.4 mmol) in dimethylformamide (0.5 ml) was placed under argon in a sealed-tube and heated to 130 °C for 40 h. The reaction mixture was poured into ethyl acetate (5 ml) and washed with water (2 × 10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **25a** (0.038 g, 0.084 mmol, 42%) as a white powder.

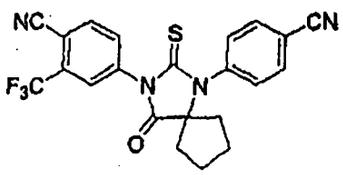


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53-1.56 (m, 2H), 1.90-1.93 (m, 2H), 2.14-2.18 (m, 2H), 2.37-2.40 (m, 2H), 7.54-7.57 (m, 2H), 7.85 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 8.39-8.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 36.5, 75.3, 110.3, 114.8, 121.8 (q, J = 272.6 Hz), 125.2, 127.0 (q, J = 4.7 Hz), 131.4, 132.1, 133.6 (q, J = 34.3 Hz), 135.3, 136.9, 141.7, 148.1, 175.6, 180.2.

Example 26

26). 4-[1-(4-cyanophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl]-2-trifluoromethylbenzonitrile, 26a, [RD54]

A mixture of **24c** (0.0678 g, 0.2 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.061 g, 0.4 mmol) and 4-fluorocyanobenzene (0.048 g, 0.4 mmol) in dimethylformamide (0.5 ml) was placed under argon in a sealed-tube and heated to 140 °C for 5 days. The reaction mixture was poured into ethyl acetate (5 ml) and washed with water (2 × 10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **26a** (0.023 g, 0.052 mmol, 26%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51-1.55 (m, 2H), 1.90-1.93 (m, 2H), 2.12-2.16 (m, 2H), 2.33-2.38 (m, 2H), 7.47-7.50 (m, 2H), 7.81-7.87 (m, 3H), 7.95-7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 36.5, 75.3, 110.3, 113.9, 114.7, 117.5, 121.8 (q, J = 272.6 Hz), 127.0 (q, J = 4.8 Hz), 131.2, 132.1, 133.6 (q, J = 34.3 Hz), 133.8, 135.3, 136.9, 140.0, 175.6, 180.1.

Example 27

27-1). 1-methyl-4-(4-methylphenylamino)piperidine-4-carbonitrile, 27a

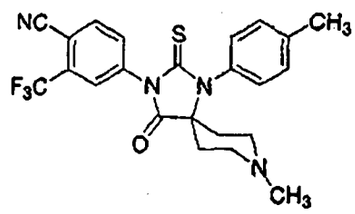
Sodium cyanide (0.318 g, 6.5 mmol) was added to a mixture of *p*-toluidine (0.535 g, 5 mmol) and 1-methyl-4-piperidinone (0.678 g, 6 mmol) in acetic acid 90% (5 ml). The reaction mixture was stirred at room temperature for 6 h and then 100 ml of dichloromethane was added. The organic layer was washed with a solution NaOH, 2N (2 × 50 ml), dried over magnesium sulfate, concentrated and chromatographed (DCM and then acetone) to obtained **27a** (0.722 g, 3.15 mmol, 63%).

27.2). 4-(4-imino-8-methyl-2-thioxo-1-(4-methylphenyl)-1,3,8-triazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 27b

Triethylamine (0.02, 0.2 mmol) was added to a solution of **1a** (0.228 g, 1 mmol) and **27a** (0.114 g, 0.5 mmol) in dry THF (2 ml). The reaction mixture was stirred at room temperature for 20 h and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 90:10, and then acetone) to afford **27b** (0.059 g, 0.13 mmol, 26%).

27-3). 4-(8-methyl-4-oxo-2-thioxo-1-(4-methylphenyl)-1,3,8-triazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 27c, [RD53]

A mixture of **27b** (0.059 g, 0.13 mmol) in HCl aq., 2N (1 ml) and methanol (3 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (5 ml) and extracted with ethyl acetate (10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 60:40) to yield **27c** (0.055 g, 0.012 mmol, 92%) as a white powder.

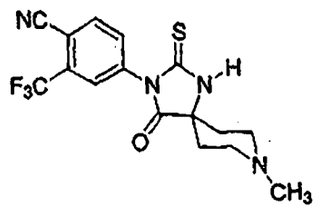


^{1}H NMR (Acetone-d_6, 400 MHz) δ 1.93-1.99 (m, 1H), 2.00-2.04 (m, 1H), 2.18 (s, 3H), 2.24-2.28 (m, 2H), 2.38 (s, 3H), 2.61-2.72 (m, 4H), 7.18-7-20 (m, 2H), 7.32-7.35 (m, 2H), 8.03 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 20.3, 31.4, 45.1, 49.8, 65.1, 109.1, 114.8, 122.4 (q, J = 275.1 Hz), 127.7 (q, J = 4.8 Hz), 130.0, 130.5, 131.9 (q, J = 32.6 Hz), 132.6, 133.5, 135.6, 138.3, 139.4, 174.0, 180.6.

Example 28

4-(8-methyl-4-oxo-2-thioxo-1,3,8-triazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 28a, [RD52]

Compound **28a** was synthesized according to the procedure described in patent US 5958936.

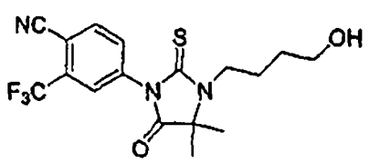


^{1}H NMR (Acetone-d_6, 400 MHz) δ 1.93-2.00 (m, 2H), 2.09-2.16 (m, 2H), 2.25 (s, 3H), 2.42-2.49 (m, 2H), 2.75-2.80 (m, 2H), 7.97 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 8.11 (d, J = 1.8 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 9.80 (bs, NH); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 32.9, 45.4, 50.1, 62.3, 109.1, 114.8, 122.4 (q, J = 271.6 Hz), 127.5 (q, J = 4.8 Hz), 131.8 (q, J = 32.7 Hz), 133.2, 135.6, 135.6, 138.0, 175.2, 180.4.

Example 29

4-[3-(4-hydroxybutyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, RU 59063

Compound **RU 59063** was synthesized according to the procedure described by Teutsch *et al* [*J. Steroid. Biochem. Molec. Biol.* **1994**, *48(1)*, 111-119].



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55 (s, 6H), 1.58-1.62 (m, 2H), 1.86-1.89 (m, 2H), 2.25 (bs, OH), 3.65-3.71 (m, 4H), 7.74 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1, 24.7, 29.6, 43.9, 61.7, 65.2, 109.7, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.8 Hz), 132.2, 133.7 (q, J = 34.3 Hz), 135.2, 137.2, 175.3, 178.2.

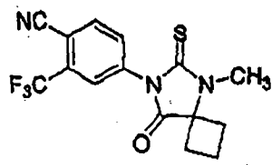
Example 30

30-1). 1-methylaminocyclobutanecarbonitrile, 30a

Methylamine was bubbled into a refrigerated mixture of cyclobutanone (0.21 g, 3 mmol) and trimethylsilyl cyanide (0.396 g, 4 mmol) until the volume doubled. The mixture was stirred 3 h and then concentrated to dryness to obtain **30a** (0.33 g, quantitative).

30-2). 4-(5-methyl-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylenzonitrile, 30b, [RD73]

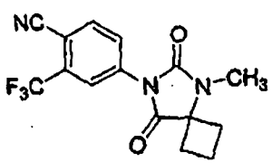
A mixture of **1a** (0.114 g, 0.5 mmol) and **30a** (0.055 g, 0.5 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 0.5 h. To this mixture were added 10 ml of methanol and 2 ml of 2N HCl. The second mixture was refluxed for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **30b** (0.148 g, 0.435 mmol, 87%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95-2.06 (m, 1H), 2.21-2.32 (m, 1H), 2.58-2.71 (m, 4H), 3.44 (s, 3H), 7.77 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 30.3, 30.4, 66.1, 109.7, 114.9, 121.9 (q, J = 272.6 Hz), 126.9 (q, J = 4.8 Hz), 132.1, 133.2 (q, J = 34.3 Hz), 135.2, 137.3, 175.1, 178.7.

30-3). 4-(5-methyl-6,8-dioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 30c, [RD74]

Hydrogen peroxide (2 ml, 30%) was added to the mixture of **30b** (0.068 g, 0.2 mmol) in glacial acetic acid (3 ml). After being stirred at room temperature for 10 h, the reaction mixture was poured into ethyl acetate (20 ml) and then washed with water (2 × 20 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone) to yield **30c** (0.057 g, 0.176 mmol, 88%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91-2.35 (m, 1H), 2.21-2.31 (m, 1H), 2.50-2.61 (m, 4H), 3.12 (s, 3H), 7.89 (d, J = 8.2 Hz, 1H), 7.97 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1H), 8.12 (d, J = 2.0 Hz, 1H),; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 25.4, 29.3, 63.4, 108.1, 115.1, 121.6 (q, J = 272.6 Hz), 122.9 (q, J = 4.8 Hz), 127.9, 133.5 (q, J = 34.3 Hz), 135.3, 136.5, 152.7, 174.4.

Example 31

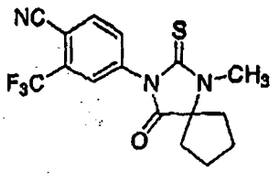
31-1). 1-methylaminocyclopentanecarbonitrile, 31a

Methylamine was bubbled into a refrigerated mixture of cyclopentanone (0.252 g, 3 mmol) and trimethylsilyl cyanide (0.396 g, 4 mmol) until the volume doubled. The mixture was stirred 3 h and then concentrated to dryness to obtain **31a** (0.372 g, quantitative).

31-2). 4-(1-methyl-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 31b, [RD75]

A mixture of **1a** (0.114 g, 0.5 mmol) and **31a** (0.062 g, 0.5 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 0.5 h. To this mixture were added 10 ml of methanol and 2 ml of 2N HCl. The

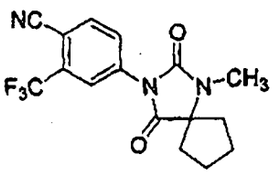
second mixture was refluxed for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **31b** (0.159 g, 0.45 mmol, 90%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91-2.05 (m, 6H), 2.16-2.21 (m, 2H), 3.27 (*s*, 3H), 7.77 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.89 (d, J = 1.8 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 30.3, 35.4, 73.2, 109.5, 114.9, 121.9 (q, J = 272.6 Hz), 126.9 (q, J = 4.8 Hz), 132.2, 133.2 (q, J = 34.3 Hz), 135.2, 137.5, 176.8, 178.5.

31-3). 4-(1-methyl-2,4-dioxo-1,3-diaza-spiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 31c, [RD76]

Hydrogen peroxide (2 ml, 30%) was added to the mixture of **31b** (0.07 g, 0.2 mmol) in glacial acetic acid (3 ml). After being stirred at room temperature for 10 h, the reaction mixture was poured into ethyl acetate (20 ml) and then washed with water (2 × 20 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone) to yield **31c** (0.057 g, 0.168 mmol, 84%) as a white powder.

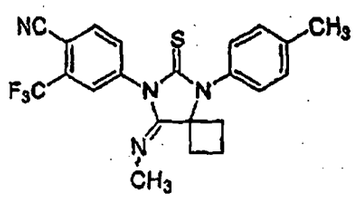


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88-1.99 (m, 6H), 2.12-2.17 (m, 2H), 2.98 (s, 3H), 7.88 (d, J = 8.2 Hz, 1H), 7.97 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 8.12 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 26.5, 34.8, 70.1, 108.0, 115.1, 122.0 (q, J = 272.5 Hz), 122.9 (q, J = 4.9 Hz), 127.9, 133.5 (q, J = 32.9 Hz), 135.3, 136.6, 152.7, 176.1.

Example 32

4-(8-methylimino-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-7-yl)-2-trifluoromethyl-benzonitrile, 32a, [RD90]

A mixture of **7b** (0.042 g, 0.1 mmol), DBU (0.023 g, 0.15 mmol) and iodomethane (0.073 g, 0.5 mmol) in DMF (0.3 ml) was stirred for 15 h at room temperature. After DMF being evaporated, the medium was chromatographed (dichloromethane) to yield **32a** (0.011g, 0.026 mmol, 26%) as white powder.

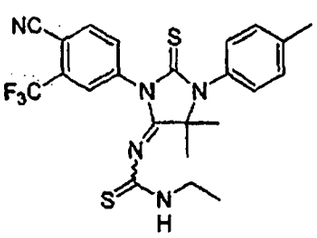


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58-1.65 (m, 1H), 2.04-2.13 (m, 1H), 2.45 (s, 3H), 2.70-2.77 (m, 2H), 3.06-3.10 (m, 2H), 3.58 (s, CH_3-N, major isomer) [2.70 (s, CH_3-N, minor isomer)], 7.20-7.34 (m, 4H), 7.75-7.91 (m, 3H); ($CDCl_3$, 100 MHz) δ 12.6, 21.4, 30.2, 33.7 (35.3 for the other isomer), 66.9, 109.1, 115.2, 122.1 (q, J = 272.5 Hz), 128.5 (q, J = 4.9 Hz), 129.8, 130.4, 130.6, 132.8, 133.2 (q, J = 32.9 Hz), 133.5, 134.9, 139.8, 157.0, 180.2.

Example 33

1-[3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene]-3-ethyl-thiourea, 33a, [RD91]

A mixture of **5b** (0.06 g, 0.149 mmol), ethylthioisocyanate (0.087 g, 1 mmol) and CuI (0.01 g, 0.05 mmol) in DMF (0.1 ml) was heated under microwave for 45 minutes. Then the medium was washed with brine and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and chrpmatographed (HPLC, alumina column) to yield **33a** (0.054 g, 0.108 mmol, 72%) as white powder.

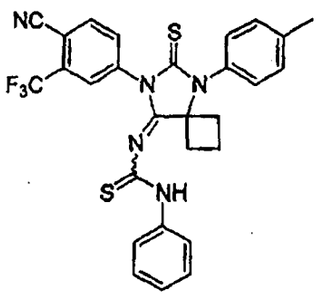


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, J = 7.23 Hz, 3H), 1.70 [1.75 minor isomer] (s, 6H), 2.42 (s, 3H), 3.28-3.39 (m, 2H) [3.15-3.22 (m, 2H), minor isomer], 6.50 (bs, 1H) [6.93 (bs, 1H), minor isomer], 7.14-7.18 (m, 2H), 7.32-7.35 (m, 2H), 7.77-7.94 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.31 (13.83 minor), 21.3, 25.22 (24.89 minor), 40.31 (40.67 minor), 68.1, 109.9, 114.9, 122.3 (q, J = 272.5 Hz), 127.6 (q, J = 4.9 Hz), 129.1, 129.59 (129.55 minor), 130.52 (130.57 minor), 132.27 (132.15 minor), 132.9 (q, J = 32.9 Hz), 134.27 (134.15 minor), 134.9, 135.2, 156.33 (156.06 minor), 180.28 (180.06 minor), 187.24 (186.63 minor).

Example 34

1-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-3-phenyl-thiourea, 34a, [RD92]

A mixture of **7b** (0.021 g, 0.05 mmol) and phenylthioisocyante (0.027 g, 0.2 mmol) in DMF (0.3 ml) was stirred for 2 days at 60°C. After DMF being evaporated, the medium was chromatographed (dichloromethane) to yield **34a** (0.015 g, 0.028 mmol, 57%) as white powder.

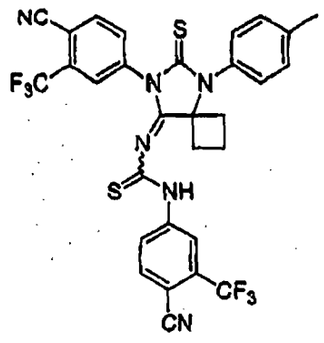


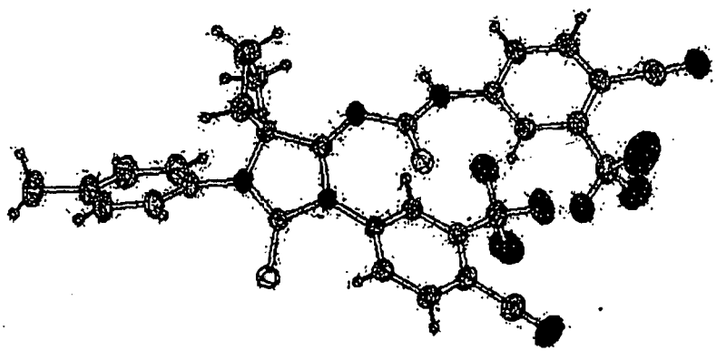
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.59-1.67 (m, 1H), 2.12-2.22 (m, 1H), 2.45 (s, 3H), 2.61-2.71 (m, 2H), 2.81-2.87 (m, 2H), 7.18-7.27 (m, 6H), 7.33-7.41 (m, 5H), 7.60-7.62 (m, 1H), 8.40 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 21.4, 32.3, 69.6, 110.7, 114.8, 121.6, 122.0 (q, J = 272.5 Hz), 126.3, 128.0 (q, J = 4.9 Hz), 128.9, 129.4, 130.7, 132.5, 133.2 (q, J = 32.9 Hz), 134.1, 134.9, 137.7, 139.2, 140.2, 154.8, 180.3, 185.5.

Example 35

1-(4-Cyano-3-trifluoromethyl-phenyl)-3-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-thiourea, 35a, [RD93]

A mixture of **1a** (0.5.02 g, 2.2 mmol) and **7a** (0.186 g, 1 mmol) in DMF (1 ml) was stirred at room temperature. After 20 hours of stirring, the mixture was concentrated under reduced pressure to yield an orange viscous liquid, which was chromatographed (dichloromethane:acetone, 99:1) to yield **35a** (0.269 g, 0.42 mmol, 42%) as a yellow powder.





X-ray structure of **35a**

Example 36

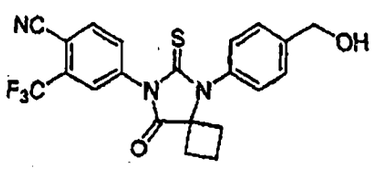
36-1). 1-(4-hydroxymethylphenylamino)-cyclobutanecarbonitrile, 36a

Trimethylsilyl cyanide (0.66 ml, 5 mmol) was added dropwise to a mixture of 4-aminobenzoic acid (0.492 g, 4 mmol) and cyclobutanone (0.35 g, 5 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **36a** (0.677 g, 3.36 mmol, 84%) as a brown solid.

36-2). 4-[8-(4-hydroxymethylphenyl)-5-oxo-7-thioxo-6-azaspiro[3.4]oct-6-yl]-2-trifluoromethyl-benzonitrile, 36b, [RD110]

A mixture of **1a** (0.342 g, 1.5 mmol) and **36a** (0.21 g, 1 mmol) in dry DMF (0.5 ml) was stirred at room temperature for 24 h. To this mixture were added methanol (20 ml) and HCl aq. 2N (5 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (40 ml) and extracted with ethyl acetate (60 ml). The organic layer was dried over

$MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 90:10) to yield **36b** (0.296 g, 0.69 mmol, 69%) as a white powder.

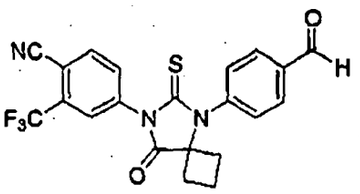


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63-1.68 (m, 1H), 2.17-2.26 (m, 1H), 2.52-2.68 (m, 4H), 4.75 (s, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.88 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 64.4, 67.5, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 128.3, 130.0, 132.2, 133.3, 133.4 (q, J = 33.2 Hz), 134.2, 137.2, 142.9, 174.9, 179.9.

Example 37

4-[5-(4-formylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethyl-benzonitrile, 37a, [RD114]

To a mixture of **36b** (0.303 g, 0.7 mmol) and Dess-Martin periodinane (0.417g, 1 mmol) in dichloromethane (5 ml) was added pyridine (1.01g, 1 mmol). The mixture was stirred for 2 hours at room temperature and then ethyl ether (10 ml) was added to precipitate the by-product of the reaction. After filtration and concentration under reduced pressure, the mixture was chromatographed (dichloromethane:acetone, 95:5) to yield **37a** (0.24 g, 0.56 mmol, 80%) as white powder.

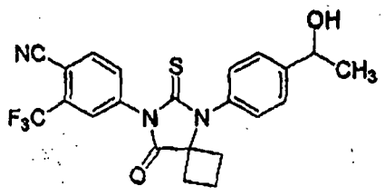


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62-1.73 (m, 1H), 2.24-2.30 (m, 1H), 2.50-2.58 (m, 2H), 2.69-2.75 (m, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.97-7.99 (m, 2H), 8.11 (d, J = 8.1 Hz, 2H), 10.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.7, 67.5, 110.2, 114.8, 121.9 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 129.1, 131.0, 131.2, 132.2, 133.3 (q, J = 33.2 Hz), 135.3, 136.9, 140.5, 174.5, 179.8, 190.8.

Example 38

4-{5-[4-(1-hydroxyethyl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethyl-benzonitrile, 38a [RD116]

The mixture of **37a** (0.043 g, 0.1 mmol) and dry THF (1 ml) in a flamed-dried flash was placed under argon and cooled to -78°C. Then, methylmagnesium iodide (1.1 ml, 0.1 M) was added. The mixture was stirred at -78°C for 30 minutes and warmed slowly to room temperature. The medium was washed with water (3 ml) and extracted with ethyl acetate (10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield **38a** (0.037 g, 0.082 mmol, 82%) as a white powder.

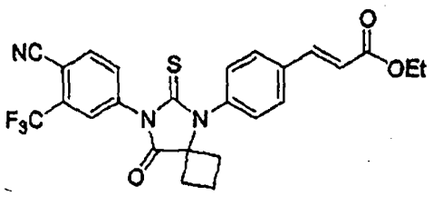


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57 (d, J = 6.5 Hz, 3H), 1.61-1.71 (m, 1H), 2.09 (d, J = 3.2 Hz, OH), 2.16-2.28 (m, 1H), 2.52-2.60 (m, 2H), 2.63-2.69 (m, 2H), 5.00 (dd, J_1 = 6.5 Hz, q, J_2 = 3.1 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 25.3, 31.5, 67.4, 69.8, 110.0, 114.9, 121.9 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 127.1, 129.9, 132.2, 133.4 (q, J = 33.2 Hz), 134.1, 135.2, 137.1, 147.6, 174.9, 179.9.

Example 39

3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-acrylic acid ethyl ester, 39a [RD117]

A mixture of **37a** (0.043 g, 0.1 mmol) and (carbethoxyethylidene)triphenylphosphorane (0.039 g, 0.12 mmol) in dichloromethane (2 ml) was stirred at room temperature for 10 hours. The medium was concentrated and chromatographed (dichloromethane) to yield **39a** (0.048 g, 0.096 mmol, 96%) as white powder.

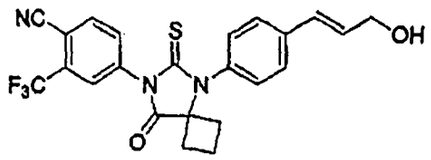


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, J = 7.1 Hz, 3H), 1.66-1.70 (m, 1H), 2.19-2.65 (m, 1H), 2.51-2.69 (m, 2H), 2.66-2.72 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 6.51 (d, J = 16.1 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 16.1 Hz, 1H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 14.3, 31.6, 60.8, 67.5, 110.0, 114.9, 120.5, 121.8 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 129.5, 130.5, 132.2, 133.4 (q, J = 33.2 Hz), 135.2, 136.0, 136.5, 137.0, 142.7, 166.5, 174.7, 179.8.

Example 40

4-{5-[4-(3-hydroxypropenyl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethylbenzonitrile, 40a [RD120]

To a mixture of 39a (0.05 g, 0.1 mmol) in dichloromethane (2 ml) at -78°C was added a solution of diisobutylaluminum hydride in THF (0.11 ml, 1M, 0.11 mmol). The mixture was stirred at -78°C for 3 hours. After being warmed to room temperature, the mixture was washed with an aqueous solution of sodium thiosulfate and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield 40a (0.040 g, 0.089 mmol, 89%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57-1.68 (m, 1H), 2.17-2.39 (m, 1H), 2.55-2.61 (m, 2H), 2.61-2.67 (m, 2H), 4.39 (d, J = 4.7 Hz, 2H), 6.47 (dt, J_1 = 16.0 Hz, J_2 = 5.3 Hz, 1H), 6.70 (d, J = 16.0 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 63.4, 67.4, 110.0, 114.8, 120.5, 121.8 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 127.9, 129.2, 130.1, 131.1, 132.1, 133.4 (q, J = 33.2 Hz), 135.2, 137.1, 138.4, 174.8, 179.9.

Example 41

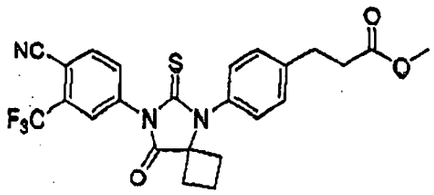
41-1) 3-[4-(1-cyanocyclobutylamino)-phenyl]-propionic acid, 41a (41-1)

Trimethylsilyl cyanide (0.4 g, 4 mmol) was added dropwise to a mixture of 3-(4-aminophenyl)-propionic acid (0.33 g, 2 mmol), cyclobutanone (0.35 g, 5 mmol) and sodium sulfate (1 g) in 1,4-dioxane (5 ml). The mixture was stirred for 15 hours. After filtration to eliminate sodium sulfate, the medium was concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane:acetone, 50:50) to yield 41a (0.472 g, 1.93 mmol, 97%) as a yellowish solid.

41-2) 3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-propionic acid methyl ester, 41b (41-2) [RD128]

A mixture of 1a (0.661 g, 2.9 mmol) and 41a (0.472 g, 1.93 mmol) in dry DMF (2 ml) was stirred at room temperature for 15 hours. To this mixture were added methanol (10 ml) and HCl aq. (5 ml, 2M). The second mixture was refluxed for 3 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (3 × 30 ml). The organic layer was

dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **41b** (0.582 g, 1.19 mmol, 62%) as a white powder.



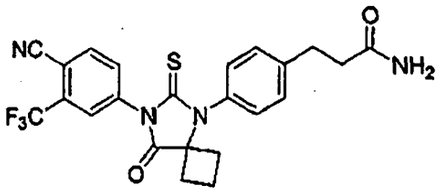
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.70 (m, 1H), 2.14-2.26 (m, 1H), 2.51-2.56 (m, 2H), 2.58-2.67 (m, 2H), 2.71 (t, J = 7.8 Hz, 2H), 3.05 (t, J = 7.8 Hz, 2H), 3.69 (s, 3H), 7.23 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 30.5, 31.4, 35.1, 51.8, 67.5, 109.9, 114.9, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.9, 130.0, 133.2, 132.3, 133.3 (q, J = 33.2 Hz), 135.7, 137.2, 142.5, 173.1, 174.9, 179.9.

41-3) 3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-propionic acid, 41c (41-3) [RD132]

A mixture of **41b** (0.487 g, 1 mmol) in methanol (10 ml) and solution of sodium hydroxide (10 ml, 2M) was stirred at room temperature for 5 hours. Methanol was evaporated. The residue was adjusted to pH = 5 by HCl aq. (2M) and then extracted with ethyl acetate (3 ×50 ml). The organic layer was dried over $MgSO_4$ and concentrated to dryness to obtain **41c** (0.472 g, 0.99 mmol, 99%).

41-4) 3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-propionamide, 41d (41-4) [RD133]

To a suspension of **41c** (0.094 g, 0.2 mmol) in THF (10 ml) at -5°C was added thionyl chloride (0.019 ml, 0.26 mmol). The medium was stirred at -5°C for one hour. Then ammonia was bubbled into the mixture. The excess of ammonia was condensed by reflux condenser at -78°C for 30 minutes and then was allowed to evaporate. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield **41d** (0.09 g, 0.19 mmol, 95%) as an off-white powder.

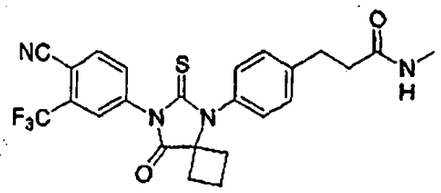


^{1}H NMR (acetone-d_6, 400 MHz) δ 1.52-160 (m, 1H), 2.01-2.09 (m, 1H), 2.49-2.58 (m, 4H), 2.61-2.67 (m, 2H), 2.98 (t, J = 7.5 Hz, 2H), 6.20 (bs, 1H), 6.78 (bs, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 8.03 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 8.15 (d, J = 1.8 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H); ^{13}C

NMR (acetone-d_6, 100 MHz) δ 13.4, 30.7, 31.2, 36.4, 67.5, 109.0, 114.8, 122.5 (q, J = 271.5 Hz), 127.5 (q, J = 4.7 Hz), 129.5, 130.0, 131.8 (q, J = 32.5 Hz), 133.3, 133.8, 135.6, 138.4, 143.2, 171.6, 174.9, 178.0.

41-5) 3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-N-methyl-propionamide, 41e (41-5) [RD134]

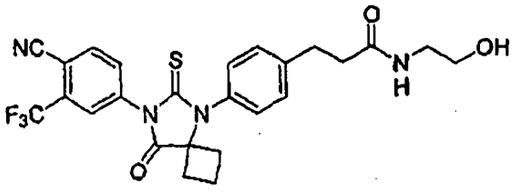
To a suspension of **41c** (0.094 g, 0.2 mmol) in THF (10 ml) at -5°C was added thionyl chloride (0.019 ml, 0.26 mmol). The medium was stirred at -5°C for one hour. Then methylamine was bubbled into the mixture at -5°C for 30 minutes. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 75:25) to yield **41e** (0.092 g, 0.19 mmol, 95%) as an off-white powder.



^{1}H NMR (acetone-d_6, 400 MHz) δ 1.51-1.60 (m, 1H), 2.01-2.11 (m, 1H), 2.48-2.58 (m, 4H), 2.61-2.67 (m, 2H), 2.77 (d, J = 4.6 Hz, 3H), 2.98 (t, J = 7.5 Hz, 2H), 7.03 (bs, NH), 7.33 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 8.01 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 8.13 (d, J = 1.8 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 13.4, 25.3, 30.0, 31.2, 37.0, 67.6, 109.0, 114.8, 122.5 (q, J = 271.5 Hz), 127.4 (q, J = 4.7 Hz), 129.5, 130.0, 131.9 (q, J = 32.5 Hz), 133.3, 133.8, 135.6, 138.4, 143.1, 171.7, 175.0, 178.0.

41-6) 3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-N-(2-hydroxyethyl)-propionamide, 41f (41-6) [RD135]

To a suspension of **41c** (0.094 g, 0.2 mmol) in THF (10 ml) at -5°C was added thionyl chloride (0.019 ml, 0.26 mmol). The medium was stirred at -5°C for one hour. Then 2-aminoethanol (0.0183 g, 0.03 mmol) was added into the mixture at -5°C. After stirring of an additional 30 minutes, the medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 50:50) to yield **41f** (0.093 g, 0.18 mmol, 90%) as an off-white powder.



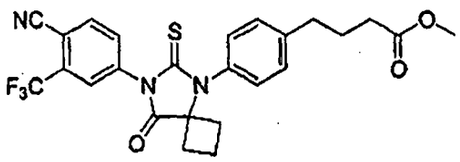
^{1}H NMR (acetone-d_6, 400 MHz) δ 1.51-161 (m, 1H), 2.01-2.11 (m, 1H), 2.49-2.66 (m, 6H), 2.99 (t, J = 7.5 Hz, 2H), 3.27 (dd, J_1 = 11.2 Hz, J_2 = 5.6 Hz, 3H), 3.51 (dd, J_1 = 11.2 Hz, J_2 = 5.6 Hz, 2H), 3.87 (bs, OH), 7.20 (bs, NH), 7.33 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 8.02 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 13.4, 31.0, 31.2, 37.1, 42.0, 61.2, 67.6, 109.0, 114.8, 122.5 (q, J = 271.5 Hz), 127.4 (q, J = 4.7 Hz), 129.6, 130.0, 131.9 (q, J = 32.5 Hz), 133.3, 133.8, 135.6, 138.4, 143.0, 171.9, 175.0, 178.1.

42-1) 4-[4-(1-Cyanocyclobutylamino)-phenyl]-butyric acid, 42a

Trimethylsilyl cyanide (0.50 g, 5 mmol) was added dropwise to a mixture of 4-(4-aminophenyl)-butyric acid (0.537 g, 3 mmol), cyclobutanone (0.35 g, 5 mmol) and sodium sulfate (1 g) in 1,4-dioxane (10 ml). The mixture was stirred for 15 hours. After filtration to elimínate sodium sulfate, the medium was concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane:acetone, 50:50) to yield **42a** (0.665 g, 2.58 mmol, 86%) as a yellowish solid.

42-2) 4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-butyric acid methyl ester, 42b [RD129]

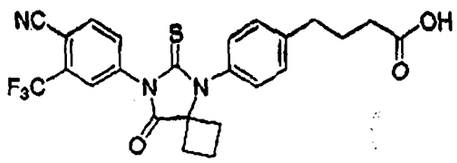
A mixture of **1a** (0.547 g, 2.4 mmol) and **42a** (0.342 g, 1.5 mmol) in dry DMF (2 ml) was stirred at room temperature for 15 hours. To this mixture were added methanol (10 ml) and HCl aq. (5 ml, 2M). The second mixture was refluxed for 3 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (3 × 30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **42b** (0.594 g, 1.18 mmol, 79%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.70 (m, 1H), 1.98-2.07 (m, 2H), 2.14-2.26 (m, 1H), 2.40 (t, J = 7.4 Hz, 2H), 2.52-2.60 (m, 2H), 2.62-2.68 (m, 2H), 2.74 (t, J = 7.4 Hz, 2H), 3.68 (s, 3H), 7.22 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.86 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 26.1, 31.4, 33.5, 34.8, 51.7, 67.5, 109.9, 114.9, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.7, 130.1, 132.3, 133.0, 133.3 (q, J = 33.2 Hz), 135.2, 137.2, 143.5, 173.8, 175.0, 179.9.

42-3) 4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-butyric acid, 42c [RD141]

A mixture of **42b** (0.501 g, 1 mmol) in methanol (10 ml) and solution of sodium hydroxide (10 ml, 2M) was stirred at room temperature for 5 hours. The methanol was evaporated. The residue was adjusted to pH = 5 by HCl aq. (2M) and then, the medium was extracted with ethyl acetate (3 ×50 ml). The organic layer was dried over $MgSO_4$ and concentrated to dryness to obtain **42c** (0.482 g, 0.99 mmol, 99%), the structure of which is illustrated in Formula 5.

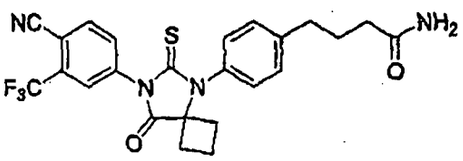


Formula 5

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.70 (m, 1H), 1.98-2.07 (m, 2H), 2.14-2.26 (m, 1H), 2.45 (t, J = 7.3 Hz, 2H), 2.51-2.59 (m, 2H), 2.62-2.68 (m, 2H), 2.77 (t, J = 7.3 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 25.9, 31.4, 33.4, 34.7, 67.5, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.8, 130.1, 132.3, 133.0, 133.4 (q, J = 33.1 Hz), 135.2, 137.2, 143.3, 174.9, 178.9, 179.9.

42-4) **4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-butyramide, 42d [RD130]**

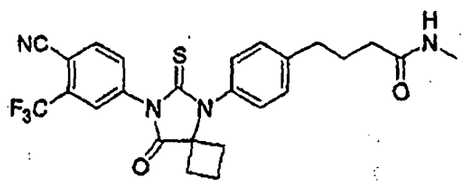
To a suspension of **42c** (0.097 g, 0.2 mmol) in THF (10 ml) at -5°C was added thionyl chloride (0.019 ml, 0.26 mmol). The medium was stirred at -5°C for one hour. Then ammonia was bubbled into the mixture. The excess of ammonia was condensed by reflux condenser at -78°C for 30 minutes and then was allowed to evaporate. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield **42d** (0.093 g, 0.19 mmol, 95%) as an off-white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57-1.70 (m, 1H), 2.00-2.08 (m, 2H), 2.16-2.25 (m, 1H), 2.31 (t, J = 7.3 Hz, 2H), 2.51-2.59 (m, 2H), 2.62-2.68 (m, 2H), 2.77 (t, J = 7.3 Hz, 2H), 5.56 (bs, 1H), 5.65 (bs, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 26.5, 31.4, 34.8, 35.0, 67.5, 109.9, 114.9, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.8, 130.1, 132.2, 133.0, 133.3 (q, J = 33.2 Hz), 135.2, 137.2, 143.5, 173.8, 174.9, 179.9.

42-5) 4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-*N*-methyl-butyramide, 42e [RD131]

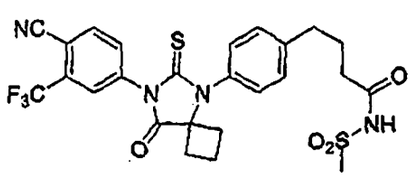
To a suspension of 42c (0.097 g, 0.2 mmol) in THF (10 ml) at -5°C was added thionyl chloride (0.019 ml, 0.26 mmol). The medium was stirred at -5°C for one hour. Then methylamine was bubbled into the mixture at -5°C for 30 minutes. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 75:25) to yield 42e (0.095 g, 0.19 mmol, 95%) as an off-white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52-1.64 (m, 1H), 1.94-2.01 (m, 2H), 2.10-2.17 (m, 1H), 2.20 (t, J = 7.3 Hz, 2H), 2.46-2.62 (m, 4H), 2.69 (t, J = 7.3 Hz, 2H), 2.73 (d, J = 4.7 Hz, 3H), 6.09 (bs, 1H), 7.16 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.82 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 26.2, 26.8, 31.4, 35.0, 35.7, 67.5, 109.7, 114.9, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.7, 130.0, 132.3, 133.8, 133.3 (q, J = 33.2 Hz), 135.2, 137.3, 143.7, 173.3, 174.9, 179.8.

42-6) *N*-(4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}-butanoyl)-methanesulfonamide, 42f [RD157]

[0099] A mixture of 4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}butanoic acid (42c) (0.049 g, 0.1 mmol), 2,4,6-trichlorobenzoyl chloride (0.244 g, 1 mmol), 4-dimethylaminopyridine (0.122 g, 1 mmol) and methanesulfonamide (0.019 g, 0.2 mmol) in dichloromethane was stirred at room temperature for 20 hours. The mixture was concentrated and chromatographed (dichloromethane:acetone, 80:20) to yield *N*-(4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}-butanoyl)-methanesulfonamide (42f) [RD157] (0.053 g, 0.094 mmol, 94%), the structure of which is illustrated in Formula 8, as a white powder.

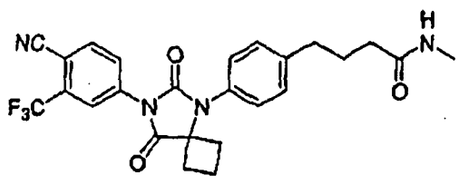


Formula 8

^{1}H NMR (acetone-d_6, 400 MHz) δ 1.51-160 (m, 1H), 1.96-2.11 (m, 3H), 2.49 (t, J = 7.3 Hz, 2H), 2.51-2.57 (m, 2H), 2.61-2.67 (m, 2H), 2.75 (t, J = 7.5 Hz, 2H), 2.94 (bs, 1H), 3.24 (s, 3H), 7.33 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 8.02 (dd, J = 8.3, 1.6 Hz, 1H), 8.02 (d, J = 1.6 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 13.4, 25.8, 31.2, 34.3, 35.2, 40.6, 67.6, 109.0, 114.8, 122.5 (q, J = 271.5 Hz), 127.5 (q, J = 4.9 Hz), 129.6, 130.1, 131.9 (q, J = 33.6 Hz), 133.3, 133.9, 135.6, 138.4, 143.1, 171.9, 175.0, 180.5.

42-7) *N*-methyl-4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-6,8-dioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}butyramide, 42g [RD158]

[00100] Hydrogen peroxide (30%, 0.4) was added dropwise to a solution of *N*-methyl-4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}butanamide (42e) (0.032 g, 0.064 mmol) in glacial acetic acid (0.5 ml). The mixture was stirred at room temperature for 5 hours and then washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated and chromatographed (dichloromethane:acetone, 80:20) to yield *N*-methyl-4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-6,8-dioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}butyramide (42g) [RD158] (0.029 g, 0.06 mmol, 94%), the structure of which is illustrated in Formula 9, as a white powder.



Formula 9

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63-1.71 (m, 1H), 1.93-2.04 (m, 2H), 2.18-2.27 (m, 3H), 2.44-2.53 (m, 2H), 2.57-2.65 (m, 2H), 2.70 (t, J = 7.3 Hz, 2H), 2.79 (d, J = 4.8 Hz, 3H), 5.79 (bs, 1H), 7.21 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H), 8.03 (dd, J = 8.3, 1.8 Hz, 1H), 8.18 (d, J = 1.8 Hz, 1H).

Example 43

43-1) 4-(4-aminophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester, 43a

A mixture of 4-iodoaniline (0.654 g, 3 mmol), piperazine-1-carboxylic acid *tert*-butyl ester (0.67 g, 3.6 mmol), potassium phosphate (1.272 g, 6 mmol), ethylene glycol (0.33 ml) and copper iodide (0.03 g, 0.15 mmol) in 2-propanol (3 ml) was placed under argon in a sealed-tube and heated to 80°C for 30 hours. After being cooled to room temperature, the medium was washed with water (50 ml) and extracted with ethyl acetate (100 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield 43a (0.36 g, 1.3 mmol, 43%) as a yellow powder.

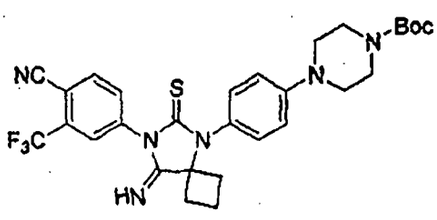
43-2) 4-[4-(1-cyanocyclobutylamino)phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester, 43b

Trimethylsilyl cyanide (0.3 g, 3 mmol) was added dropwise to a mixture of **43a** (0.415 g, 1.5 mmol), cyclobutanone (0.21 g, 3 mmol) and sodium sulfate (1 g) in dichloromethane (5 ml). The mixture was stirred for 15 hours. After filtration to eliminate sodium sulfate, the medium was concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane:acetone, 75:25) to yield **43b** (0.448 g, 1.26 mmol, 84%) as a yellow solid.

43-3) 4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-imino-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester, 43c.[RD139]

and 4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-(4-cyano-3-trifluoromethyl-phenylthiocarbamoylimino)-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester, 43d [RD140]

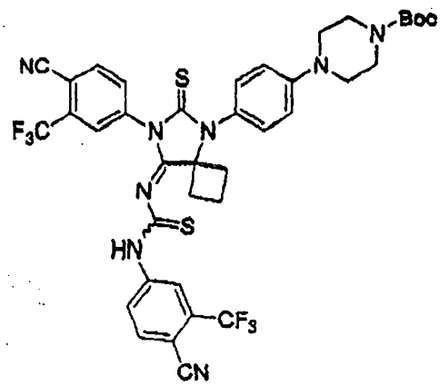
A mixture of **1a** (0.228 g, 1 mmol) and **43b** (0.472 g, 0.63 mmol) in dry DMF (1 ml) was stirred at room temperature for 20 hours. The mixture was concentrated and chromatographed (dichloromethane:acetone, 90:10) to yield 43c (0.173 g, 0.296 mmol, 47%), the structure of which is illustrated in Formula 10, as a off-white powder and **43d** (0.169 g, 0.21 mmol, 33%), the structure of which is illustrated in Formula 11, as a yellow powder.



Formula 10

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48, (s, 9H), 1.57-1.67 (m, 1H), 2.01-2.09 (m, 1H), 2.59-2.70 (m, 4H), 3.25 (t, J = 5.1 Hz, 4H), 3.59 (t, J = 4.9 Hz, 4H), 7.02 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 7.81

(d, J = 7.4 Hz, 1H), 7.93 (s, 1H), 7.97 (d, J = 8.1 Hz, 1H).

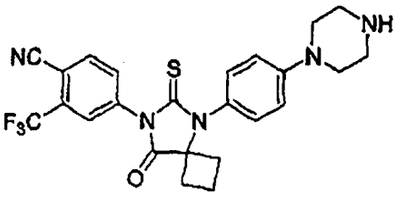


Formula 11

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48, (s, 9H), 1.57-1.64 (m, 1H), 2.01-2.10 (m, 1H), 2.60-2.89 (m, 4H), 3.24 (t, J = 5.1 Hz, 4H), 3.57 (t, J = 4.9 Hz, 4H), 7.02 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 7.54-7.98 (m, 4H), 7.97 (d, J = 8.1 Hz, 1H).

43-4) 4-[8-Oxo-5-(4-piperazin-1-yl-phenyl)-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile, 43e [RD137]

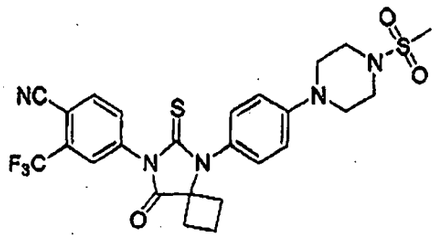
A mixture of 43c (0.117 g, 0.2 mmol), methanol (5 ml) and HCl aq. (2 ml, 2M) was refluxed for 2 hours. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (3 × 30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 50:50 and then methanol:acetone, 50:50) to yield 43e (0.089 g, 0.184 mmol, 92%) as a white powder.



^{1}H NMR (CD_3OD, 400 MHz) δ 1.51-1.61 (m, 1H), 2.01-2.11 (m, 1H), 2.48-2.59 (m, 4H), 2.90-2.97 (m, 4H), 3.25-3.30 (m, 4H), 7.03 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.9 Hz, 2H), 7.86 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 8.02 (d, J = 8.3 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 13.2, 30.9, 45.1, 48.9, 67.5, 108.9, 114.8, 115.9, 122.3 (q, J = 271.7 Hz), 126.4, 127.3 (q, J = 4.7 Hz), 130.4, 132.2 (q, J = 33.2 Hz), 133.0, 135.4, 138.1, 152.1, 175.4, 180.4.

43-5) 4-{5-[4-(4-methanesulfonylpiperazin-1-yl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethylbenzonitrile, 43f [RD138]

A mixture of 43e (0.049g, 0.1 mmol), methanesulfonyl chloride (0.012 ml, 0.15 mmol) and triethylamine (0.15 ml) in dichloromethane was stirred at room temperature for 5 hours. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane: acetone, 95:5) to yield 43f (0.042 g, 0.074 mmol, 74%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62-1.70 (m, 1H), 2.14-2.23 (m, 1H), 2.51-2.58 (m, 2H), 2.61-2.67 (m, 2H), 2.84 (s, 3H), 3.39 (s, 8H), 7.05 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 7.84 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.4, 34.6, 45.7, 48.4, 67.5, 109.8, 114.9, 117.0, 121.9 (q, J = 272.7 Hz), 126.8, 127.1 (q, J = 4.7 Hz), 130.7, 132.3, 133.4 (q, J = 33.2 Hz), 135.2, 137.3, 151.1, 175.0, 180.2.

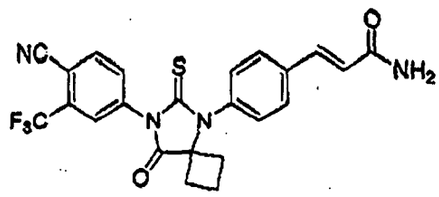
Example 44

44-1) 3-{4-[7-(4-Cyano-3-trifluoromethyl-phenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-acrylic acid, 44a

A mixture of 39a (0.025 g, 0.05 mmol) in methanol (2 ml) and solution of sodium hydroxide (2 ml, 2M) was stirred at room temperature for 5 hours. Methanol was evaporated. The residue was adjusted to pH = 5 by HCl aq. (2M) and then extracted with ethyl acetate (3 ×50 ml). The organic layer was dried over $MgSO_4$ and concentrated to dryness to obtain 44a (0.02 g, 0.042 mmol, 85%).

44-2) 3-{4-[7-(4-Cyano-3-trifluoromethyl-phenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-acrylamide, 44b [RD119]

To a suspension of 44b (0.02 g, 0.042 mmol) in THF (1 ml) at -5°C was added thionyl chloride (0.007 ml, 0.1 mmol). The medium was stirred at -5°C for one hour. Then ammonia was bubbled into the mixture. The excess of ammonia was condensed by reflux condenser at -78°C for 30 minutes and then was allowed to evaporate. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield 44b (0.014 g, 0.03 mmol, 71%) as an off-white powder.

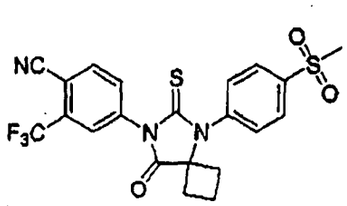


^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.49-1.52 (m, 1H), 1.88-1.93 (m, 1H), 2.37-2.46 (m, 2H), 2.57-2.62 (m, 2H), 6.66 (d, J = 15.9 Hz, 1H), 7.16 (bs, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 15.9 Hz, 1H), 7.58 (bs, 1H), 8.03 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 8.23 (d, J = 1.8 Hz, 1H), 8.34 (d, J = 8.3 Hz, 1H).

Example 45 [RD145]

[00101] Trimethylsilyl cyanide (0.4 g, 4 mmol) was added dropwise to a mixture of 4-methanesulfonylphenylamine hydrochloride (0.415 g, 2 mmol), cyclobutanone (0.28 g, 4 mmol) and sodium sulfate (1 g) in DMF (3 ml). The mixture was stirred for 15 hours at 120 °C. After filtration to remove the sodium sulfate, the filtrate was washed with brine and extracted with ethyl acetate. The organic layer was concentrated and chromatographed (dichloromethane:acetone, 90:10) to yield 1-(4-methanesulfonylphenylamino)cyclobutanecarbonitrile (45a) (0.116 g, 0.44 mmol, 22%) as a yellowish solid. 4-methanesulfonylphenylamine (0.201g, 1.17 mmol, 59%) was also recovered.

[00102] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (0.0.141 g, 0.62 mmol) and 1-(4-methanesulfonylphenylamino)cyclobutanecarbonitrile (45a) (0.11 g, 0.42 mmol) in dry DMF (2 ml) was stirred at room temperature for 3 days. To this mixture were added methanol (10 ml) and aq. 2N HCl (5 ml). The second mixture was refluxed for 3 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (3 × 30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 97:3) to yield 4-[5-(4-methanesulfonylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile (45b) [RD145] (0.031 g, 0.065 mmol, 15%), the structure of which is illustrated in Formula 14, as a white powder.



Formula 14

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63-1.72 (m, 1H), 2.21-2.28 (m, 1H), 2.46-2.54 (m, 2H), 2.68.2.74 (m,

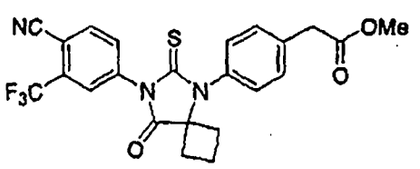
2H), 3.16 (s, 3H), 7.57 (d, J = 8.3 Hz, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 8.17 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 31.8, 44.4, 67.5, 110.2, 114.8, 122.4 (q, J = 271.5 Hz), 127.0 (q, J = 4.9 Hz), 129.4, 131.4, 132.1, 133.6 (q, J = 33.3 Hz), 135.3, 136.8, 140.3, 141.8, 174.4, 179.9.

Example 46

[00103] Trimethylsilyl cyanide (0.69 g, 7 mmol) was added dropwise to a mixture of 4-aminophenylacetic acid (0.755 g, 5 mmol) and cyclobutanone (0.49 g, 7 mmol) in dioxane (20 ml). The mixture was stirred for 8 hours at 80 °C. The mixture was concentrated and chromatographed (dichloromethane:acetone, 60:40) to yield [4-(1-cyanocyclobutylamino)phenyl]acetic acid (46a) (1.138 g, 4.95 mmol, 99%) as a white solid.

46-1) RD146

[00104] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (0.638 g, 2.8 mmol) and [4-(1-cyanocyclobutylamino)phenyl]acetic acid (46a) (0.46 g, 2.0 mmol) in DMF (5 ml) was stirred at room temperature for 15 hours. To this mixture were added methanol (20 ml) and aq. 2N HCl (10 ml). The second mixture was refluxed for 1 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (3 × 50 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane pure and then dichloromethane:acetone, 95:5) to yield {4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetic acid methyl ester (46b) [RD146] (0.532 g, 1.124 mmol, 56%), the structure of which is illustrated in Formula 15, as a white powder.

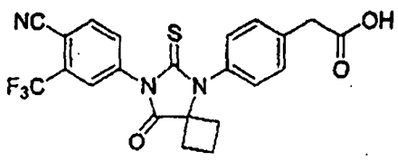


Formula 15

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.69 (m, 1H), 2.15-2.25 (m, 1H), 2.50-2.58 (m, 2H), 2.61-2.66 (m, 2H), 3.72 (bs, 5H), 7.27 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.4, 44.7, 52.3, 67.4, 109.9, 114.9, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 130.0, 131.1, 132.3, 133.0 (q, J = 33.3 Hz), 134.1, 135.2, 135.9, 137.2, 171.4, 174.9, 179.9.

46-2) RD147

[00105] A mixture of {4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetic acid methyl ester (46b) (0.095 g, 0.2 mmol) and a solution of sodium hydroxide (1 ml, 2M) in methanol (2 ml) was stirred at room temperature for 2 hours. The methanol was evaporated. The residue was adjusted to pH 5 by aq. 2M HCl and then the mixture was extracted with ethyl acetate (3 ×10 ml). The organic layer was dried over $MgSO_4$ and concentrated to dryness to obtain {4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetic acid (46c) **[RD147]** (0.087 g, 0.19 mmol, 95%), the structure of which is illustrated in Formula 16.

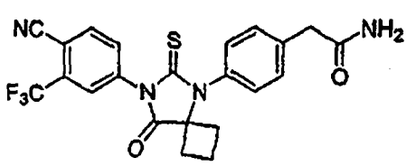


Formula 16

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.69 (m, 1H), 2.15-2.25 (m, 1H), 2.50-2.64 (m, 4H), 3.73 (s, 2H), 7.26 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.4, 40.2, 40.8, 67.4, 109.9, 114.9, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 129.9, 131.2, 132.3, 133.3 (q, J = 33.3 Hz), 133.9, 135.2, 136.1, 137.2, 174.1, 174.9, 179.9.

46-3) RD148

[00106] Thionyl chloride (0.238 g, 2 mmol) was added dropwise to a mixture of {4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetic acid (46c) (0.357 g, 0.777 mmol) in THF (5 ml) cooled to 0 °C. The mixture was stirred for 1 hour at room temperature and then ammonia was bubbled into the mixture. The excess ammonia was condensed by a reflux condenser at -78 °C for 30 minutes and then was allowed to evaporate. The medium was filtered and the filtrate was concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield 2-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetamide (46d) **[RD148]** (0.345 g, 0.75 mmol, 97%), the structure of which is illustrated in Formula 17, as an off-white powder.

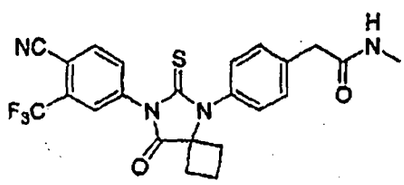


Formula 17

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62-1.66 (m, 1H), 2.18.2.23 (m, 1H), 2.49-2.55 (m, 2H), 2.61-2.66 (m, 2H), 3.63 (s, 2H), 5.91 (bs, 1H), 6.10 (bs, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.83 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 42.5, 67.4, 109.9, 114.9, 121.9 (q, J = 272.4 Hz), 127.1 (q, J = 4.9 Hz), 130.2, 131.1, 132.2, 133.3 (q, J = 33.3 Hz), 134.1, 135.2, 136.8, 137.2, 172.8, 174.8, 180.0.

46-4) RD149

[00107] Thionyl chloride (0.238 g, 2 mmol) was added dropwise to a mixture of {4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetic acid (46c) (0.357 g, 0.777 mmol) in THF (5 ml) cooled to 0 °C. The mixture was stirred for 1 hour at room temperature and then methylamine (0.5 ml) was added into the mixture. The mixture was stirred for an additional 2 hours. The medium was filtered and the filtrate was concentrated and chromatographed (dichloromethane:acetone, 80:20) to yield *N*-methyl-2-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetamide (46e) **[RD149]** (0.348 g, 0.738 mmol, 95%), the structure of which is illustrated in Formula 18, as an off-white powder.



Formula 18

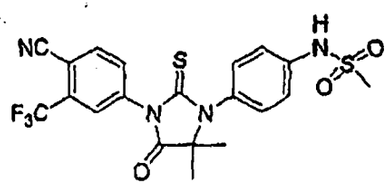
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61-1.70 (m, 1H), 2.17-2.31 (m, 1H), 2.50-2.56 (m, 2H), 2.61-2.68 (m, 2H), 2.82 (d, J = 4.8 Hz, 3H), 3.62 (s, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 26.6, 31.5, 43.1, 67.4, 110.0, 114.9, 122.0 (q, J = 272.5 Hz), 127.1 (q, J = 4.9 Hz), 130.2, 131.0, 132.2, 133.3 (q, J = 33.3 Hz), 134.1, 135.2, 137.0, 137.1, 170.1, 174.8, 179.9.

Example 47

***N*-{4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenyl}methanesulfonamide (47a) [RD150]**

[00108] A mixture of 4-[3-(4-aminophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-

trifluoromethylbenzonitrile (2d) (0.02 g, 0.05 mmol), methanesulfonyl chloride (0.009g, 0.075 mmol) and pyridine (0.006 g, 0.075 mmol) in dichloromethane (1 ml) was stirred at room temperature for 15 hours. The medium was washed with water (2 ml) and extracted with ethyl acetate (5 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (HPLC, alumina column) to yield *N*-{4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenyl}methanesulfonamide (47a) [RD150] (0.009 g, 0.018 mmol, 36%), the structure of which is illustrated in Formula 2, as a white powder.



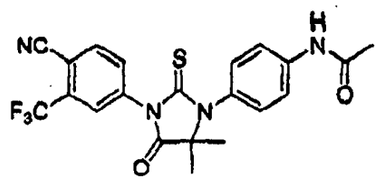
Formula 2

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.46 (s, 6H), 3.07 (s, 3H), 7.32 (s, 4H), 8.05 (dd, J = 8.2, 1.2 Hz, 1H), 8.26 (d, J = 1.2 Hz, 1H), 8.35 (d, J = 8.2 Hz, 1H), 10.08 (bs, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.3, 40.4, 66.7, 109.0, 115.5, 119.9, 122.6 (q, J = 272.2 Hz), 128.5 (q, J = 4.7 Hz), 130.8, 131.2, 131.5 (q, J = 32.3 Hz), 134.5, 136.6, 138.6, 139.5, 175.4, 180.4.

Example 48

***N*-{4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenyl}acetamide, 48a, [RD151]**

[00109] A mixture of 4-[3-(4-aminophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile (2d) [RD9] (0.008 g, 0.02 mmol), acetyl chloride (0.004g, 0.03 mmol) and triethylamine (0.003 g, 0.03 mmol) in dichloromethane (1 ml) was stirred at 0 °C for 2 hours. The mixture was concentrated and chromatographed (dichloromethane:acetone, 90:10) to yield *N*-{4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenyl}acetamide, 48a, [RD151] (0.007 g, 0.016 mmol, 80%), the structure of which is illustrated in Formula 3, as a white powder.



Formula 3

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58 (s, 6H), 2.21 (s, 3H), 7.24 (d, J = 8.6 Hz, 2H), 7.48 (bs, 1H), 7.69 (d, J = 8.6 Hz, 2H), 7.83 (dd, J = 8.2, 1.9 Hz, 1H), 7.96 (d, J = 1.2 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6, 53.4, 66.4, 110.0, 114.8, 120.7, 122.6 (q, J = 272.2 Hz), 127.1 (q, J = 4.7 Hz), 129.1, 130.2, 132.2, 133.5 (q, J = 32.3 Hz), 135.2, 137.1, 139.2, 168.1, 175.0, 180.0.

Example 49

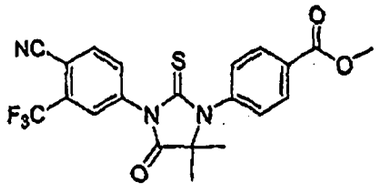
[00110] Concentrated sulfuric acid was slowly added to a mixture of 4-aminobenzoic acid (4 g, 29.2 mmol) in methanol cooled to 0 °C. After the addition, the mixture was stirred at room temperature for 5 hours. The mixture was washed with a saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to obtain 4-aminobenzoic acid methyl ester (49a) (4.22 g, 27.9 mmol, 96%) as an off-white solid.

[00111] A mixture of 4-aminobenzoic acid methyl ester (0.32 g, 2.12 mmol), acetonecyanohydrin (3ml) and sodium sulfate (1 g) was refluxed for 15 hours. After filtration to remove the sodium sulfate, the filtrate was washed with brine and extracted with ethyl acetate. The organic layer was concentrated and chromatographed (dichloromethane:acetone, 60:40) to yield 4-[(cyanodimethylmethyl)-amino]-benzoic acid methyl ester (49b) (0.398 g, 1.95 mmol, 92%) as a white solid.

49-1) RD152

[00112] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (0.228 g, 1 mmol) and 4-[(cyanodimethylmethyl)-amino]-benzoic acid methyl ester (49b) (0.14 g, 0.64 mmol) in DMF (2 ml) was heated under microwave irradiation at 60 °C for 12 hours. To this mixture were added methanol (6 ml) and aq. 2N HCl (2 ml). The second mixture was refluxed for 4 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (3 × 30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane; dichloromethane:acetone, 75:25) to yield 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]benzoic acid methyl ester (49c) **[RD152]** (0.18 g, 0.4 mmol,

63%), the structure of which is illustrated in Formula 19, as a white powder.

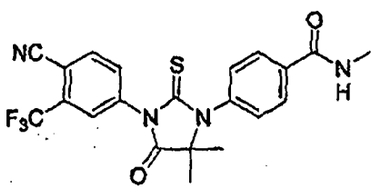


Formula 19

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60 (s, 6H), 3.95 (s, 3H), 7.40 (d, J = 8.6 Hz, 2H), 7.84 (dd, J = 8.2, 1.9 Hz, 1H), 7.96 (d, J = 1.2 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 8.21 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 52.6, 66.6, 110.3, 114.8, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.8, 131.2, 131.4, 132.2, 133.5 (q, J = 32.3 Hz), 135.3, 137.0, 139.2, 165.9, 174.7, 179.7.

49-2) RD153

[00113] A mixture of 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]benzoic acid methyl ester (49c) (0.02 g, 0.0435 mmol) and methylamine (2 ml distilled from its 40% aqueous solution) was kept at -20 °C for 15 hours. After evaporation of the methylamine, the mixture was chromatographed (dichloromethane:acetone, 80:20) to yield 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-N-methylbenzamide (49d) **[RD153]** (0.01 g, 0.0224, 51%), the structure of which is illustrated in Formula 20. The ester 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]benzoic acid methyl ester *(49c) (0.08 g, 0.0179* mmol, 41%) was also recovered.



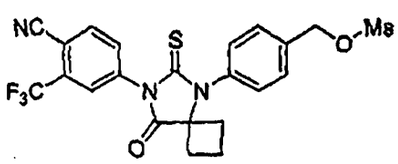
Formula 20

^{1}H NMR (Acetone-d_6, 400 MHz) δ 1.60 (s, 6H), 2.90 (d, J = 4.6 Hz, 3H), 7.48 (d, J = 8.6 Hz, 2H), 7.80 (bs, 1H), 7.99 (d, J = 8.6 Hz, 2H), 8.06 (dd, J = 8.2, 1.8 Hz, 1H), 8.18 (d, J = 1.8 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 23.8, 54.0, 66.5, 110.3, 114.8, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 128.2, 129.9, 133.5 (q, J = 32.3 Hz), 135.7, 135.8, 138.2, 138.3, 139.2, 166.0, 174.9, 179.7.

Example 50

50-1) RD154

[00114] A mixture of 4-[8-(4-hydroxymethylphenyl)-5-oxo-7-thioxo-6-azaspiro[3.4]oct-6-yl]-2-trifluoromethyl-benzonitrile (36b) (0.086 g, 0.2 mmol) and methanesulfonyl anhydride (0.07 g, 0.4 mmol) in dichloromethane (1 ml) was stirred at room temperature for 15 hours. The mixture was concentrated and chromatographed (dichloromethane:acetone, 98:2) to yield Methanesulfonic acid 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenylmethyl ester (50a) **[RD154]** (0.089 g, 0.175 mmol, 88%), the structure of which is illustrated in Formula 22, as a white powder.

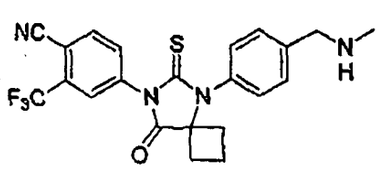


Formula 22

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63-1.70 (m, 1H), 2.17-2.31 (m, 1H), 2.48-2.57 (m, 2H), 2.64-2.70 (m, 2H), 3.04 (s, 3H), 5.30 (s, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 1.6 Hz, 1H).

50-2) RD155

[00115] Methylamine (0.5 ml) was bubbled into a mixture of Methanesulfonic acid 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenylmethyl ester (50a) (0.059 g, 0.115 mmol) in THF (3 ml) cooled to -78 °C. After 1 hour of reaction at -78 °C, the mixture was concentrated and chromatographed (dichloromethane:acetone, 95:5; methanol) to yield 4-[5-(4-methylaminomethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile (50b) **[RD155]** (0.042 g, 0.095 mmol, 82%), the structure of which is illustrated in Formula 23, as a white powder.

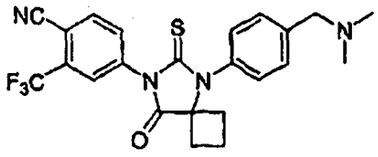


Formula 23

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57-1.70 (m, 1H), 2.16-2.24 (m, 1H), 2.52 (s, 3H), 2.53-2.57 (m, 2H), 2.60-2.68 (m, 2H), 3.85 (s, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 36.4, 55.6, 67.4, 110.0, 114.9, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 129.1, 129.6, 129.8, 132.2, 133.3 (q, J = 33.3 Hz), 133.7, 135.2, 142.4, 174.8, 179.9.

50-3) RD156

[00116] A mixture of Methanesulfonic acid 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenylmethyl ester (50a) (0.02 g, 0.039 mmol) and dimethylamine (0.5 ml; distilled from its 40% aqueous solution) in THF (1 ml) was stirred for 2 hours at -78 °C. The mixture was concentrated and chromatographed (dichloromethane:acetone, 95:5;acetone) to yield 4-[5-(4-dimethylaminomethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile (50c) [**RD156**] (0.017 g, 0.037 mmol, 95%), the structure of which is illustrated in Formula 24, as a white powder.



Formula 24

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57-1.70 (m, 1H), 2.16-2.24 (m, 1H), 2.32 (s, 6H), 2.55-2.60 (m, 2H), 2.63-2.69 (m, 2H), 3.53 (s, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 45.5, 63.7, 67.4, 110.0, 114.9, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 129.1, 129.6, 129.8, 132.2, 133.3 (q, J = 33.3 Hz), 133.7, 135.2, 142.4, 174.8, 179.9.

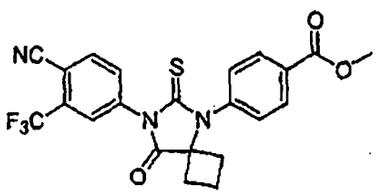
Example 51

[00117] Sodium cyanide (0.245 g, 5 mmol) was added to a mixture of 4-aminobenzoic acid (0.274 g, 2 mmol) and cyclobutanone (0.21 g, 3 mmol) in 90% acetic acid (4.5 ml). The reaction mixture was stirred at room temperature for 15 hours. The mixture was washed with aqueous HCl (pH 2) and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to

dryness under vacuum to yield 4-(1-cyanocyclobutylamino)benzoic acid (51a) (0.426 g, 1.97 mmol, 99%) as a white solid.

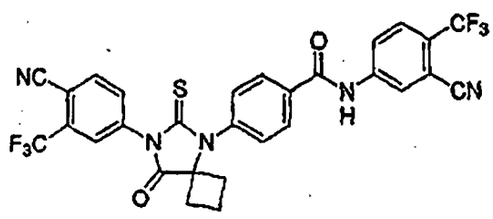
51-1) RD159 and RD160

[00118] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (0.51 g, 2.22 mmol) and 4-(1-cyanocyclobutylamino)benzoic acid (51a) (0.343 g, 1.59 mmol) in *DMF* (2 ml) was heated under microwave irradiation at 60 °C and stirred for 16 hours. To this mixture were added methanol (10 ml) and aq. 2M HCl (5 ml). The second mixture was refluxed for 12 hours. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (3 × 30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-benzoic acid methyl ester (51b) **[RD159]** (0.09 g, 0.196 mmol, 12%), the structure of which is illustrated in Formula 25, as a white powder and *N*-(3-cyano-4-trifluoromethylphenyl)-4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]benzamide (51b') **[RD160]** (0.28 g, 0.45 mmol, 29%), the structure of which is illustrated in Formula 26, as a white powder.



Formula 25

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67-1.71 (m, 1H), 2.20-2.26 (m, 1H), 2.49-2.57 (m, 2H), 2.66-2.73 (m, 2H), 3.96 (s, 3H), 7.42 (d, J = 8.4 Hz, 2H), 7.85 (dd, J = 8.3, 1.7 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 1.7 Hz, 1H), 8.26 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.6, 52.6, 67.5, 110.1, 114.8, 121.8 (q, J = 272.7 Hz), 127.0 (q, J = 4.7 Hz), 130.2, 131.4, 131.5, 132.2, 133.4 (q, J = 33.2 Hz), 135.2, 137.0, 139.2, 165.9, 174.6, 179.7.

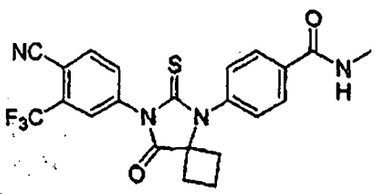


Formula 26

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67-1.71 (m, 1H), 2.18-2.26 (m, 1H), 2.50-2.58 (m, 2H), 2.68-2.74 (m, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.7 Hz, 1H), 7.84 (dd, J = 8.3, 1.9 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 9.97 (d, J = 1.9 Hz, 1H), 8.10-8.14 (m, 3H), 8.21 (d, J = 1.9 Hz, 1H), 8.88, (s, 1H).

51 -2) RD161

[00119] A mixture of 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-benzoic acid methyl ester (51b) (0.046 g, 0.1 mmol) and methylamine (1 ml distilled from its 40% aqueous solution) was kept at -20 °C for 15 hours. After evaporation of the methylamine, the mixture was chromatographed (dichloromethane:acetone, 80:20) to yield *N*-methyl-4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]benzamide (51c) **[RD161]** (0.041 g, 0.085, 84%), the structure of which is illustrated in Formula 27.



Formula 27

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63-1.70 (m, 1H), 2.18-2.26 (m, 1H), 2.48-2.56 (m, 2H), 2.65-2.71 (m, 2H), 3.05 (d, J = 4.8 Hz, 3H), 6.32 (bs, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.7 Hz, 1H), 7.95-7.98 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 27.0, 31.6, 67.4, 110.3, 114.8, 121.8 (q, J = 272.7 Hz), 127.0 (q, J = 4.7 Hz), 128.7, 130.3, 132.1, 133.3 (q, J = 33.2 Hz), 135.2, 136.3, 137.0, 137.8, 167.2, 174.6, 179.8.

Example 52 [RD162]

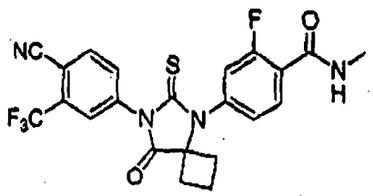
[00120] Thionyl chloride (2.38 g, 20 mmol) was added slowly to a solution of 2-fluoro-4-nitrobenzoic acid (2.97 g, 16 mmol) in DMF (50 ml) cooled at -5 °C. The mixture was stirred for an additional 1 hour at -5 °C. Methylamine (0.62 g, 20 mmol; freshly distilled from its 40% aqueous solution) was added to the reaction medium. The second mixture was stirred for an additional 1 hour. Ethyl acetate (300 ml) was added to the mixture, which was washed with brine (3 × 150 ml). The organic layer was dried over $MgSO_4$, and concentrated to yield *N*-methyl-2-fluoro-4-nitrobenzamide (52a) (2.89

g, 14.6 mmol, 91%) as a yellow solid. ^{1}H NMR (Acetone d6, 400 MHz) δ 3.05 (d, J = 4.3 Hz, 3H), 6.31 (dd, J = 13.5, 2.1 Hz, 1H), 6.40 (dd, J = 8.5, 2.1 Hz, 1H), 7.64 (dd, J = 8.6, 8.6 Hz, 1H).

[00121] A mixture of *N*-methyl-2-fluoro-4-nitrobenzamide (52a) (2.89 g, 14.6 mmol) and iron (5.04 g, 90 mmol) in ethyl acetate (40 ml) and acetic acid (40 ml) was refluxed for 1 hour. The solid particles were filtered off. The filtrate was washed with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield *N*-methyl-2-fluoro-4-aminobenzamide (52b) (2.3 g, 13.7 mmol, 94%) as an off-white solid. ^{1}H NMR (acetone-d_6, 400 MHz) δ 2.86 (d, J = 4.3 Hz, 3H), 5.50 (bs, 2H), 6.37 (dd, J_1 = 14.7 Hz, J_2 = 2.1 Hz, 1H), 6.50 (dd, J = 8.5, 2.1 Hz, 1H), 7.06 (bs, 1H), 7.68 (dd, J = 8.8 8.8 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 25.8, 99.6 (d, J = 13.8 Hz), 109.2 (d, J = 12.8 Hz), 110.0 (d, J = 1.6 Hz), 132.5 (d, J = 4.8 Hz), 153.5 (d, J = 12.6 Hz), 162.2 (d, J = 242.5 Hz), 164.0 (d, J = 3.1 Hz).

[00122] Sodium cyanide (1.47 g, 30 mmol) was added to a mixture of *N*-methyl-2-fluoro-4-aminobenzamide (52b) (1.68 g, 10 mmol) and cyclobutanone (1.4 g, 20 mmol) in 90% acetic acid (20 ml). The reaction mixture was stirred at 80 °C for 24 hours. The mixture was washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to dryness under vacuum. The solid was washed with a 50:50 mixture of ethyl ether and hexane (10 ml) to remove cyclobutanone cyanohydrin to afford after filtration *N*-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide (52c) (2.19 g, 8.87 mmol, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.87-1.95 (m, 1H), 2.16-2.27 (m, 1H), 2.35-2.41 (m, 2H), 2.76-2.83 (m, 2H), 2.97 (d, J = 4.4 Hz, 3H), 4.68 (bs, 1H), 6.29 (dd, J = 14.3, 1.8 Hz, 1H), 6.48 (dd, J = 8.3, 1.8 Hz, 1H), 6.75 (q, J = 4.4 Hz, 1H), 7.90 (dd, J = 8.3, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 26.7, 33.9, 49.4, 100.2 (d, J = 29.5 Hz), 110.6, 111.0 (d, J = 11.8 Hz), 133.1 (d, J = 4.2 Hz), 148.4 (d, J = 12.0 Hz), 162.0 (d, J = 244.1 Hz), 164.4 (d, J = 3.6 Hz).

[00123] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (2.16 g, 9.47 mmol) and *N*-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide (52c) (1.303 g, 5.27 mmol) in DMF (20 ml) was heated under microwave irradiation at 80 °C for 16 hours. To this mixture was added methanol (50 ml) and aq. 2*N* HCl (20 ml). The second mixture was refluxed for 3 hours. After being cooled to room temperature, the reaction mixture was poured into cold water (100 ml) and extracted with ethyl acetate (150 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield *N*-methyl-4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-2-fluorobenzamide (52d) **[RD162]** (1.43 g, 3.0 mmol, 57%), the structure of which is illustrated in Formula 28, as a yellow powder.



Formula 28

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65-1.75 (m, 1H), 2.18-2.30 (m, 1H), 2.49-2.57 (m, 2H), 2.67-2.73 (m, 2H), 3.07 (d, J = 4.4 Hz, 3H), 6.75 (q, J = 4.6 Hz, 1H), 7.17 (dd, J = 11.5, 1.9 Hz, 1H), 7.26 (dd, J = 8.3, 1.9 Hz, 1H), 7.83 (dd, J = 8.2, 2.0 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H) 8.30 (dd, J = 8.3, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 27.0, 31.7, 67.4, 110.3, 114.8, 118.2, 118.5, 121.9 (q, J = 272.7 Hz), 126.6, 127.0 (q, J = 4.8 Hz), 132.1, 133.3 (q, J = 33.2 Hz), 133.8, 135.3, 136.8, 139.1 (d, J = 10.9 Hz), 160.5 (d, J = 249.1 Hz), 162.7 (d, J = 3.3 Hz), 174.3, 179.8; ^{19}F NMR ($CDCl_3$, 100 MHz) δ -111.13, -62.58.

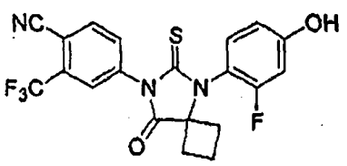
Example 53 [RD163]

[00124] A mixture of 4-nitro-3-fluorophenol (0.314 g, 2 mmol) and iron (0.56 g, 10 mmol) in ethyl acetate (4 ml) and acetic acid (2 ml) was refluxed for 3 hour. The solid particles were filtered off. The filtrate was washed with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated to yield 4-amino-3-fluorophenol (53a) (0.25 g, 19.6 mmol, 98%) as a brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.48-6.58 (m, 2H), 6.61-6.70 (m, 1H), 7.87 (bs, 3H).

[00125] Sodium cyanide (0.194 g, 4 mmol) was added to a mixture of 4-amino-3-fluorophenol (0.29 g, 2.28 mmol) and cyclobutanone (0.175 g, 2.5 mmol) in 90% acetic acid (3 ml). The reaction mixture was stirred at room temperature for 15 hours. The medium was washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated and chromatographed (dichloromethane:acetone, 90:10) to yield 1-(2-fluoro-4-hydroxyphenylamino)-cyclobutanecarbonitrile (53b) (0.271 g, 1.31 mmol, 58%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13-2.20 (m, 2H), 2.36-2.41 (m, 2H), 2.70.2.75 (m, 2H), 4.00 (bs, 1H), 6.46 (bs, 1H), 6.52 (ddd, J_1 = 2.2 Hz, J_2 = 0.65 Hz, J_3 = 0.22 Hz, 1H), 6.57 (d, J = 2.3 Hz), 6.62 (dd, J_1 = 3.0 Hz, J_2 = 0.67 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.1, 50.9, 104.0 (d, J = 21.9 Hz), 111.0 (d, J = 3.4 Hz), 115.8 (d, J =3.7 Hz), 121.8, 125.3 (d, J = 12.3 Hz), 150.1 (d, J = 10.4 Hz), 152.8 (d, J = 239.3 Hz).

[00126] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (0.228 g, 1.0 mmol) and 1-(2-fluoro-4-hydroxyphenylamino)-cyclobutanecarbonitrile (53b) (0.145 g, 0.7 mmol) in dry DMF (2 ml) was stirred at room temperature for 24 hours. To this mixture were added methanol (10 ml) and

aq. 2M HCl (2 ml). The second mixture was refluxed for 1 hour. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (50 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane pure and then dichloromethane:acetone, 90:10) to yield 4-[5-(2-fluoro-4-hydroxyphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile (53o) [RD163] (0.17 g, 0.39 mmol, 56%), the structure of which is illustrated in Formula 29, as a off-white powder.



Formula 29

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.66-1.75 (m, 1H), 2.18-2.28 (m, 1H), 2.42-2.50 (m, 1H), 2.54-2.67 (m, 3H), 6.76 (d, J = 2.2 Hz, 2H), 7.15 (t, J = 2.1 Hz, 1H), 7.35 (bs, 1H), 7.87 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 31.0, 67.6, 104.8 (d, J = 22.3 Hz), 109.8, 112.6, 114.4 (d, J = 13.1 Hz), 114.9, 121.9 (q, J = 272.8 Hz), 127.1 (q, J = 4.8 Hz), 132.0, 132.3, 133.5 (q, J = 33.3 Hz), 135.3, 137.2, 159.3 (d, J = 11.2 Hz), 159.6 (d, J = 249.7 Hz), 175.2, 180.5; ^{19}F NMR ($CDCl_3$, 100 MHz) δ -117.5, -62.49.

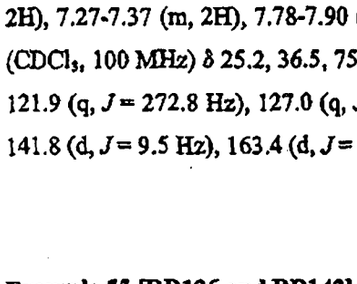
Example 54 [RD168]

[00127] A mixture of 4-nitro-2-fluorobenzonitrile (1.83 g, 5 mmol) and iron (1.68 g, 6 mmol) in a mixture of acetic acid (40 ml) and ethyl acetate (40 ml) was refluxed for 2 hours. The solid was filtered off and the filtrate was washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield 4-amino-2-fluorobenzonitrile (54a) (0.653 g, 4.8 mmol, 96%).

[00128] Sodium cyanide (0.74 g, 15 mmol) was added to a mixture of 4-amino-2-fluorobenzonitrile (1.36 g, 10 mmol) and cyclopentanone (1.26 g, 15 mmol) in 90% acetic acid (10 ml). The reaction mixture was stirred at room temperature for 3 hours and then the medium was hearted to 80 °C and stirred for an additional 5 hours. The medium was washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated and chromatographed (dichloromethane:acetone, 97:3) to yield 4-(1-cyanocyclopentylamino)-2-fluorobenzonitrile (54b) (2.07 g, 9.03 mmol, 90%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.69-1.91 (m, 4H), 2.13-2.18 (m,

2H), 2.37-2.42 (m, 2H), 5.08 (bs, 1H), 6.54-6.62 (m, 2H), 7.39 (t, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 39.8, 56.8, 89.6 (d, J = 15.8 Hz), 101.2 (d, J = 23.8 Hz), 110.9, 115.2, 120.8, 134.1 (d, J = 2.4 Hz), 150.3 (d, J = 11.2 Hz), 164.5 (d, J = 254.1 Hz).

[00129] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (0.171 g, 0.75 mmol) and 4-(1-cyanocyclopentylamino)-2-fluorobenzonitrile (54b) (0.115 g, 0.5 mmol) in dry DMF (1 ml) was heated under microwave irradiation at 60 °C for 48 hours. To this mixture were added methanol (3 ml) and aq 2M HCl (2 ml). The second mixture was refluxed for 1 hour. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (15 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 98:2) to yield 4-[1-(4-cyano-3-fluorophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl]-2-trifluoromethylbenzonitrile (54c) **[RD168]** (0.017 g, 0.037 mmol, 7%), of which the structure is illustrated in Formula 30, as an off-white powder.

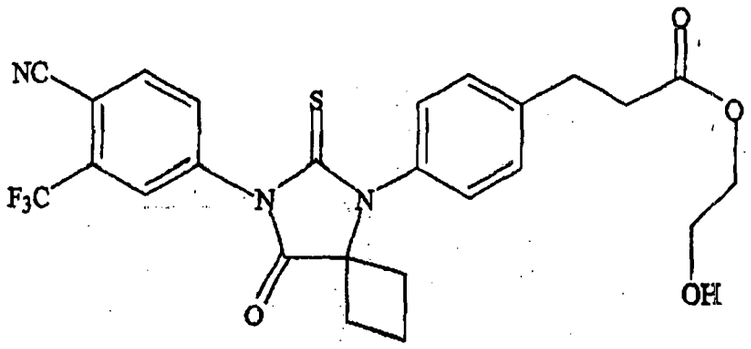


Formula 30

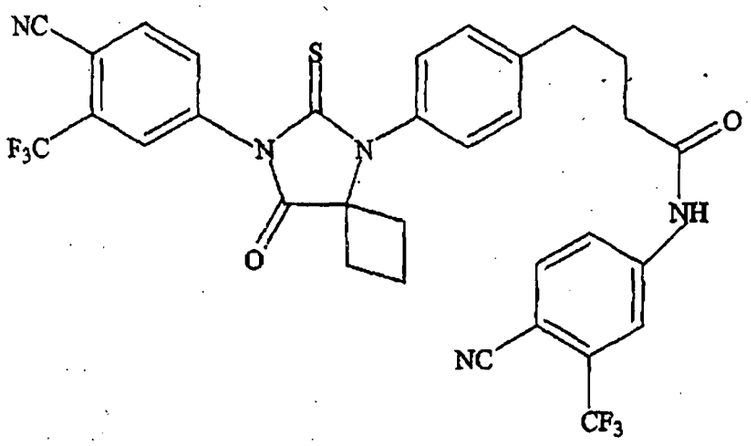
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53-1.63 (m, 2H), 1.89-2.00 (m, 2H), 2.09-2.16 (m, 2H), 2.35-2.42 (m, 2H), 7.27-7.37 (m, 2H), 7.78-7.90 (m, 3H), 7.95 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 36.5, 75.3, 103.2 (d, J = 15.3 Hz), 110.4, 112.8, 114.7, 119.2 (d, J = 20.7 Hz), 121.9 (q, J = 272.8 Hz), 127.0 (q, J = 4.8 Hz), 132.1, 133.7 (q, J = 33.2 Hz), 134.6, 135.3, 135.8, 136.8, 141.8 (d, J = 9.5 Hz), 163.4 (d, J = 261.5 Hz), 175.3, 180.1.

Example 55 [RD136 and RD142]

[00130] Additional diarylhydantoin compounds can be synthesized, including the following compounds illustrated in Formulas 35 and 36.



Formula 35 [RD136]

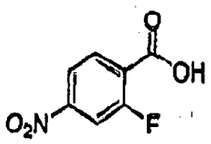


Formula 36 [RD142]

Example 56 [RD162']

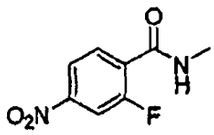
[00131] In the following, air or moisture sensitive reactions were conducted under argon atmosphere using oven-dried glassware and standard syringe/septa techniques. The reactions were monitored with a SiO_2 TLC plate under UV light (254 nm) followed by visualization with a *p*-anisaldehyde or ninhydrin staining solution. Column chromatography was performed on silica gel 60. ^1H NMR spectra were measured at 400 MHz in $CDCl_3$ unless stated otherwise and data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration,

coupling constant in Hz.).



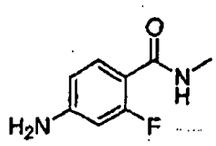
Formula 37

[00132] Periodic acid (1.69 g, 7.41 mmol) was dissolved in acetonitrile (25 mL) by vigorous stirring, and then chromium trioxide (0.16 g, 1.60 mmol) was dissolved into the solution. 2-Fluoro-4-nitrotoluene (0.33 g, 2.13 mmol) was added to the above solution with stirring. A white precipitate formed immediately with exothermic reaction. After 1 h of stirring, the supernatant liquid of the reaction mixture was decanted to a flask, and the solvent was removed by evaporation. The residues were extracted with methylene chloride (2×30 mL) and water (2×30 mL). The organic layer was dried over $MgSO_4$, and concentrated to give 2-Fluoro-4-nitrobenzoic acid (Formula 37) (0.32 mg, 81%) as a white solid. ^{1}H NMR δ 8.06 (ddd, 1 H, *J*=9.9, 2.2 and 0.3), 8.13 (ddd, 1 H, *J*=8.6, 2.2 and 0.9), 8.25 (ddd, 1 H, *J*=8.6, 7.0 and 0.3).



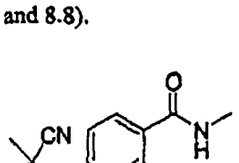
Formula 38

[00133] Thionyl chloride (0.15 g, 1.30 mmol) was added slowly to a solution of 2-fluoro-4-nitrobenzoic acid (Formula 37) (0.20 g, 1.10 mmol) in DMF (5 mL) cooled at -5 °C. The mixture was stirred for an additional 1 hour at -5 °C. Excess methylamine (freshly distilled from its 40% aqueous solution) was added to the reaction medium. The second mixture was stirred for an additional 1 hour. Ethyl acetate (50 mL) was added to the mixture, which was washed with brine (2 × 50 ml). The organic layer was dried over $MgSO_4$, and concentrated to yield *N*-Methyl-2-fluoro-4-nitrobenzamide (Formula 38) (0.18 g, 85%) as a yellowish solid. ^{1}H NMR (acetone-d_6) δ 3.05 (d, 3 H, *J*=4.3), 6.31 (dd, 1 H, *J*=13.5 and 2.1), 6.40 (dd, 1H, *J*=8.6 and 2.1), 7.64 (dd, 1H, *J* = 8.6 and 8.6).



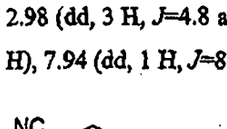
Formula 39

[00134] A mixture of *N*-Methyl-2-fluoro-4-nitrobenzamide (Formula 38) (0.18 g, 0.91 mmol) and iron (0.31 g, 5.60 mmol) in ethyl acetate (5 mL) and acetic acid (5 mL) was refluxed for 1 h. The solid particles were filtered off. The filtrate was washed with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane:acetone, 95:5) to give *N*-Methyl-2-fluoro-4-aminobenzamide (Formula 39) (0.14 g, 92%) as an off-white solid. ^1H NMR (acetone-d_6) δ 2.86 (d, 3 H, J=4.3), 5.50 (br s, 2 H), 6.37 (dd, 1 H, J=14.7 and 2.1), 6.50 (dd, 1H, J=8.6 and 2.1), 7.06 (br s, 1H), 7.68 (dd, 1H, J=8.8 and 8.8).



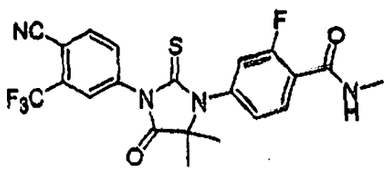
Formula 40

[00135] A mixture of *N*-Methyl-2-fluoro-4-aminobenzamide (Formula 39) (96 mg, 0.57 mmol), acetone cyanohydrin (0.3 mL, 3.14 mmol) and magnesium sulfate (50 mg) was heated to 80 °C and stirred for 12 h. To the medium was added ethyl acetate (25 mL) and then washed with water (2 × 25 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane:acetone, 95:5) to give *N*-Methyl-2-fluoro-4-(1,1-dimethyl-cyanomethyl)-aminobenzamide (Formula 40) (101 mg, 75%) as a white solid. ^1H NMR δ 1.74 (s, 6 H), 2.98 (dd, 3 H, J=4.8 and 1.1), 6.58 (dd, 1 H, J=14.6 and 2.3), 6.63 (dd, 1 H, J=8.7 and 2.3), 6.66 (br s, 1 H), 7.94 (dd, 1 H, J=8.7 and 8.7).



Formula 41

[00136] 4-Amino-2-trifluoromethylbenzonitrile (2.23 g, 12 mmol) was added portionwise over 15 min into a well-stirred heterogeneous mixture of thiophosgene (1 mL, 13 mmol) in water (22 mL) at room temperature. Stirring was continued for an additional 1 h. The reaction medium was extracted with chloroform (3 × 15 ml). The combined organic phase was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to yield desired product 4-Isothiocyanato-2-trifluoromethylbenzonitrile (Formula 41) as brownish solid and was used as such for the next step (2.72 g, 11.9 mmol, 99%). ^1H NMR δ 7.49 (dd, 1 H, J=8.3 and 2.1), 7.59 (d, 1 H, J=2.1), 7.84 (d, 1 H, J=8.3).

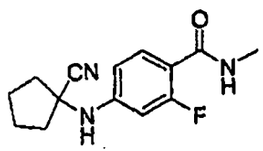


RD162' (Formula 42)

56-1) RD162'

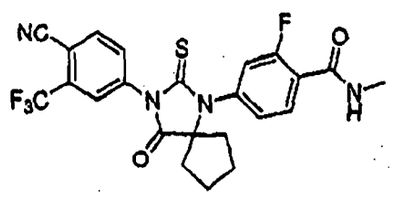
[00137] A mixture of *N*-Methyl-2-fluoro-4-(1,1-dimethyl-cyanomethyl)-aminobenzamide (Formula 40) (30 mg, 0.13 mmol) and 4-*Isothiocyanato*-2-trifluoromethylbenzonitrile (Formula 41) (58 mg, 0.26 mmol) in DMF (1 mL) was heated under microwave irradiation at 100 °C for 11 hours. To this mixture was added methanol (20 mL) and *aq.* 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane:acetone, 95:5) to give **RD162'** (Formula 42) (15 mg, 25%) as a colorless crystal. ^{1}H NMR δ 1.61 (s, 6 H), 3.07 (d, 3 H, *J*=4.1), 6.71 (m, 1 H), 7.15 (dd, 1H, *J*=11.7 and 2.0), 7.24 (dd, 1H, *J*=8.4 and 2.0), 7.83 (dd, 1H, *J*=8.2 and 2.1), 7.95 (d, 1H, *J*=2.1), 7.99 (d, 1H, *J*=8.2), 8.28 (dd, 1H, *J*=8.4 and 8.4).

Example 57



Formula 43

[00138] A mixture of N-Methyl-2-fluoro-4-aminobenzamide (Formula 39) (62 mg, 0.37 mmol), cyclopentanone (0.07 mL, 0.74 mmol) and TMSCN (0.1 mL, 0.74 mmol) was heated to 80 °C and stirred for 13 h. To the medium was added ethyl acetate (2 × 20 mL) and then washed with water (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 95:5) to give *N*-Methyl 2-fluoro-4-(1-cyanocyclopentyl)aminobenzamide (Formula 43) (61 mg, 63%) as a white solid. ^{1}H NMR δ 7.95 (dd, 1H, *J* = 8.8, 8.8 Hz), 6.65 (br s, 1H), 6.59 (dd, 1H, *J* = 8.8, 2.3 Hz), 6.50 (dd, 1H, *J* = 14.6, 2.3 Hz), 4.60 (br s, 1H), 2.99 (dd, 3H, *J* = 4.8, 1.1 Hz), 2.36-2.45 (m, 2H), 2.10-2.18 (m, 2H), 1.82-1.95 (m, 4H).

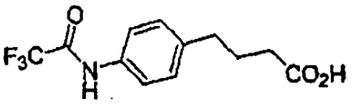


RD162" (Formula 44)

57-1) RD162"

[00139] A mixture of *N*-Methyl 2-fluoro-4-(1-cyanocyclopentyl)aminobenzamide (Formula 43) (57 mg, 0.22 mmol) and 4-isothiocyanato-2-trifluoromethyl benzonitrile (0.15 g, 0.65 mmol) in DMF (3 mL) was heated under microwave irradiation (open vessel) at 130 °C for 12 hours. To this mixture was added methanol (20 mL) and *aq.* 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 95:5) to give 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]nonan-1-yl)-2-fluoro-*N*-methylbenzamide, **RD162"** (Formula 44) (8 mg, 7%) as a pale yellowish solid. ^{1}H NMR δ 8.28 (dd, 1H, J = 8.4, 8.4 Hz), 7.98 (d, 1H, J = 8.3 Hz), 7.96 (d, 1H, J = 1.8 Hz), 7.84 (dd, 1H, J = 8.3, 1.8 Hz), 7.27 (dd, 1H, J = 8.4, 1.8 Hz), 7.17 (dd, 1H, J = 11.7, 1.8 Hz), 6.67-6.77 (m, 1H), 3.07 (d, 3H, J = 4.3 Hz), 2.32-2.41 (m, 2H), 2.13-2.21 (m, 2H), 1.85-1.96 (m, 2H), 1.49-1.59 (m, 2H).

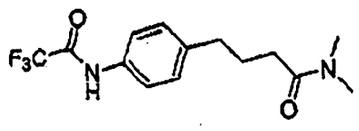
Example 58



Formula 45

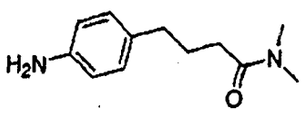
[00140] Trifluoroacetic anhydride (0.85 mL, 6.14 mmol) was added to a solution of 4-(4-aminophenyl)butyric acid (0.5 g, 2.79 mmol) in chloroform (10 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 3 hours. The mixture was partitioned with chloroform (20 mL) and water (20 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 9:1) to give 4-[4-(2,2,2-Trifluoroacetylamino)phenyl]butanoic acid (Formula 45) (0.53 g, 69%). ^{1}H NMR δ 7.81 (br s, 1H), 7.48

(d, 2H, J = 8.5 Hz), 7.22 (d, 2H, J = 8.5 Hz), 2.68 (t, 2H, J = 7.5 Hz), 2.38 (t, 2H, J = 7.5 Hz), 1.96 (p, 2H, J = 7.5 Hz).



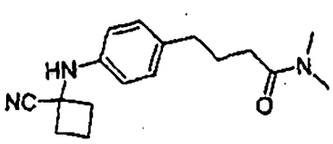
Formula 46

[00141] Thionyl chloride (71 mg, 0.60 mmol) was added slowly to a solution of 4-[4-(2,2,2-Trifluoroacetylamino)phenyl]butanoic acid (Formula 45) (0.15 g, 0.55 mmol) in DMF (5 mL) cooled at -5 °C. The mixture was stirred for an additional 1 hour at -5 °C. Excess dimethylamine (freshly distilled from its 40% aqueous solution) was added to the reaction medium. The second mixture was stirred for an additional 1 hour. Ethyl acetate (50 mL) was added to the mixture, which was washed with brine (2 × 50 ml). The organic layer was dried over $MgSO_4$, and concentrated to yield *N,N*-Dimethyl 4-[4-(2,2,2-Trifluoroacetylamino)phenyl]butanamide (Formula 46) (0.17 g, quant.) as a yellowish solid. ^{1}H NMR δ 9.70 (br s, 1H), 7.55 (d, 2H, J = 8.6 Hz), 7.11 (d, 2H, J = 8.6 Hz), 2.91 (s, 3H), 2.89 (s, 3H), 2.60 (t, 2H, J = 7.7 Hz), 2.27 (t, 2H, J = 7.7 Hz), 1.89 (p, 2H, J = 7.7 Hz).



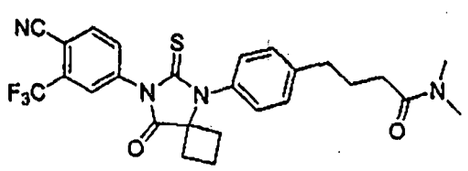
Formula 47

[00142] 1 N NaOH solution (3 mL) was added to a solution of *N,N*-Dimethyl 4-[4-(2,2,2-Trifluoroacetylamino)phenyl]butanamide (Formula 46) (0.17 g, 0.55 mmol) in methanol (2 mL) at room temperature. The mixture was stirred for 14 hour. The mixture was partitioned with chloroform (25 mL) and water (25 mL). The organic layer was dried over $MgSO_4$, and concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 9:1) to give *N,N*-Dimethyl 4-(4-aminophenyl)butanamide (Formula 47) (74 mg, 66%) as a white solid. ^{1}H NMR δ 6.97 (d, 2H, J = 8.3 Hz), 6.61 (d, 2H, J = 8.3 Hz), 3.56 (br s, 2H), 2.92 (s, 6 H), 2.56 (t, 2H, J = 7.7 Hz), 2.28 (t, 2H, J = 7.7 Hz), 1.91 (p, 2H, J = 7.7 Hz).



Formula 48

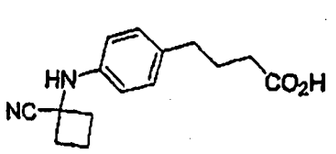
[00143] A mixture of *N,N*-Dimethyl 4-(4-aminophenyl)butanamide (Formula 47) (74 mg, 0.36 mmol), cyclobutanone (54 mg, 0.78 mmol) and TMSCN (77 mg, 0.78 mmol) was heated to 80 °C and stirred for 15 h. To the medium was added ethyl acetate (2 × 20 mL) and then washed with water (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 9:1) to give *N,N*-Dimethyl 4-[4-(1-cyanocyclobutylamino)phenyl]butanamide (Formula 48) (58 mg, 57%) as a white solid. ^{1}H NMR δ 7.07 (d, 2H, J = 8.5 Hz), 6.59 (d, 2H, J = 8.5 Hz), 3.94 (br s, 1H), 2.94 (s, 3H), 2.93 (s, 3H), 2.75-2.83 (m, 2H), 2.60 (t, 2H, J = 7.6 Hz), 2.33-2.42 (m, 2H), 2.30 (t, 2H, J = 7.6 Hz), 2.11-2.28 (m, 2H), 1.93 (p, 2H, J = 7.6 Hz).



RD169 Formula 49

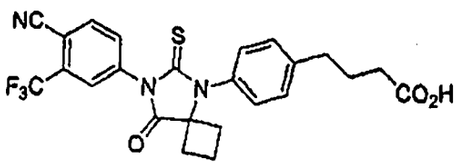
[00144] A mixture of *N,N*-Dimethyl 4-[4-(1-cyanocyclobutylamino)phenyl]butanamide (Formula 48) (58 mg, 0.20 mmol) and 4-isothiocyanato-2-trifluoromethyl benzonitrile (74 mg, 0.32 mmol) in DMF (3 mL) was heated under reflux for 2 hours. To this mixture was added methanol (20 mL) and *aq*. 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 95:5) to give 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)-*N,N*-dimethylbutanamide, **RD169** (Formula 49) (44 mg, 42%) as a pale yellowish solid. ^{1}H NMR δ 7.98 (s, 1H), 7.97 (d, 1H, J = 8.2 Hz), 7.86 (d, 1H, J = 8.2 Hz), 7.42 (d, 2H, J = 8.3 Hz), 7.22 (d, 2H, J = 8.3 Hz), 2.99 (s, 3H), 2.96 (s, 3H), 2.78 (t, 2H, J = 7.5 Hz), 2.62-2.70 (m, 2H), 2.52-2.63 (m, 2H), 2.40 (t, 2H, J = 7.5 Hz), 2.15-2.30 (m, 1H), 2.04 (p, 2H, J = 7.5 Hz), 1.62-1.73 (m, 1H).

Example 59



Formula 50

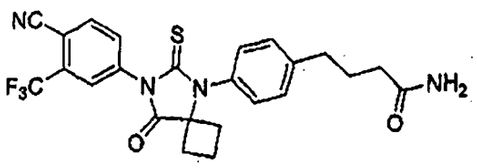
[00145] A mixture of 4-(4-aminophenyl)butyric acid (0.20 g, 1.12 mmol), cyclobutanone (0.17 mL, 2.23 mmol) and TMSCN (0.30 mL, 2.23 mmol) was heated to 80 °C and stirred for 13 h. To the medium was added ethyl acetate (2 × 30 mL) and then washed with water (2 × 30 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 9:1) to give 4-[4-(1-Cyanocyclobutylamino)phenyl]butanoic acid (Formula 50) (0.21 g, 74%) as a yellowish solid. ^{1}H NMR δ 7.06 (d, 2H, J = 8.6 Hz), 6.59 (d, 2H, J = 8.6 Hz), 2.75-2.83 (m, 2H), 2.59 (t, 2H, J = 7.5 Hz), 2.37 (t, 2H, J = 7.5 Hz), 2.33-2.42 (m, 2H), 2.11-2.28 (m, 2H), 1.92 (p, 2H, J = 7.5 Hz).



Formula 51

[00146] A mixture of 4-[4-(1-Cyanocyclobutylamino)phenyl]butanoic acid (Formula 50) (0.21 g, 0.83 mmol) and 4-isothiocyanato-2-trifluoro benzonitrile (0.25 g, 1.08 mmol) in toluene (10 mL) was heated under reflux for 1 hours. To this mixture was added *aq.* 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 95:5) to give 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)butanoic acid, RD141 (Formula 51) (60 mg, 15%). ^{1}H NMR δ 7.98 (d, 1H, J = 1.8 Hz), 7.97 (d, 1H, J = 8.3 Hz), 7.86 (dd, 1H, J = 8.3, 1.8 Hz), 7.42 (d, 2H, J = 8.5 Hz), 7.24 (d, 2H, J = 8.5 Hz), 2.79 (t, 2H, J = 7.5 Hz), 2.62-2.68 (m, 2H), 2.51-2.59 (m, 2H), 2.47 (t, 2H, J = 7.5 Hz), 2.14-2.26 (m, 1H), 2.06 (p, 2H, J = 7.5 Hz), 1.60-1.70 (m, 1H).

Example 60

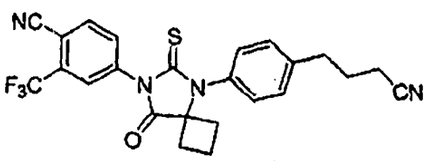


RD130 Formula 52

[00147] To a solution of 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-

diazaspiro[3.4]octan-5-yl)phenyl)butanoic acid, RD141 (Formula 51) (60 mg, 0.12 mmol) in DMF (3 mL) was added thionyl chloride (0.01 mL, 0.15 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hour. Then ammonia was bubbled into the mixture. The mixture was partitioned with ethyl acetate (25 mL) and water (25 mL). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)butanamide, **RD130** (Formula 52) (37 mg, 61%) as a white powder. ^{1}H NMR δ 7.97 (d, 1H, J = 1.8 Hz), 7.95 (d, 1H, J = 8.3 Hz), 7.85 (dd, 1H, J = 8.3 Hz), 7.39 (d, 2H, J = 8.3 Hz), 7.22 (d, 2H, J = 8.3 Hz), 5.59 (br s, 2H), 2.77 (t, 2H, J = 7.5 Hz), 2.62-2.68 (m, 2H), 2.51-2.59 (m, 2H), 2.31 (t, 2H, J = 7.5 Hz), 2.16-2.25 (m, 1H), 2.05 (p, 2H, J = 7.5 Hz), 1.57-1.70 (m, 1H).

Example 61

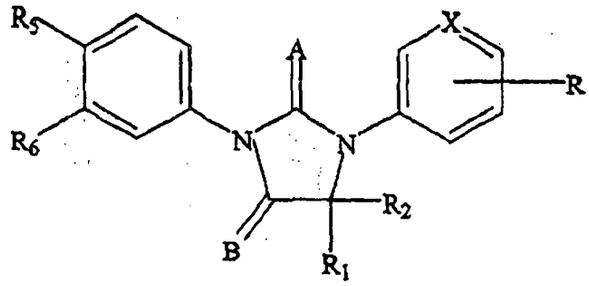


RD170 Formula 53

A solution of DMSO (0.01 mL, 0.12 mmol) in dry dichloromethane (1 mL) was added to a stirred solution of oxalyl chloride (0.01 mL, 0.09 mmol) in dry dichloromethane (2 mL) at -78 °C. After 15 min, a dichloromethane solution of 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)butanamide, RD130 (Formula 52) (35 mg, 0.07 mmol) was added to the reaction mixture. Stirring was continued for 20 min at -78 °C, and then triethylamine (0.03 mL, 0.22 mmol) was added. After 30 min at -78 °C, the reaction mixture was warmed to room temperature and then reaction was quenched with saturated *aq*. NH_4Cl solution. The reaction mixture was diluted with dichloromethane, and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield 4-(5-(4-(3-Cyanopropyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-7-yl)-2-(trifluoromethyl)benzonitrile, **RD170** (Formula 53) (29 mg, 87%) as a viscous oil. ^{1}H NMR δ 7.98 (d, 1H, J = 1.8 Hz), 7.98 (d, 1H, J = 8.3 Hz), 7.86 (dd, 1H, J = 8.3, 1.8 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.27 (d, 2H, J = 8.4 Hz), 2.90 (t, 2H, J = 7.3 Hz), 2.63-2.73 (m, 2H), 2.52-2.62 (m, 2H), 2.42 (t, 2H, J = 7.3 Hz), 2.18-2.30 (m, 1H), 2.07 (p, 2H, J = 7.3 Hz), 1.63-1.73 (m, 1H).

[00148] One skilled in the art could modify and/or combine the syntheses described herein to make other diarylhydantoin compounds.

[00149] Inventive compounds also include those with the following formulas.



Where R is selected from hydrogen, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated akynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, halogen, SO_2R_{11}, $NR_{11}R_{12}$, $NR_{12}(CO)OR_{11}$, $NH(CO)NR_{11}R_{12}$, $NR_{12}(CO)R_{11}$, $O(CO)R_{11}$, $O(CO)OR_{11}$, $O(CS)R_{11}$, $NR_{12}(CS)R_{11}$, $NH(CS)NR_{11}R_{12}$, $NR_{12}(CS)OR_{11}$.

R_1 and R_2 are independently selected from hydrogen, aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated akynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocylic aromaric or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl.

R_1 and R_2 can be connected to form a cycle which can be heterocyclic, substituted heterocyclic, cycloakyl, substituted cycloalkyl.

R_3 is selected from aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, SO_2R_{11}, $NR_{11}R_{12}$, $(CO)OR_{11}$, $(CO)NR_{11}R_{12}$, $(CO)R_{11}$, $(CS)R_{11}$, $(CS)R_{11}$, $(CS)NR_{11}R_{12}$, $(CS)OR_{11}$.

R_5 is CN or NO_2 or SO_2R_{11}

R_6 is CF_3, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated akynyl, halogen.

A is sulfur atom (S) or oxygen atom (O).

B is O or S or NR_3

X is carbon or nitrogen and can be at any position in the ring.

R_{11} and R_{12} are independently selected from hydrogen, aryl, aralkyl, substituted aralkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated akynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cyclolakyl, substituted cycloalkyl.

R_{11} and R_{12} can be connected to form a cycle which can be heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic, cycloakyl, substituted cycloalkyl.

[00150]

Pharmacological examination of the compounds

[00151] Compounds for which synthetic routes are described above were identified through screening on hormone refractory prostate cancer cells for antagonistic and agonistic activities against AR utilizing screening procedures similar to those in PCT applications US04/42221 and US05/05529, which are hereby incorporated by reference. A number of compounds exhibited potent antagonistic activities with minimal agonistic activities for over expressed AR in hormone refractory prostate cancer.

In vitro biological assay

Effect of compounds on AR by a reporter assay

[00152] The compounds were subjected to tests using an artificial AR response reporter system in a hormone refractory prostate cancer cell line. In this system, the prostate cancer LNCaP cells were engineered to stably express about 5-fold higher level of AR than endogenous level. The exogenous AR has similar properties to endogenous AR in that both are stabilized by a synthetic androgen R1881. The AR-over expressed cells were also engineered to stably incorporate an AR response reporter and the reporter activity of these cells shows features of hormone refractory prostate cancer. It responds to low concentration of a synthetic androgen R1881, is inhibited only by high concentrations of bicalutamide (see Table 1), and displays agonistic activity with bicalutamide (Figure 1 and Table 2). Consistent with published data, bicalutamide inhibited AR response reporter and did not have agonistic activity in hormone sensitive prostate cancer cells (Figure 2).

[00153] We examined the antagonistic activity of the compounds for which the synthesis is described above in the presence of 100 pM of R1881. Engineered LNCaP cells (LNCaP-AR, also abbreviated LN-AR) were maintained in Iscove's medium containing 10% fetal bovine serum (FBS). Two days prior to drug treatment, the cells were grown in Iscove's medium containing 10% charcoal-stripped FBS (CS-FBS) to deprive of androgens. The cells were split and grown in Iscove's medium containing 10% CS-FBS with 100 pM of R1881 and increasing concentrations of test compounds. After two days of incubation, reporter activities were assayed.

[00154] Table 1 lists the IC50 of these compounds to inhibit AR in hormone refractory prostate

cancer. The control substance bicalutamide has an IC50 of 889 nM. Most of the compounds identified (diarylthiohydantoins) have IC50s between 100 to 200 nM in inhibiting AR in hormone refractory prostate cancer. In contrast, antiandrogenic compounds listed as examples in US patent no. 5,705,654, such as examples 30-2, 30-3, 31-2, 31-3, and 24-3 (RD73-RD77) have no inhibitory activities on AR in this system.

Table 1

Antagonistic activities against AR in hormone refractory prostate cancer,

measured by an AR response reporter and by endogenous PSA expression.

		IC50 (nM)	IC50 (nM)
Example	**Name**	***Reporter***	**PSA**
Bicalutamide Comparative	N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide	889	>1000
29 Comparative	4-[3-(4-hydroxybutyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	No(*)	No
6-2 (6b) [RD10]	4-[3-phenyl-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	149	n/a (**)
5-3b (5c) [RD7]	4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile	125	132
3-3 (3c) [RD8]	4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	137	122
2-4 (2d) [RD9]	4-[3-(4-aminophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	273	n/a
4 (4a) [RD13]	Chloroacetic acid 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]phenyl ester	131	n/a
8-2 (8b) [RD35]	4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	147	n/a
7-3b (7c) [RD37]	4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	124	128

9-3 (9c) [RD48]	4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile	194	n/a
10-3 (10c) [RD49]	4-(4-oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]undec-3-yl)-2-trifluoromethylbenzonitrile	232	n/a
28 Comparative (28a) [RD52]	4-(8-methyl-4-oxo-2-thioxo-1,3,8-triazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile	No	n/a
27-3 (27c) [RD53]	4-(8-methyl-4-oxo-2-thioxo-1-(4-methylphenyl)-1,3,8-triazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile	638	n/a
26 (26a) [RD54]	4-[1-(4-cyanophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl]-2-trifluoromethylbenzonitrile	469	n/a
25 (25a) [RD55]	4-[1-(4-nitrophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl]-2-trifluoromethylbenzonitrile	498	n/a
12-2 (12b) [RD57]	4-(8-oxo-6-thioxo-5-(4-biphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	283	n/a
11-2 (11b) [RD58]	4-(8-oxo-6-thioxo-5-(4-hydroxyphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	162	n/a
17 (17a) [RD59]	4-[3-(4-hydroxyphenyl)-4,4-dimethyl-2,5-dithioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	278	287
18 (18a) [RD60]	4-[3-(4-hydroxyphenyl)-4,4-dimethyl-2,5-dioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	369	511
22-2 (22b) [RD65]	2-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]benzoic acid	523	>500
20-2 (20b) [RD66]	4-(4,4-dimethyl-5-oxo-2-thioxo-3-(4-trifluoromethylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile	143	144
21-2 (21b) [RD67]	4-(4,4-bischloromethyl-5-oxo-2-thioxo-3-(4-methylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile	521	>500
19-2 (19b) [RD68]	4-(4-fluoromethyl-4-methyl-5-oxo-2-thioxo-3-(4-methylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile	126	129

23-2 (23b) [RD71]	4-(8-oxo-6-thioxo-5-(2-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	258	232
30-2 Comparative (30b) [RD73]	4-(5-methyl-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylenzonitrile	No	No
30-3 Comparative (30c) [RD74]	4-(5-methyl-6,8-dioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	No	No
31-2 Comparative (31b) [RD75]	4-(1-methyl-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	No	No
31-3 Comparative (31c) [RD76]	4-(1-methyl-2,4-dioxo-1,3-diaza-spiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	No	No
24-3 Comparative (24c) [RD77]	4-(4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	No	No
15-2 (15b) [RD82]	4-[4,4-dimethyl-3-(4-pyridin-2-yl)-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	723	n/a
14-2 (14b) [RD83]	4-[4,4-dimethyl-3-(4-methylpyridin-2-yl)-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	457	n/a
16-2 Comparative (16b) [RD84]	4-[5-(5-methyl-2H-pyrazol-3-yl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-7-yl]-2-trifluoromethyl-benzonitrile	>1000	n/a
13-2 (12b) [RD85]	4-(8-oxo-6-thioxo-5-(4-biphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	>1000	n/a
32 (32a) [RD90]	4-(8-methylimino-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-7-yl)-2-trifluoromethyl-benzonitrile	222	421
33 (33a) [RD91]	1-[3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene]-3-ethyl-thiourea	157	239
34 (34a) [RD92]	1-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-3-phenyl-thiourea	176	276

35 (35a) [RD93]	1-(4-Cyano-3-trifluoromethyl-phenyl)-3-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-thiourea	144	158
36-2 (36b) [RD110]	4-[8-(4-hydroxymethyl-phenyl)-5-oxo-7-thioxo-6-aza-spiro[3.4]oct-6-yl]-2-trifluoromethyl-benzonitrile	311	337
37 (37a) [RD114]	4-[5-(4-formylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethyl-benzonitrile	n/a	263
38 (38a) [RD116]	4-{5-[4-(1-hydroxyethyl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethyl-benzonitrile	n/a	187
39 (39a) [RD117]	3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-acrylic acid ethyl ester	n/a	197
40 (40a) [RD120]	4-{5-[4-(3-hydroxypropenyl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethylbenzonitrile	n/a	114
41-2 (41b) [RD128]	3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-propionic acid methyl ester	No	n/a
41-4 (41d) [RD133]	3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-propionamide	224	n/a
41-5 (41e) [RD134]	3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-N-methyl-propionamide	234	n/a
41-6 (41f) [RD135]	3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-N-(2-hydroxyethyl)-propionamide	732	n/a
42-2 (42b) [RD129]	4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-butyric acid methyl ester	432	n/a
42-4	4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-	112	n/a

(42d) [RD130]	thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-butyramide		
42-5 (42e) [RD131]	4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-N-methyl-butyramide	92	n/a
43-4 (43e) [RD137]	4-[8-Oxo-5-(4-piperazin-1-yl-phenyl)-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile	718	n/a
43-5 (43f) [RD138]	4-{5-[4-(4-methanesulfonylpiperazin-1-yl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethylbenzonitrile	138	n/a
44-2 (44b) [RD119]	44-2) 3-{4-[7-(4-Cyano-3-trifluoromethyl-phenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-acrylamide,		113

(*) No: the compound did not inhibit AR response reporter; (**) n/a: the compound was not examined in this assay.

[00155] One previously unrecognized property of AR overexpression in hormone refractory prostate cancer is its ability to switch antagonists to agonists. Therefore, only those compounds with minimal or no agonistic activities are qualified to be anti-androgens for this disease. To determine agonistic activities of different compounds, we examined their stimulating activities on AR using the AR response reporter as the measure in the LN-AR system in the absence of R1881. Table 2 lists the agonistic activities of different compounds. Consistent with previous results, bicalutamide activated AR in hormone refractory prostate cancer. The diarylthiohydantoin derivatives such as examples 7-3b (RD37), 33 (RD91), 34 (RD92), and 35 (RD93) have no agonistic activity. In contrast, RU59063, and other anti-androgenic compounds listed as examples in US Patent Number 5,705,654, such as examples 30-2, 30-3, 31-2, 31-3, and 24-3 (RD73-RD77) strongly activated AR in hormone refractory prostate cancer.

Table 2

Agonistic activities of selective test substances on

AR response reporter in hormone refractory prostate cancer

Fold induction by increasing

		concentrations of compounds		
Example	Name	0.1 μM	1 μM	10 μM
DMSO	Dimethyl sulfoxide	1.00 (*)	1.00	1.00
R1881	methyltrienolone	44.33	n/a(**)	n/a
Bicaluta mide	N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide	1.66	3.04	10.40
29 Comp.	4-[3-(4-hydroxybutyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	10.99	20.84	34.62
7-3b (7c) [RD37]	4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	0.87	1.19	0.89
33 (33a) [RD91]	1-[3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene]-3-ethyl-thiourea	1.30	1.18	1.28
34 (34a) [RD92]	1-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-3-phenyl-thiourea	1.19	1.41	1.17
35 (35a) [RD93]	1-(4-Cyano-3-trifluoromethyl-phenyl)-3-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-thiourea	1.26	1.10	1.30
30-2 Comp. (30b) [RD73]	4-(5-methyl-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylenzonitrile	14.88	19.41	35.22
30-3 Comp. (30c) [RD74]	4-(5-methyl-6,8-dioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	11.39	14.26	30.63
31-2 Comp. (31b) [RD76]	4-(1-methyl-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	17.03	16.63	33.77
31-3	4-(1-methyl-2,4-dioxo-1,3-diaza-spiro[4.4]non-	11.99	19.77	38.95

Comp. (31c) [RD76]	3-yl)-2-trifluoromethylbenzonitrile			
24-3 Comp. (24c) [RD77]	4-(4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	14.88	22.48	37.09

(*) Fold induction: activities induced by a specific test substance over activities in DMSO vehicle; (**) n/a: the compound was not examined in this assay.

[00156] To examine the specificity of AR inhibitors, selective compounds were tested in LNCaP cells with an over expression of glucocorticoid receptor (GR), the closest member of AR in the nuclear receptor family. These cells also carry a GR response reporter and the reporter activity was induced by dexamethasone, a GR agonist and the induction was blocked by RU486, a GR inhibitor. Example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethyl benzonitrile) had no effect on GR in this system.

Effect of compounds on AR by measuring secreted levels of

prostate specific antigen (PSA)

[00157] It is well established that PSA levels are indicators of AR activities in prostate cancer. To examine if the compounds affect AR function in a physiological environment, we determined secreted levels of endogenous PSA induced by R1881 in the AR-overexpressed LNCaP cells (LNCaP-AR, also abbreviated LN-AR). The LNCaP-AR cells are a line of lymph node carcinoma of prostate cells transduced with a plasmid that makes express androgen receptors. LNCaP-AR cells were maintained in Iscove's medium containing 10% FBS. Two days prior to drug treatment, the cells were grown in Iscove's medium containing 10% CS-FBS to deprive of androgens. The cells were split and grown in Iscove's medium containing 10% CS-FBS with appropriate concentrations of R1881 and the test compounds. After four days incubation, secreted PSA levels were assayed using PSA ELISA kits (American Qualex, San Clemente, CA)

[00158] The secreted PSA level of LNCaP-AR cells was strongly induced by 25 pM of R1881. In contrast, PSA was not induced in the parental LNCaP cells until concentration of R1881 reached 100 pM. This is consistent with our previous report that the AR in hormone refractory prostate cancer is hyper-

sensitive to androgens. A dose-dependent inhibition on AR activity was carried out to determine the IC50s of different compounds in inhibiting PSA expression, and the results were listed in Table 1. IC50s of the selective compounds on PSA expression closely resemble those measured by the reporter assay, confirming that the diarylhydantoin derivatives are strong inhibitors of AR in hormone refractory prostate cancer.

[00159] We also examined agonistic activities of selective compounds on AR in hormone refractory prostate cancer using secreted PSA as the surrogate marker. To do this, androgen-starved AR over expressed LNCaP cells were incubated with increasing concentrations of the compounds for which a synthesis is described above in the absence of R1881 and secreted PSA in the culture medium was measured 4 days later.

[00160] Table 3 lists the agonistic activities of the selective compounds. Consistent with the results obtained from the reporter assay, the diarylthiohydantoin derivatives such as examples 7-3b (RD37), 33 (RD91), 34 (RD92), and 35 (RD93) have no agonistic activities. In contrast, RU59063, and other antiandrogenic compounds listed as examples in US patent no. 5,705,654, such as examples 30-2 (RD73), 30-3 (RD74), and 31-2 (RD75) stimulated PSA expression in hormone refractory prostate cancer.

Table 3

Agonistic activities of selective test substances on endogenous PSA in hormone refractory prostate cancer

Fold induction by increasing concentrations of compounds

Example	Name	0.1 µM	1 µM	10 µM
DMSO	Dimethyl sulfoxide	1.00 (*)	1.00	1.00
R1881	methyltrienolone	20.69	n/a(**)	n/a
Bicaluta mide	N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide	2.00	2.55	5.55
29 Comp.	4-[3-(4-hydroxybutyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	6.88	11.50	21.50
7-3b (7c) [RD37]	4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	1.25	1.20	1.15
33	1-[3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-	1.06	1.30	0.85

(33a) [RD91]	dimethyl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene]-3-ethyl-thiourea			
34 (34a) [RD92]	1-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-3-phenyl-thiourea	1.31	1.05	0.90
35 (35a) [RD93]	1-(4-Cyano-3-trifluoromethyl-phenyl)-3-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-thiourea	1.44	1.30	1.05
30-2 Comp. (30b) [RD73]	4-(5-methyl-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylenzonitrile	6.25	17.95	25.65
30-3 Comp. (30c) [RD74]	4-(5-methyl-6,8-dioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	7.50	15.20	23.75
31-2 Comp. (31b) [RD75]	4-(1-methyl-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	8.13	18.20	17.50

(*) Fold induction: activities induced by a specific test substance over activities in DMSO vehicle; (**) n/a: the compound was not examined in this assay.

[00161]

Effect of compounds on AR mitochondrial activity by MTS assay

[00162] LNCaP-AR cells were maintained in Iscove's medium containing 10% FBS. The compounds were examined for their effect on growth of hormone refractory prostate cancer cells. Overexpressed LNCaP cells were used because these cells behave as hormone refractory prostate cancer cells in vitro and in vivo *(1)*. We measured mitochondria activity by MTS assay, a surrogate for growth. LNCaP cells with overexpressed AR (LN-AR) were maintained in Iscove's medium containing 10% FBS. Two days prior to drug treatment, the cells were grown in Iscove's medium containing 10% CS-FBS to deprive of androgens. The cells were then split and grown in Iscove's medium containing 10% CS-FBS with appropriate concentrations of R1881 and increasing concentrations of the test compounds. After four days incubation, cell growth was monitored by MTS (Promega, Madison, WI).

[00163] Consistent with the reporter assay and PSA assay, growth of the AR-overexpressed LNCaP was stimulated by 25 microM of R1881, but the parental cells were not stimulated until R1881 concentration reached 100 microM. Figure 2 shows the inhibitory effect of selected compounds on growth of hormone refractory prostate cancer in the presence of 100 pM of R1881. The current clinical drug bicalutamide did not inhibit hormone refractory prostate cancer. In contrast, example 5-3b (RD7) (4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile) and example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) inhibited hormone refractory prostate cancer with high potency.

[00164] We examined if growth inhibition in the MTS assay occurs by targeting AR, example 5-3b (RD7) (4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile) and example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) were tested in DU-145 cells, a prostate cancer cell line that lacks AR expression. These compounds had no growth inhibitory effect on DU-145 cells. The compounds did not inhibit cells other than AR-expressed prostate cancer cells, as they had no growth effect on MCF7 and SkBr3, two commonly used breast cancer cells, or 3T3, a normal mouse fibroblast cell line.

[00165] Examples of in vitro biological activity of diarylthiohydantoin derivatives are shown in the Figures 3, 4 and 5. For example, based on relative luciferase activity, Fig. 3 indicates that at a concentration of 500 nM the compounds ranked, in order of most active to least active as follows: RD152 > RD153 > RD145 > RD163 > RD161 = RD162 > bicalutamide. For example, based on relative PSA level, Fig 4 indicates that at a concentration of 500 nM the compounds ranked, in order of most active to least active as follows: RD138 > RD131 > RD37 > RD133 > RD134 > RD137 > RD138 > RD135 > bicalutamide. For example, based on relative MTS units, Fig. 5 indicates that at a concentration of 500 nM the compounds ranked, in order of most active to least active as follows: RD168 > RD37 > RD141 > RD162 > bicalutamide.

Inhibitory effect on hormone refractory prostate cancer xenograft tumors.

[00166] Example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) was used to examine if the diarylhydantoin derivatives have in vivo effects on hormone refractory prostate cancer. First we examined this compound on xenograft tumors established from AR-overexpressed LNCaP cells. The engineered cells in Matrigel (Collaborative Biomedical) were injected subcutaneously into the flanks of the castrated male SCID mice. Tumor size was measured weekly in three dimensions using calipers. After xenograft tumors established (tumor size reached at least 40 mm^3), mice with tumors were randomized and treated with different doses of

compounds orally once daily. Consistent with clinical observation, current clinical drug bicalutamide did not inhibit growth of hormone refractory prostate cancer (same as vehicle) (Figure 7a). In contrast, example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) strongly inhibited growth of these tumors (Figure 7a) and the inhibition is dose-dependent (Figure 7b). Furthermore, example 7-3b (RD37) inhibited PSA expression (Figure 8), the clinical marker for hormone refractory prostate cancer.

[00167] Example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) was also tested in another xenograft model of hormone refractory prostate cancer, hormone refractory LAPC4. This model was established from passaging of hormone sensitive prostate cancer in castrated mice, which mimics the clinical progression of prostate cancer *(2)*. Similar to the finding using AR-overexpressed LNCaP xenograft model, current clinical drug bicalutamide did not inhibit growth and PSA expression in hormone refractory LAPC4 xenograft model (same as vehicle) (Figure 9a and 9b). In contrast, example 7-3b (RD37) strongly inhibited growth and PSA expression of these tumors (Figure 9a and 9b).

Inhibitory effect on growth of hormone sensitive prostate cancer cells.

[00168] To determine if the diarylthiahydantoin derivatives also inhibit hormone sensitive prostate cancer cells, we tested some selective compounds on growth of LNCaP cells by measuring MTS of mitochondria activities. In contrast to have no effect on growth of hormone refractory prostate cancer, the current clinical drug bicalutamide mildly inhibited hormone sensitive LNCaP cells in a dose-dependent manner. Example 5-3b (RD7) (4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile) and example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) inhibited hormone sensitive prostate cancer with a 10-fold higher potency than bicalutamide (Figure 10).

In vivo biological assay

[00169] All animal experiments were performed in compliance with the guidelines of the Animal Research Committee of the University of California at Los Angeles. Animals were bought from Taconic and maintained in a laminar flow tower in a defined flora colony. LNCaP-AR and LNCaP-vector cells were maintained in RPMI medium supplemented with 10% FBS. 10^6 cells in 100 µl of 1:1 Matrigel to RPMI medium were injected subcutaneously into the flanks of intact or castrated male SCID mice. Tumor size was measured weekly in three dimensions (length x width x depth) using calipers. Mice were randomized to treatment groups when tumor size reached approximately 100 mm^3. Drugs were given orally every day at 10 mg/kg and 50 mg/kg. To obtain pharmacodynamic readout, the animals were

imaged via an optical CCD camera, 3 hours after last dose of the treatment. A ROI is drawn over the tumor for luciferase activity measurement in photon/second. The right panels were a representation of the ROIs measurements. Data are shown in figures 11 and 12. Over 18 days RD162 was effective to prevent tumor growth and even to cause tumor shrinkage, and was distinctly more effective than bicalutamide.

[00170] The pharmacokinetics of bicalutamide, 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-toluene [RD37], *N*-methyl-4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}butanamide [RD131], and *N*-methyl-4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-2-fluorobenzamide (52d) [RD162] were evaluated in vivo using 8 week-old FVB mice which were purchased from Charles River Laboratories. Mice were divided into groups of three for each time points. Two mice were not treated with drug and two other mice were treated with vehicle solution. Each group was treated with 10 mg per kilogram of body weight.

[00171] The drug was dissolved in a mixture 1:5:14 of DMSO : PEG400 : H_20. (Vehicle solution) and was administered into mice through the tail vein. The animals are warmed under a heat lamp for approximately 20 minutes prior to treatment to dilate their tail vein. Each mouse was placed into a mouse restrainer (Fisher Sci. Cat# 01-288-32A) and was injected with 200 µl of drug in vehicle solution into the dilated tail vein. After drug administration, the animals were euthanized via CO_2 inhalation at different timepoints: 5 mn, 30 mn, 2 h, 6 h, 16 h. Animals were immediately bleed after exposure to CO_2 via cardiac puncture (1 ml BD syringe + 27G 5/8 needle). For oral dosage, the drug was dissolved in a mixture 50:10:1:989 of DMSO : Carboxymethylcellulose : Tween80:H20 before oral administration via a feeding syringe.

[00172] The serum samples were analyzed to determine the drug's concentration by the HPLC which (Waters 600 pump, Waters 600 controller and Waters 2487 detector) was equipped with an Alltima C18 column (3µ, 150 mm×4.6 mm). The RD37, RD131, and RD162 compounds were detected at 254 nm wave length and bicalutamide was detected at 270 nm wave length.

[00173] The samples for HPLC analysis were prepared according to the following procedure:

- Blood cells were separated from serum by centrifugation.

- To 400 µl of serum were added 80 µl of a 10 µM solution of an internal standard and 520 µl of acetonitrile. Precipitation occurred.

- The mixture was vortexed for 3 minutes and then placed under ultrasound for 30 minutes.

- The solid particles were filtered off or were separated by centrifugation.

- The filtrate was dried under an argon flow to dryness. The sample was reconstructed to 80 µl with acetonitrile before analyzing by HPLC to determine the drug concentration.

- Standard curve of drug was used to improve accuracy.

[00174] The concentration of RD162 in plasma as a function of time resulting from intravenous and from oral administration is shown in figure 13. The steady state concentration (Css) of bicalutamide, RD131, and RD162 is shown in Table 4. The concentration at steady state of RD162 is essentially as good as that of bicalutamide, and substantially better than RD131.

Name	IC50 [nM]	LogP	Css,10 mg/kg [µM]	Css,25 mg/kg [µM]	Css,50 mg/kg [µM]
Bic.	1000	2.91	10.0	11.4	11.9
RD131	92	3.44	0.39	0.43	0.40
RD162	122	3.20	9.9	10.7	10.2

Table 4. Steady-state concentration of bicalutamide, RD131, and RD162 in mice plasma.

Ranking of Compounds in Tiers

[00175] Tables 5 – 10 present diarylhydantoin compounds grouped into Tiers 1-6. Table 11 presents diarylhydantoin compounds which have not been placed into a tier. The placement of compounds into tiers was based on available data coupled with analytical judgment. Data considered included in vitro assays (AR response reporter system in LNCaP cell line, PSA level measurement, MTS mitochondrial assay) and in vivo experiments (tumor size measured directly or by emission induced by luciferase reporter gene, pharmacokinetic assays based on blood plasma levels). Not every compound was subjected to each assay. Not all data that was generated is shown. Judgment was applied in ranking compounds relative to each other for their utility in treating prostate cancer, in particular when ranking two compounds for which the same experiments were not performed. Characteristics considered in establishing the ranking include AR antagonism activity, lack of AR agonism in hormone refractory cells, prevention of tumor growth, tumor shrinkage, and pharmacokinetic behavior, with a longer residence time in blood being advantageous.

Tier 1

[00176] Generally, Tier 1 compounds are diarylthiohydantoins with a disubstituted left hand aryl ring that are disubstituted on the right hydantoin carbon, and have either an oxygen or N substituent on the left hydantoin carbon. It is expected that the amido substituent hydrolyzes to an oxygen in aqueous solutions such as encountered in biological systems, in vitro and in vivo. RD100 has good activity with an iodine instead of a CF_3 substituent on the left hand aryl ring.

[00177] Tier 1 compounds (see Table 5) were judged to be much better than bicalutamide for treating prostate cancer. However, RD37 and RD131 were found to metabolize fast, that is, have a short residence time in blood. RD162 had desirable pharmacokinetics.

[00178] Figure 17 shows that under treatment with bicalutamide, PSA levels for LNCaP cells stayed the same or increased relative to treatment with vehicle solution, whereas under treatment with RD162, PSA levels decreased. Figure 18 illustrates that under treatment with vehicle solution, tumors continued to increase in size. By contrast, under treatment with RD162 at a dose of 1 mg per kg body weight per day, the rate of tumor increase decreased, and the size of the tumor appeared to be stabilizing after about 17 days. Under treatment with RD162 at a dose of 10 mg per kg body weight per day, tumor size decreased with time. Figure 19 illustrates that under treatment with RD162 at a dose of 10 mg per kg body weight per day, photon emission associated with luciferase activity decreased. Figure 20 shows that treatment with RD162 at this dose resulted in a decrease or stabilization of tumor size and a decrease in photon emission associated with luciferase activity.

[00179] Figure 21 shows that under treatment with RD162, RD162', RD162", RD169, and RD170 at doses of 100, 200, 500, and 1000 nM, PSA levels of LN-AR cells decreased. Moreover, the higher the dose, the lower the PSA level. Figure 23 presents urogenital tract weight and rate of photon emission associated with luciferase activity initially and after 14 days of treatment with bicalutamide or with RD162 for intact and castrated mice. The weight and rate of photon emission increased for both intact and castrated mice. Treatment of castrated mice with RD162 resulted in a decrease in weight and photon emission with respect to the untreated castrated mice, as did treatment with bicalutamide.

[00180] Thus, Tier 1 compounds are particularly advantageous for use as AR antagonists, and as therapeutic agents for hormone refractory prostate cancer. They may be useful to treat other AR related diseases or conditions such as benign prostate hyperplasia, hair loss, and acne. These and related compounds may also be useful as modulators of other nuclear receptors, such as glucocorticoid receptor, estrogen receptor, and peroxisome proliferator-activated receptor, and as therapeutic agents for diseases in which nuclear receptors play a role, such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases. They may be useful in assays e.g. as standards, or as intermediates or prodrugs.

TABLE 5

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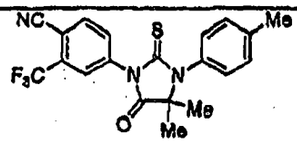
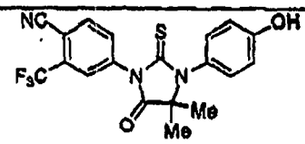
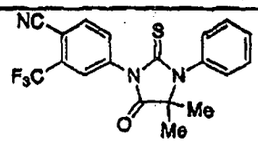
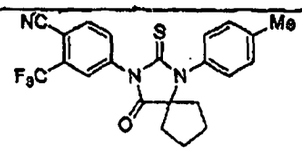
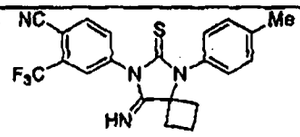
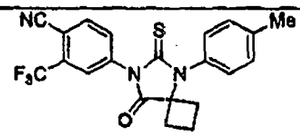
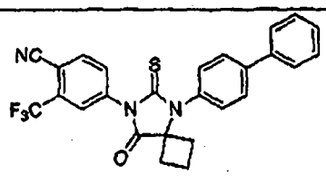
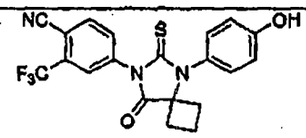
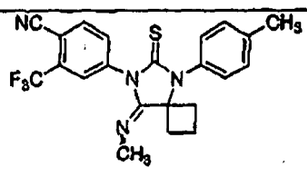
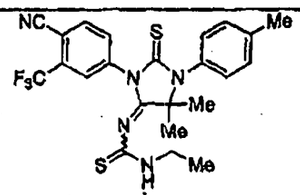
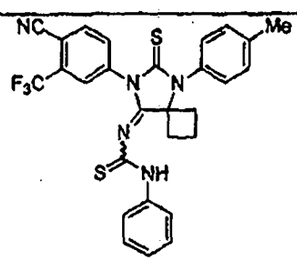
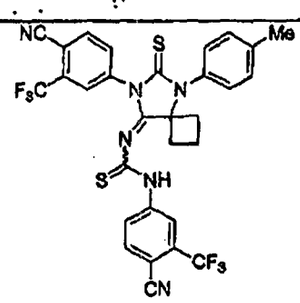
RD7 	RD8 
RD10 	RD35 
RD36 	RD37 
RD57 	RD58 
RD90 	RD91 
RD92 	RD93 

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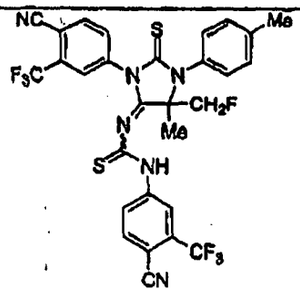
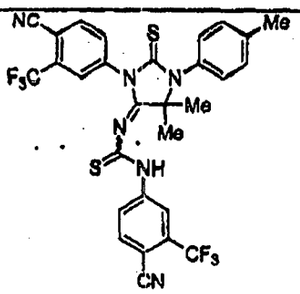
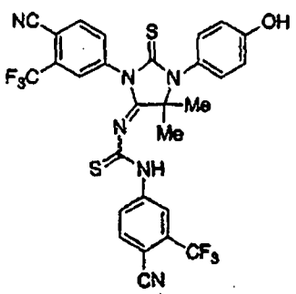
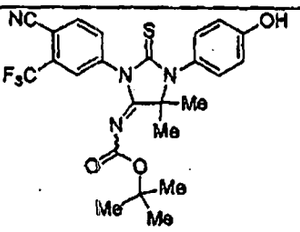
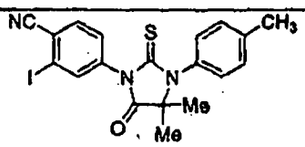
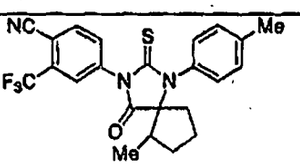
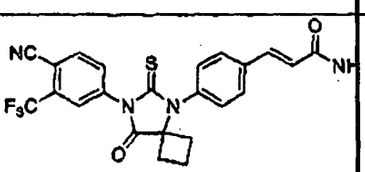
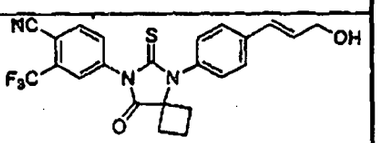
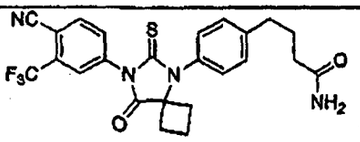
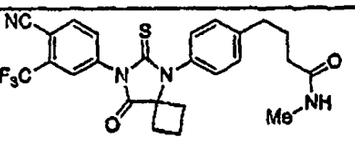
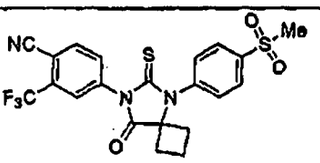
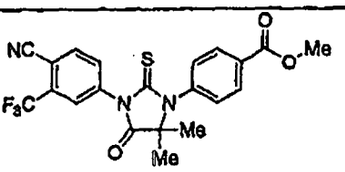
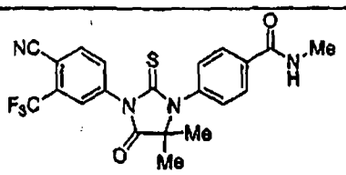
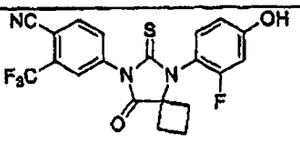
RD94 	RD95 
RD96 	RD97 
RD100 	RD102 
RD119 	RD120 
RD130 	RD131 
RD145 	RD152 
RD153 	RD163 

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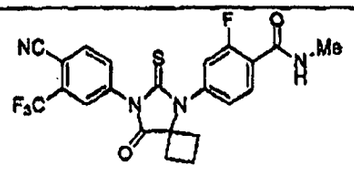
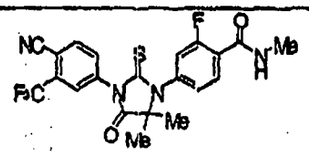
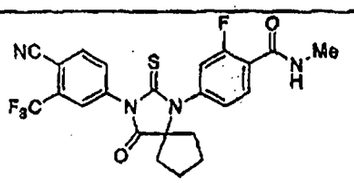
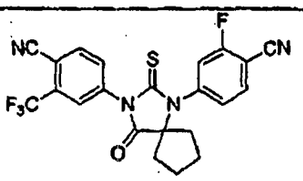
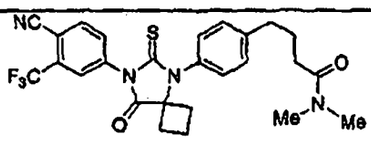
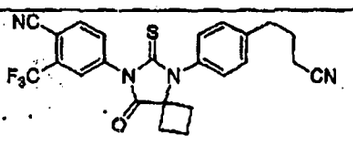
RD162		RD162'	
RD162"		RD168	
RD169		RD170	

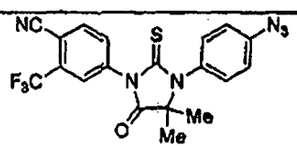
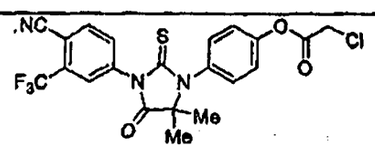
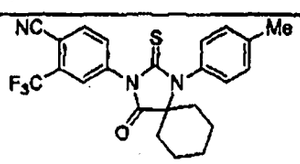
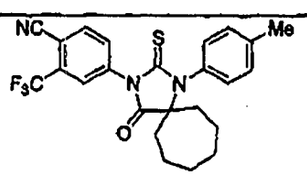
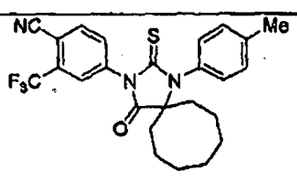
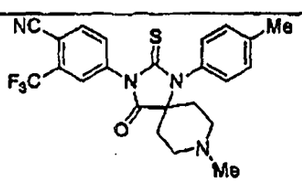
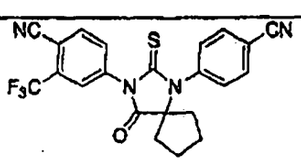
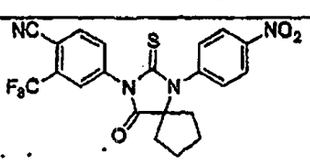
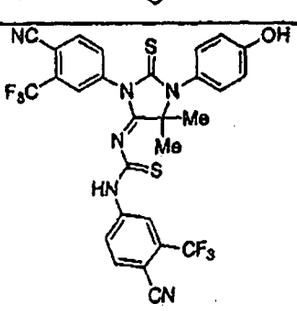
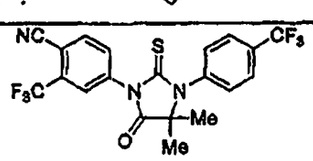
Tier 2

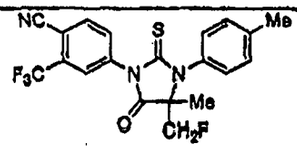
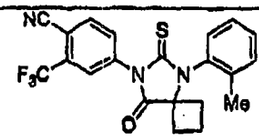
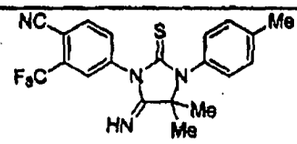
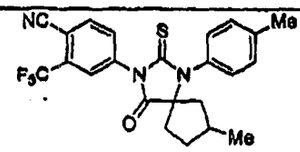
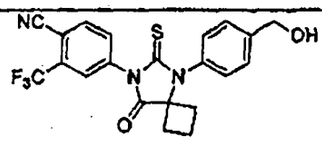
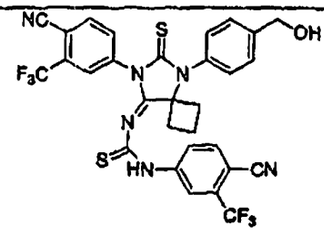
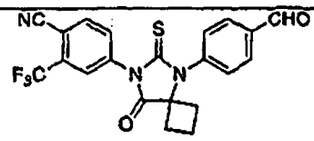
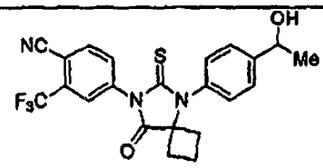
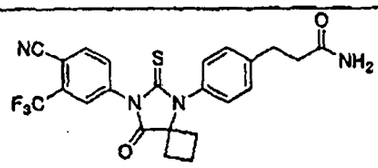
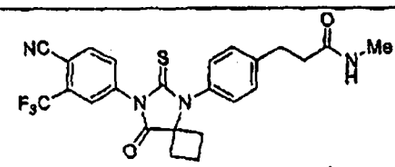
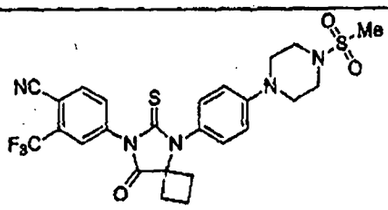
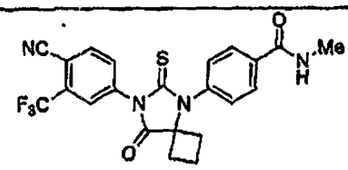
[00181] Tier 2 compounds (see Table 6) were significantly better than bicalutamide for treating prostate cancer, although there were indications that RD54 could act as an agonist. Figure 3 illustrates that compounds RD145, RD152, RD153, RD162, and RD163 in Tier 1 and RD161 in Tier 2 dosed at concentrations ranging from 125 nM to 1000 nM acted to reduce luciferase activity in LNCaP-AR cells whereas control solutions of DMSO and of bicalutamide had little or no effect. Figure 4 illustrates, for example, that at concentrations of 1000 nM, compounds RD37 and RD131, in Tier 1, caused a greater decrease in PSA level of LNCaP-AR cells than RD133, RD134, and RD138 in Tier 2. Figure 11 presents tumor volume over time, and illustrates that under treatment with bicalutamide or vehicle solution, tumors continued to grow, whereas under treatment with RD162, in Tier 1, tumors decreased in size. Figure 12 illustrates that photon emission associated with luciferase activity remained about the same or increased under treatment with bicalutamide relative to treatment with vehicle solution, whereas photon emission decreased under treatment with RD162. Figure 14 illustrates that under treatment with bicalutamide, there was little or no decrease in PSA levels, whereas under treatment with RD131 and RD162, PSA levels decreased. Figure 15 illustrates that the IC_{50} for RD37, RD 131, and RD162, in Tier 1, was much lower than the IC_{50} for bicalutamide.

[00182] Generally, Tier 2 compounds are structurally similar to Tier 1 compounds, but with different substituents on the right hand aryl ring. Tier 2 compounds are advantageous for use as AR antagonists, and as therapeutic agents for hormone refractory prostate cancer. They may be useful to treat other AR related diseases or conditions such as benign prostate hyperplasia, hair loss, and acne.

These and related compounds may also be useful as modulators of other nuclear receptors, such as estrogen receptor and peroxisome proliferator-activated receptor, and as therapeutic agents for diseases in which nuclear receptors play a role, such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases. They may be useful in assays e.g. as standards, or as intermediates or prodrugs.

TABLE 6

TIER 2 COMPOUNDS	
RD6  (comparative)	RD13 
RD48 	RD49 
RD51 	RD53 
RD54 	RD55 
RD63 	RD68 

TIER 2 COMPOUNDS	
RD88 	RD71 
RD87 	RD103 
RD110 	RD111 
RD114 	RD116 
RD133 	RD134 
RD138 	RD161 

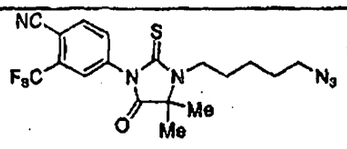
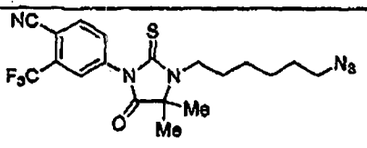
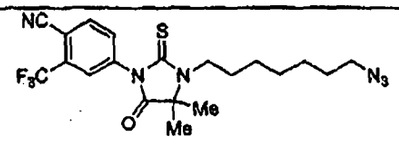
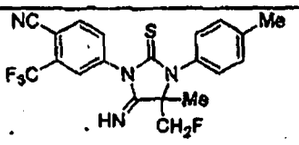
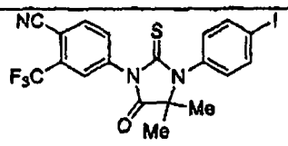
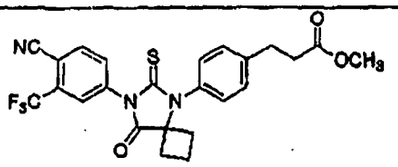
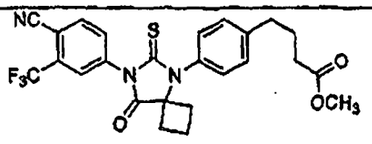
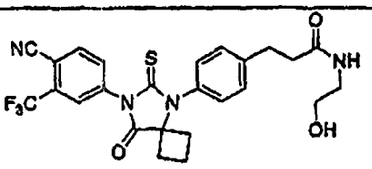
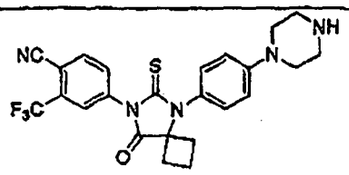
Tier 3

[00183] Tier 3 compounds (see Table 7) were judged to be slightly better than bicalutamide for treating prostate cancer. RD133, RD134, and RD138 (in Tier 2) caused a greater decrease in PSA level of LNCaP-AR cells than RD135 and RD137, in Tier 3. All of these compounds caused a greater decrease in PSA level than bicalutamide.

[00184] Other Tier 3 compounds (not shown) were not diarylthiohydantoins, and were comparable in activity to prior art monoarylhydantoin compounds RD2, RD4, and RD5.

[00185] Thus, Tier 3 compounds are useful as AR antagonists, and as therapeutic agents for hormone refractory prostate cancer. They may be useful to treat other AR related diseases or conditions such as benign prostate hyperplasia, hair loss, and acne. These and related compounds may also be useful as modulators of other nuclear receptors, such as estrogen receptor and peroxisome proliferator-activated receptor, and as therapeutic agents for diseases in which nuclear receptors play a role, such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases. They may be useful in assays e.g. as standards, or as intermediates or prodrugs.

TABLE 7

TIER 3 COMPOUNDS	
RD3  (comparative)	RD4  (comparative)
RD5  (comparative)	RD89 
RD127 	RD128 
RD129 	RD135 
RD137 	

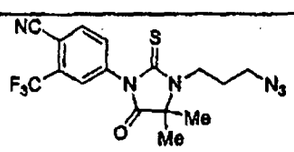
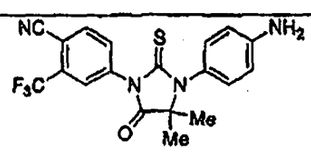
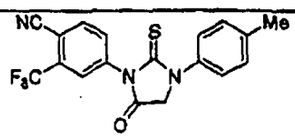
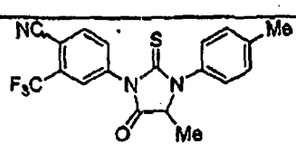
Tier 4

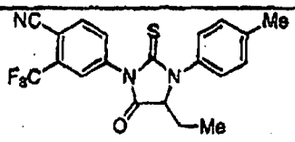
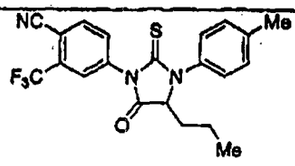
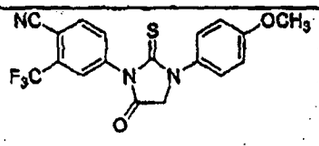
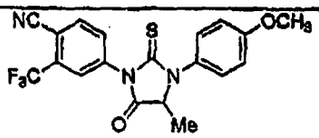
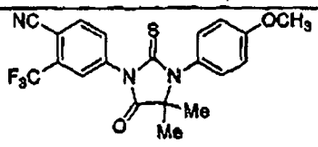
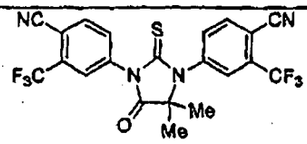
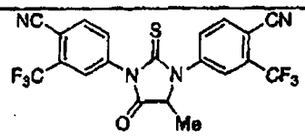
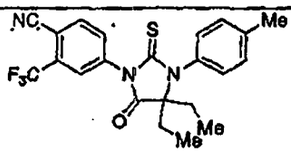
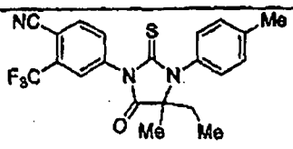
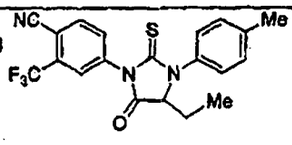
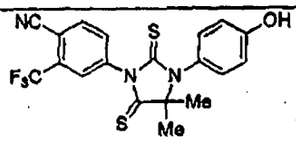
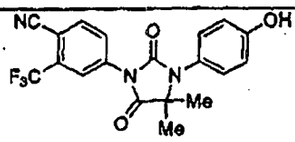
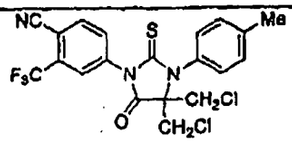
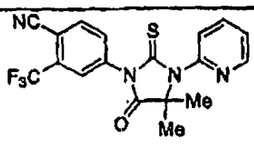
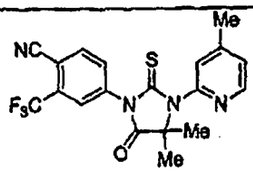
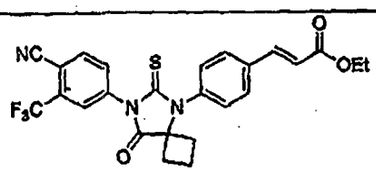
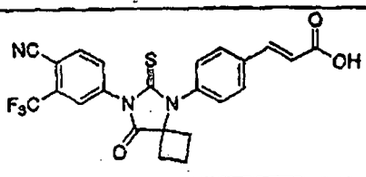
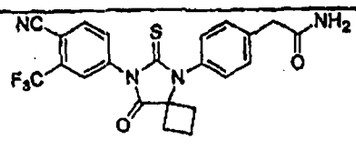
[00186] Tier 4 compounds (see Table 8) were judged to be no better than bicalutamide for treating prostate cancer. Tier 4 RD 39 and RD40 and Tier 1 RD37, for example, differ only in the substituent on the lower right carbon of the hydantoin ring. The substituents on the right hand aryl ring may also affect activity.

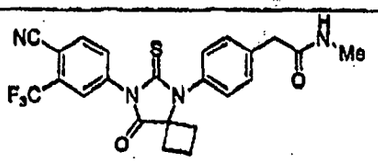
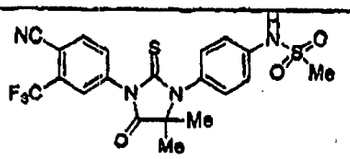
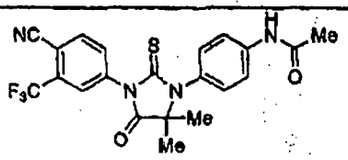
[00187] Some Tier 4 compounds (including those shown and others that are not shown) were not diaryl compounds (lacking the right hand aryl ring), were not thiohydantoins, were not disubstituted on the carbon on the lower right hand of the hydantoin ring, and/or had substituents other than oxygen or amido on the lower left hand carbon of the hydantoin ring. This provides evidence of the surprising advantages of diarylthiohydantoins that are disubstituted on the lower right hand carbon of the hydantoin ring and have oxygen or amido on the lower left hand carbon of the hydantoin ring.

Thus, Tier 4 compounds may be useful as AR antagonists, and as therapeutic agents for hormone refractory prostate cancer, at least to the extent that they are comparable to bicalutamide. They may be useful to treat other AR related diseases or conditions such as benign prostate hyperplasia, hair loss, and acne. These and related compounds may also be useful as modulators of other nuclear receptors, such as estrogen receptor and peroxisome proliferator-activated receptor, and as therapeutic agents for diseases in which nuclear receptors play a role, such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases. They may be useful in assays e.g. as standards, or as intermediates or prodrugs.

TABLE 8

TIER 4 COMPOUNDS	
RD2  (comparative)	RD9 
RD21 	RD22 

TIER 4 COMPOUNDS	
RD23 	RD24 
RD25 	RD26 
RD27 	RD30 
RD31 	RD39 
RD40 	RD44 
RD59 	RD60 
RD67 	RD82 
RD83 	RD117 
RD118 	RD148 

TIER 4 COMPOUNDS	
RD149 	RD150 
RD151 	

Tier 5

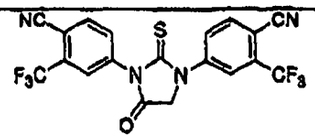
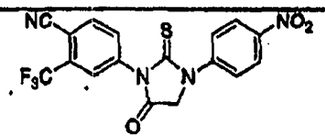
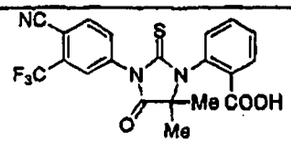
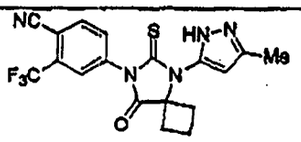
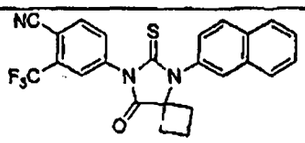
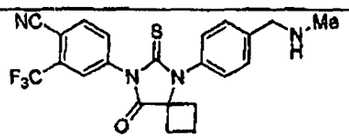
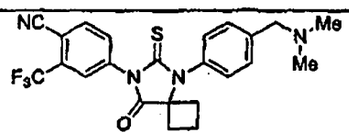
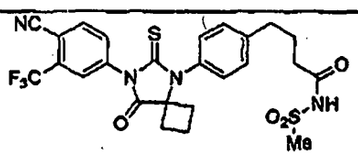
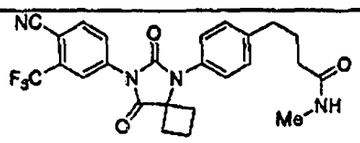
[00188] Tier 5 compounds (see Table 9) were inactive or nearly inactive, and thus, were worse than bicalutamide for treating prostate cancer. The substituents on the right hand aryl ring are important to determining activity.

[00189] Some Tier 5 compounds (some of which are shown and some that are not shown) were not diaryl compounds (lacking the right hand aryl ring), were not thiohydantoins, were not disubstituted on the carbon on the lower right hand of the hydantoin ring, and/or had substituents other than oxygen or amido on the lower left hand carbon of the hydantoin ring. This provides evidence of the surprising advantages of diarylthiohydantoins that are disubstituted on the lower right hand carbon of the hydantoin ring and have oxygen or amido on the lower left hand carbon of the hydantoin ring. In particular, the terminal substituent in RD155, RD 156, and 158 ($CH_2NR_xR_y$, where $R_{x,y}$ = H or methyl) is not seen as contributing to activity in these compounds.

[00190] Tier 5 compounds would not be desirable for treatment of prostate cancer or as AR antagonists, although these and related compounds may be useful as modulators of other nuclear receptors, such as estrogen receptor and peroxisome proliferator-activated receptor, and as therapeutic agents for diseases in which nuclear receptors play a role, such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases. They may be useful in assays e.g. as standards, or as intermediates or prodrugs.

TABLE 9

TIER 5 COMPOUNDS

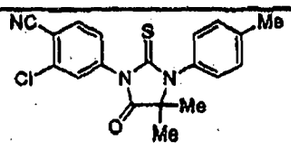
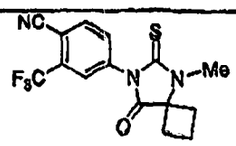
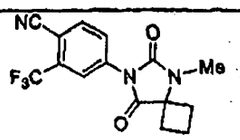
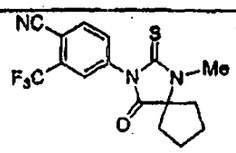
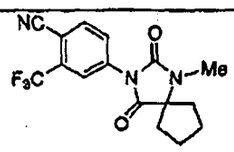
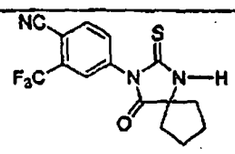
TIER 5 COMPOUNDS	
RD32 	RD33 
RD85 	RD84 
RD85 	RD155 
RD158 	RD157 
RD158 	

Tier 6

[00191] Tier 6 compounds (see Table 10) were inactive or nearly inactive, and furthermore were strong agonists, and thus were much worse than bicalutamide for treating prostate cancer. The comparative compounds ranked very poor relative to the inventive compounds. Notably, RD72 had very poor activity, with a chlorine substituent on the left hand aryl ring, whereas RD7, with a trifluoromethane, and RD100, with iodine, ranked in Tier 1. The results for the Tier 6 compounds provide evidence of the surprising advantages of diarylthiohydantoins that are disubstituted on the lower right hand carbon of the hydantoin ring and have oxygen or amido on the lower left hand carbon of the hydantoin ring, and have certain substituents on the left hand aryl ring.

[00192] Tier 6 compounds would not be desirable for treatment of prostate cancer or as AR antagonists.

TABLE 10

TIER 6 COMPOUNDS	
RD72 	RD73  (comparative)
RD74  (comparative)	RD75 
RD76  (comparative)	RD77 

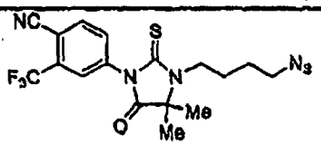
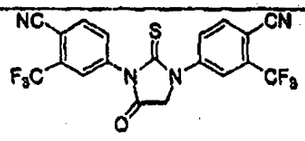
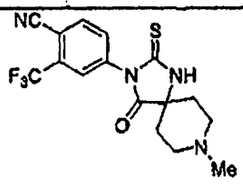
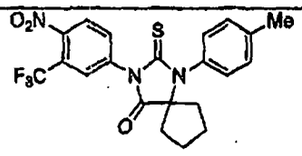
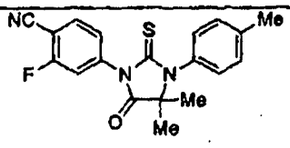
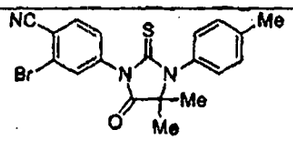
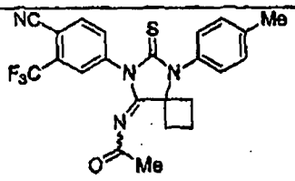
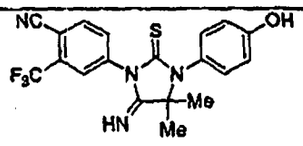
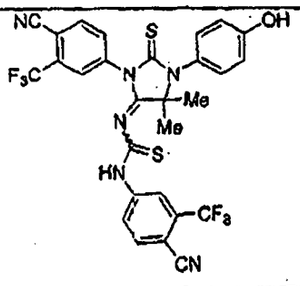
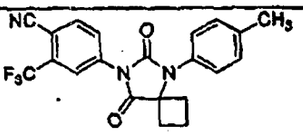
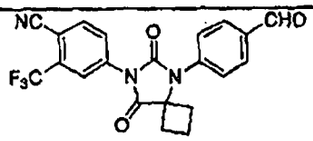
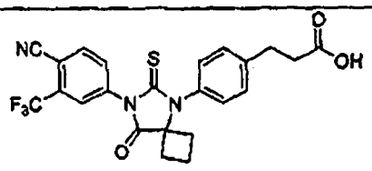
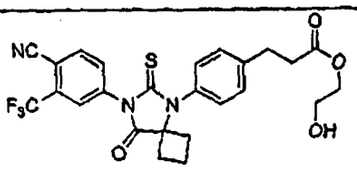
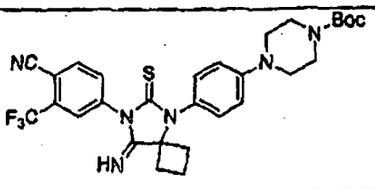
Untiered compounds

[00193] For several compounds, there was insufficient experimental data to rank them. These untiered compounds are presented in Table 11.

[00194] Based on the data and methods of the invention, and applying judgment based on review of many compounds, including some not shown here, one can make some observations about the untiered compounds. Comparative example RD1 is expected to be in Tier 3 with comparative examples RD3-RD5. RD89 is expected to hydrolyze to RD37 (Tier 1), and should therefore have comparable activity. RD104 is expected to hydrolyze to RD58 (Tier 1), and should therefore have comparable activity. RD105 is expected to hydrolyze to RD8 (Tier 1), and RD 139 and RD140 are expected to hydrolyze to RD138 (Tier 2), and they should therefore have comparable activity.

TABLE 11

UNTIERED COMPOUNDS

UNTIERED COMPOUNDS	
RD1  (comparative)	RD19 
RD52 	RD79 
RD80 	RD81 
RD89 	RD104 
RD105 	RD106 
RD115 	RD132 
RD136 	RD139 

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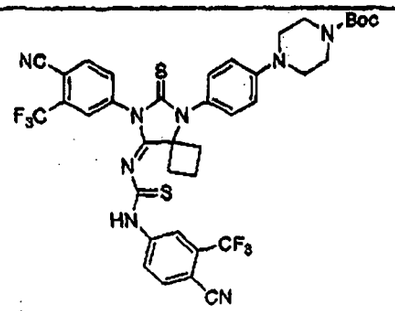
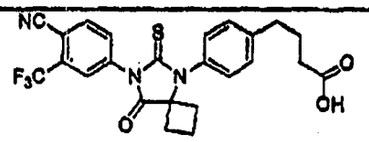
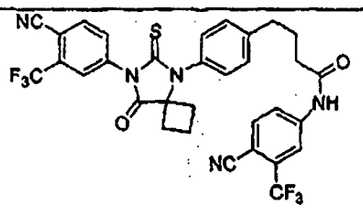
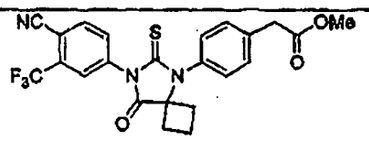
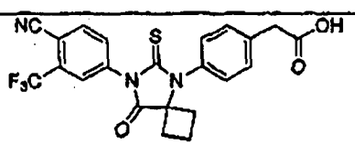
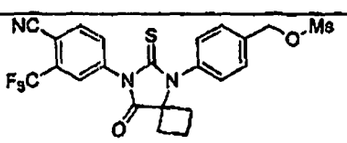
RD140 	RD141 
RD142 	RD148 
RD147 	RD154 

[00195] In short, novel compounds which show evidence of being far superior to bicalutamide in treating prostate cancer were identified and produced.

Sensitivity of Anti-Cancer Activity of Compounds to Structural Differences

[00196] The inventors have determined that what might appear to be a small change in the structure of hydantoin compounds may result in a large change in that compound's performance in treating prostate cancer. For example, RD161 and RD162 differ only by a single fluorine substituent on an aryl ring, and RD162 is in Tier 1, while RD161 is in Tier 2, both being better than bicalutamide for the treatment of prostate cancer, but RD162 being superior. However, RD149, which differs from RD 161 only in having an additional carbon atom between the methylcarbamoyl group and the aryl ring, is no better than bicalutamide for the treatment of prostate cancer and is ranked in Tier 4. The effect of RD161, RD162, and RD149 on luciferase activity can be seen in Figure 24. At a given concentration of compound, the luciferase activity upon exposure to RD161 and RD162 is less than the luciferase activity upon exposure to RD149.

[00197] RD9 differs from RD8 only in that an amino group is substituted for a hydroxyl group. However, whereas RD8 is in Tier 1, much better than bicalutamide for the treatment of prostate cancer, RD9 is in Tier 4, no better than bicalutamide. The effect of RD8 and RD9 on luciferase activity in the 1AR cell line can be seen in Figure 27. For a given dose, the luciferase activity upon exposure to RD8 is less than the luciferase activity upon exposure to RD9. The effect of RD8 and RD9 on luciferase activity in the 4AR cell line can be seen in Figure 26. For a given dose, the luciferase activity upon exposure to RD8 is less than the luciferase activity upon exposure to RD9. The effect of RD8 and RD9 on PSA levels in the LN/AR cell line can be seen in Figure 25. For a given dose, the PSA level upon exposure to RD8 is less than the PSA level upon exposure to RD9.

[00198] RD130 and RD131 differ from each other only by a methyl substituent on the end of a carbamoyl group and both compounds are ranked in Tier 1, although RD131 has been found to be particularly advantageous. RD129 is similar to RD130, with the exception of a methoxy group being substituted for an amino group. However, RD129 is ranked in Tier 3. RD128 is similar to RD129, but has one less carbon in the chain linking the carbamoyl to the aryl ring; RD128 is ranked in Tier 3. The effect of RD130, RD131, RD128, and RD129 on PSA levels in the LN/AR cell line can be seen in Figure 28. For a given concentration, the PSA level upon exposure to RD130 and RD131 is less than the PSA level upon exposure to RD128 and RD129.

[00199] RD153 and RD155 differ from each other in that the former has a methylcarbamoyl group attached to an aryl ring and a dimethyl substituent attached to the thiohydantoin group, whereas the latter has a methylamino group attached to the right hand aryl ring and a cyclobutyl substituent attached to the thiohydantoin group. Whereas RD153 is in Tier 1, much better than bicalutamide for the treatment of prostate cancer, RD155 is in Tier 5, inactive or nearly inactive in the treatment of prostate cancer. The effect of RD153 and RD155 on luciferase activity in the LN/AR cell line can be seen in Figure 29. For a given concentration, the luciferase activity upon exposure to RD153 is less than the luciferase activity upon exposure to RD155.

[00200] RD58 and RD60 differ from each other in the substitution of a thio for an oxo group and a dimethyl substituent for a cyclobutyl substituent. Whereas RD58 is in Tier 1, RD60 is in Tier 4.

Pharmaceutical Compositions and Administration

[00201] The compounds of the invention are useful as pharmaceutical compositions prepared with a therapeutically effective amount of a compound of the invention, as defined herein, and a pharmaceutically acceptable carrier or diluent.

[00202] The diarylhydantoin compounds of the invention can be formulated as pharmaceutical

compositions and administered to a subject in need of treatment, for example a mammal, such as a human patient, in a variety of forms adapted to the chosen route of administration, for example, orally, nasally, intraperitoneally, or parenterally, by intravenous, intramuscular, topical or subcutaneous routes, or by injection into tissue.

[00203] Thus, diarylhydantoin compounds of the invention may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier, or by inhalation or insufflation. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the diarylhydantoin compounds may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The diarylhydantoin compounds may be combined with a fine inert powdered carrier and inhaled by the subject or insufflated. Such compositions and preparations should contain at least 0.1% diarylhydantoin compounds. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of a given unit dosage form. The amount of diarylhydantoin compounds in such therapeutically useful compositions is such that an effective dosage level will be obtained.

[00204] The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the diarylhydantoin compounds may be incorporated into sustained-release preparations and devices. For example, the diarylhydantoin compounds may be incorporated into time release capsules, time release tablets, and time release pills.

[00205] The diarylhydantoin compounds may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the diarylhydantoin compounds can be prepared

in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

[00206] The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the diarylhydantoin compounds which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00207] Sterile injectable solutions are prepared by incorporating the diarylhydantoin compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

[00208] For topical administration, the diarylhydantoin compounds may be applied in pure form. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

[00209] Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Other solid carriers include nontoxic polymeric nanoparticles or microparticles. Useful liquid carriers include water, alcohols or glycols or water/alcohol/glycol blends, in which the diarylhydantoin compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using

pump-type or aerosol sprayers.

[00210] Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

[00211] Examples of useful dermatological compositions which can be used to deliver the diarylhydantoin compounds to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508), all of which are hereby incorporated by reference.

[00212] Useful dosages of the compounds of formula I can be determined by comparing their in vitro activity, and in vivo activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949, which is hereby incorporated by reference.

[00213] For example, the concentration of the diarylhydantoin compounds in a liquid composition, such as a lotion, can be from about 0.1-25% by weight, or from about 0.5-10% by weight. The concentration in a semi-solid or solid composition such as a gel or a powder can be about 0.1-5% by weight, or about 0.5-2.5% by weight.

[00214] The amount of the diarylhydantoin compounds required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

[00215] Effective dosages and routes of administration of agents of the invention are conventional. The exact amount (effective dose) of the agent will vary from subject to subject, depending on, for example, the species, age, weight and general or clinical condition of the subject, the severity or mechanism of any disorder being treated, the particular agent or vehicle used, the method and scheduling of administration, and the like. A therapeutically effective dose can be determined empirically, by conventional procedures known to those of skill in the art. See, *e.g.*, *The Pharmacological Basis of Therapeutics*, Goodman and Gilman, eds., Macmillan Publishing Co., New York. For example, an effective dose can be estimated initially either in cell culture assays or in suitable animal models. The animal model may also be used to determine the appropriate concentration ranges and routes of administration. Such information can then be used to determine useful doses and routes for administration in humans. A therapeutic dose can also be selected by analogy to dosages for comparable

therapeutic agents.

[00216] The particular mode of administration and the dosage regimen will be selected by the attending clinician, taking into account the particulars of the case *(e.g.,* the subject, the disease, the disease state involved, and whether the treatment is prophylactic). Treatment may involve daily or multi-daily doses of compound(s) over a period of a few days to months, or even years.

[00217] In general, however, a suitable dose will be in the range of from about 0.001 to about 100 mg/kg, e.g., from about 0.01 to about 100 mg/kg of body weight per day, such as above about 0.1 mg per kilogram, or in a range of from about 1 to about 10 mg per kilogram body weight of the recipient per day. For example, a suitable dose may be about 1 mg/kg, 10 mg/kg, or 50 mg/kg of body weight per day.

[00218] The diarylhydantoin compounds are conveniently administered in unit dosage form; for example, containing 0.05 to 10000 mg, 0.5 to 10000 mg, 5 to 1000 mg, or about 100 mg of active ingredient per unit dosage form.

[00219] The diarylhydantoin compounds can be administered to achieve peak plasma concentrations of, for example, from about 0.5 to about 75 μM, about 1 to 50 μM, about 2 to about 30 μM, or about 5 to about 25 μM. Exemplary desirable plasma concentrations include at least or no more than 0.25, 0.5, 1, 5, 10, 25, 50, 75, 100 or 200 μM. For example, plasma levels may be from about 1 to 100 micromolar or from about 10 to about 25 micromolar. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the diarylhydantoin compounds, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the diarylhydantoin compounds. Desirable blood levels may be maintained by continuous infusion to provide about 0.00005 - 5 mg per kg body weight per hour, for example at least or no more than 0.00005, 0.0005, 0.005, 0.05, 0.5, or 5 mg/kg/hr. Alternatively, such levels can be obtained by intermittent infusions containing about 0.0002 - 20 mg per kg body weight, for example, at least or no more than 0.0002, 0.002, 0.02, 0.2, 2, 20, or 50 mg of the diarylhydantoin compounds per kg of body weight.

[00220] The diarylhydantoin compounds may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator.

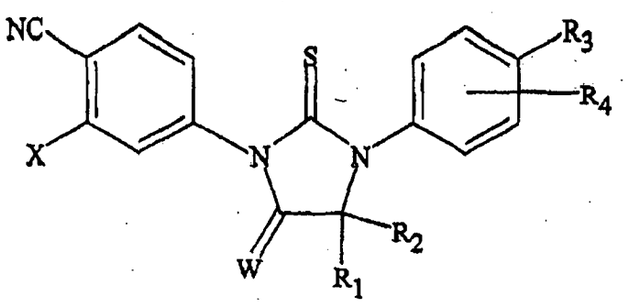
[00221] A number of the above-identified compounds exhibit little or no agonistic activities with respect to hormone refractory prostate cancer cells. Because these compounds are strong AR inhibitors, they can be used not only in treating prostate cancer, but also in treating other AR related diseases or conditions such as benign prostate hyperplasia, hair loss, and acne. Because AR belongs to

the family of nuclear receptors, these compounds may serve as scaffolds for drug synthesis targeting other nuclear receptors, such as estrogen receptor and peroxisome proliferator-activated receptor. Therefore, they may be further developed for other diseases such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases, in which nuclear receptors play a role.

[00222] The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present invention. All examples presented are representative and non-limiting. The above-described embodiments of the invention may be modified or varied, without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.

CLAIMS

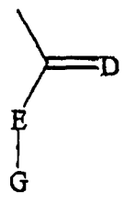
Claim 1. A compound having the formula



wherein X is selected from the group consisting of trifluoromethyl and iodo,

wherein W is selected from the group consisting of O and NR5,

wherein R5 is selected from the group consisting of H, methyl, and



wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or D is S or O and E-G together are C1-C4 lower alkyl,

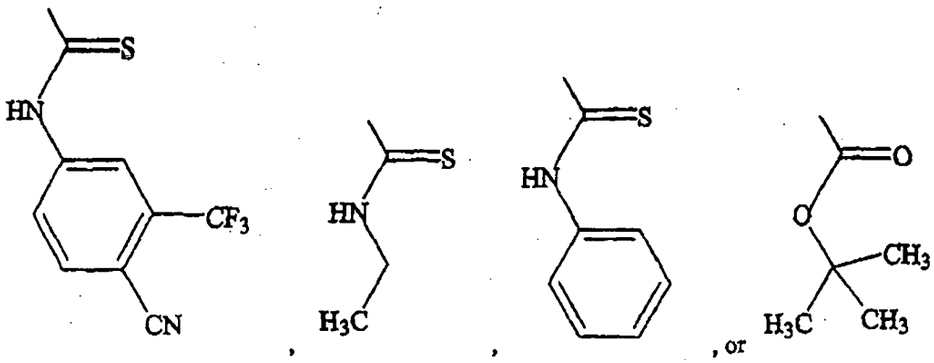
wherein R1 and R2 together comprise eight or fewer carbon atoms and are selected from the group consisting of alkyl, substituted alkyl including haloalkyl, and, together with the carbon to which they are linked, a cycloalkyl or substituted cycloalkyl group,

wherein R3 is selected from the group consisting of hydrogen, halogen, methyl, C1-C4 alkoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methoxycarbonyl, acetamido, methanesulfonamino, methanesulfonyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, and C1-C6 alkyl or alkenyl optionally substituted with hydroxyl, methoxycarbonyl, cyano, amino, amido, nitro, carbamoyl, or substituted carbamoyl including methylcarbamoyl, dimethylcarbamoyl, and hydroxyethylcarbamoyl,

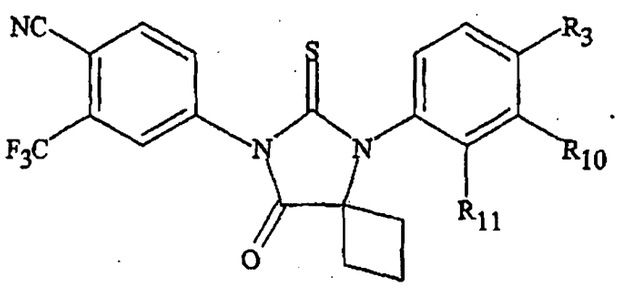
wherein R4 is selected from the group consisting of hydrogen, halogen, alkyl, and haloalkyl,

wherein R3 is not methylaminomethyl or dimethylaminomethyl.

Claim 2. The compound of claim 1, wherein R5 is



Claim 3. The compound of claim 1, having the formula



wherein R3 is selected from the group consisting of hydroxy, methylcarbamoyl, methylcarbamoylpropyl, methylcarbamoylethyl, methylcarbamoylmethyl, methylsulfonecarbamoylpropyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, carbamoylmethyl, carbamoylethyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoylpropyl, carboxypropyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, methoxycarbonyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, hydroxyethylcarbamoylethyl, and hydroxyethoxycarbonylethyl, and

wherein R10 and R11 are both H or, respectively, F and H, or H and F.

Claim 4. The compound of claim 3, wherein R10 and R11 are both H.

Claim 5. The compound of claim 3, wherein R10 and R11 are, respectively, F and H.

Claim 6. The compound of claim 3, wherein R3 is methylcarbamoyl.

Claim 7. The compound of claim 3, wherein R3 is methylcarbamoyl and R10 and R11 are, respectively, F and H.

Claim 8. The compound of claim 1,

wherein R1 and R2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms, and

R3 is selected from the group consisting of carbamoyl, alkylcarbamoyl, carbamoylalkyl, and alkylcarbamoylalkyl, and R4 is H or F.

Claim 9. The compound of claim 8, wherein R4 is 3-fluoro.

Claim 10. The compound of claim 1,

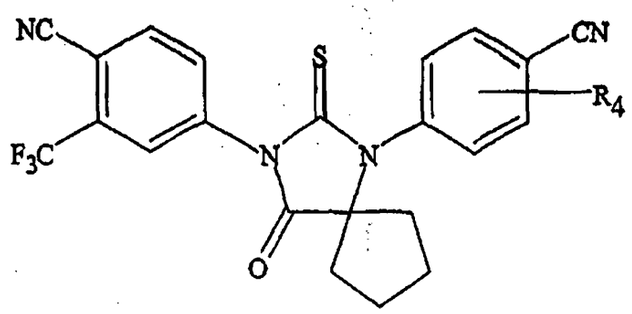
wherein R1 and R2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms,

R3 is selected from the group consisting of cyano, hydroxy, methylcarbamoyl, methylcarbamoyl-substituted alkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, acetamido, methanesulfonamido, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-(1,1-dimethylethoxy)carbonyl)-1-piperazinyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyethoxycarbonyl-substituted alkyl, and 3-cyano-4-trifluoromethylphenylcarbamoyl, and R4 is F.

Claim 11. The compound of claim 1, having the formula

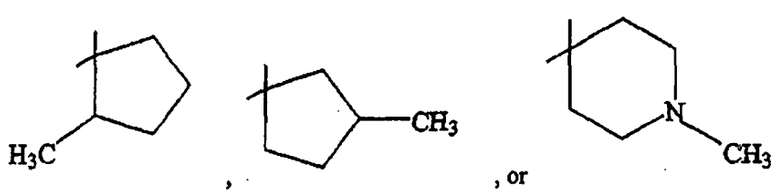
wherein R3 is selected from the group consisting of methylcarbonyl, methoxycarbonyl, acetamido, and methanesulfonamido, and R4 is selected from the group consisting of F and H.

Claim 12. The compound of claim 1, having the formula



wherein R4 is selected from the group consisting of F and H.

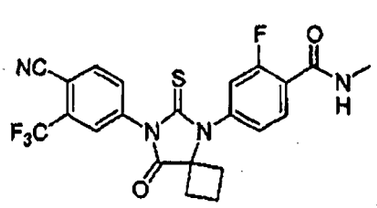
Claim 13. A compound according to claim 1, wherein R1 and R2 together with the carbon to which they are linked are



, or

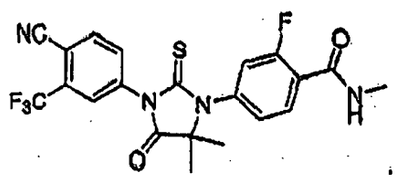
Claim 14. A compound selected from the compounds of Tier 1 and Tier 2.

Claim 15. The compound of claim 1, having the formula



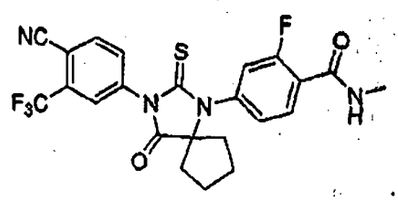
[RD162]

Claim 16. The compound of claim 1, having the formula



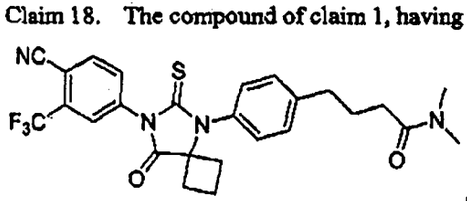
[RD162']

Claim 17. The compound of claim 1, having the formula



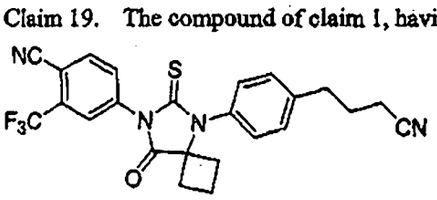
[RD162"]

Claim 18. The compound of claim 1, having the formula



[RD169]

Claim 19. The compound of claim 1, having the formula



[RD170]

Claim 20. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-19 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

Claim 21. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

Claim 22. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

23. A pharmaceutical composition as claimed in claim 20 or 21 or wherein said compound is in an amount equivalent to a dosage amount of from about 0.001 mg per kg body weight per day to about 100 mg per kg body weight per day for treatment of hyperproliferative disorder.

24. A pharmaceutical composition as claimed in claim 20 or 21 wherein said compound is in an amount equivalent to a dosage amount of from about 0.01 mg per kg body weight per day to about 100 mg per kg body weight per day.

25. A pharmaceutical composition as claimed in claim 20 or 21 wherein said compound is in an amount equivalent to a dosage amount of from about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day.

26. A pharmaceutical composition as claimed in claim 20 or 21 wherein said compound is in an amount equivalent to a dosage amount of about 1 mg per kg body weight per day.

27. The pharmaceutical composition as claimed in claim 21, wherein the compound is in a form that can be administered as an intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally.

28. The composition of claim 27, wherein the composition is administered orally

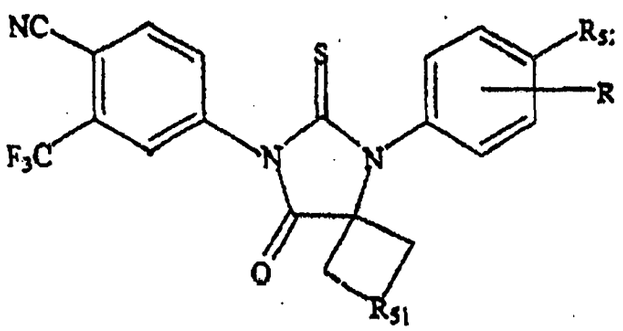
29. The pharmaceutical composition as claimed in claim 21, wherein the composition has a form selected from the group consisting of a solution, dispersion, suspension, powder, capsule, tablet, pill, time release capsule, time release tablet, and time release pill.

30. The pharmaceutical composition as claimed in claim 28, wherein the composition has a form selected from the group consisting of a capsule, tablet, and pill.

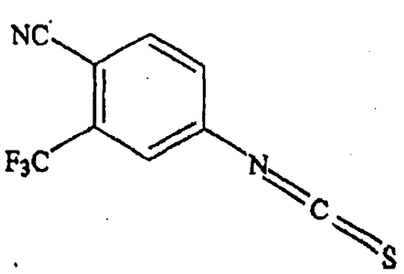
31. The pharmaceutical composition as claimed in claim 28, wherein the compound is selected from the group consisting of RD162', RD162", RD 169, or RD170, or a pharmaceutically acceptable salt thereof.

32. The pharmaceutical composition as claimed in claim 28, wherein the compound is N-methyl-4-[7-(4-cyano-3- trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-2-fluorobenzamide [RD162] or a pharmaceutically acceptable salt thereof.

33. A method of synthesizing a diaryl compound of formula:

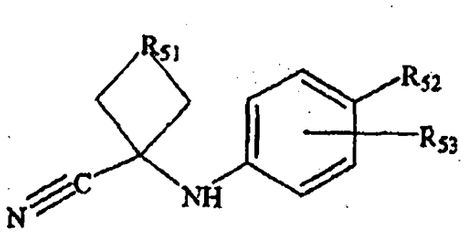


comprising mixing Compound I



Compound I

with Compound II

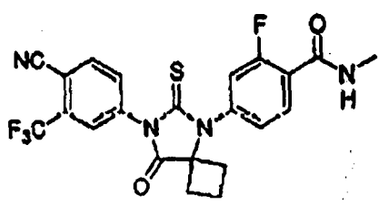


in a first polar solvent to form a mixture, heating the mixture, adding a second polar solvent, the same as or different from the first polar solvent, and an aqueous acid to the mixture, refluxing the mixture, cooling the mixture and combining with water, and separating the diaryl compound from the mixture, wherein R51 comprises an alkyl chain of from 1 to 4 carbon atoms, R52 is selected from the group consisting of cyano, hydroxy, methylcarbamoyl, methylcarbamoyl-substituted alkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, carbamoyl- substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3- trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-methanesulfonyl-1- piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, and

hydroxyethoxycarbonyl- substituted alkyl, and R53 is selected from the group consisting of F and H.

34. The method of claim 31, wherein R51 comprises an alkyl chain of from 1 to 2 carbon atoms, R52 is selected from the group consisting of carbamoyl and methylcarbamoyl, and R53 is F.

35. A method of synthesizing a compound of formula:



[RD 162]

comprising mixing 4-isothiocyanato-2-trifluoromethylbenzonitrile and N-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide in dimethylformamide to form a first mixture, heating the first mixture to form a second mixture, adding alcohol and acid to the second mixture to form a third mixture, refluxing the third mixture to form a fourth mixture, cooling the fourth mixture, combining the fourth mixture with water and extracting an organic layer; isolating the compound from the organic layer.

36. A method of synthesizing the compound of claim 16 [RD 162'] , comprising mixing N-Methyl-2-fluoro-4-(1,1-dimethyl-cyanomethyl)-aminobenzamide and 4- Isothiocyanato-2-trifluoromethylbenzonitrile in DMF and heating to form a first mixture; adding an alcohol and an acid to the first mixture to form a second mixture; refluxing the second mixture; cooling the second mixture, combining the second mixture with water and extracting an organic layer; isolating the compound from the organic layer.

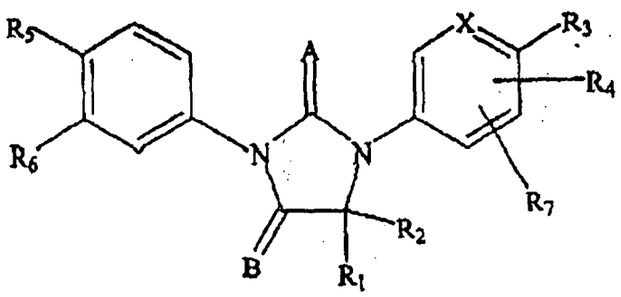
37. A method of synthesizing the compound of claim 17 [RD162"], comprising mixing N-Methyl-2-fluoro-4-(1 -cyanocyclopentyl)aminobenzamide, 4-isothiocyanato-2- trifluoromethyl benzonitrile, and DMF and heating under reflux to form a first mixture; adding an alcohol and an acid to the first mixture to form a second mixture; refluxing the second mixture; cooling the second mixture;

combining the second mixture with water and extracting an organic layer; isolating the compound from the organic layer.

38. A method of synthesizing the compound of claim 18 [RD 169], comprising mixing N,N-Dimethyl 4-[4-(1-cyanocyclobutylamino)phenyl]butanamide, 4-isothiocyanato-2- trifluoromethyl benzonitrile, and DMF and heating under reflux to form a first mixture; adding an alcohol and an acid to the first mixture to form a second mixture; refluxing the second mixture; cooling the second mixture; combining the second mixture with water and extracting an organic layer; isolating the compound from the organic layer.

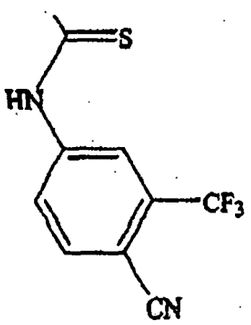
39. A method of synthesizing the compound of claim 19[RD170], comprising mixing DMSO, dichloromethane, and oxalyl chloride to form a first mixture, adding 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5- yl)phenyl)butanamide to the first mixture to form a second mixture; adding triethylamine to the second mixture to form a third mixture; warming the third mixture and quenching with aqueous NH_4Cl to form a fourth mixture; extracting an organic layer from the fourth mixture; isolating the compound from the organic layer.

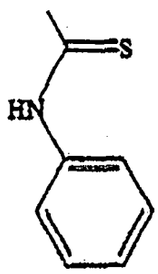
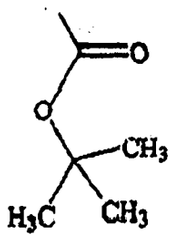
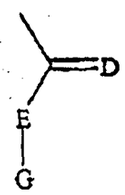
40. A compound having the formula



wherein R_5 is CN or NO_2 or SO_2Rn, wherein R_6 is CF_3, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated akynyl, halogen, wherein A is sulfur (S) or oxygen (O),

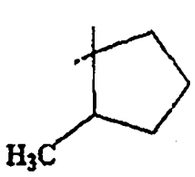
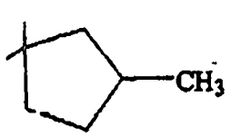
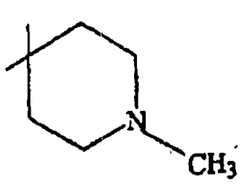
wherein B is O or S or NR_8, wherein R_8 is selected from the group consisting of H, methyl, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, SO_2R_n, $NRnRi_2$, $(CO)OR_{11}$, $(CO)NR_{11}R_{12}$, $(CO)R_{11}$, $(CS)R_{11}$, $(CS)NR_{11}R_{12}$, $(CS)OR_{11}$,




, and

, and


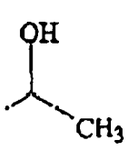
wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or

D is S or O and E-G together are C1-C4 lower alkyl, wherein RI and R2 are independently alkyl, haloalkyl, hydrogen, aryl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkenyl, halogenated akynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocylic aromatic or non-aromatic, substituted heterocyclic aromatic or non- aromatic, cycloalkyl, substituted cycloalkyl, or R_1 and R_2 are connected to form a cycle which can be heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl,



, or


wherein X is carbon or nitrogen and can be at any position in the ring, and wherein R3, R4, and R7 are independently selected from the group consisting of hydrogen, halogen, methyl, methoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methylcarbamoyl-substituted alkyl, dimethylcarbamoyl-substituted alkyl,

methoxycarbonyl, acetamido, methanesulfonamino, carbamoyl-substituted alkyl, methanesulfonyl, 4- methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyl- substituted alkyl, hydroxyl-substituted alkenyl, carbamoyl-substituted alkenyl, methoxycarbonyl-



substituted alkyl, cyano-substituted alkyl,

, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkenyl, halogenated alkynyl, SO_2R_{11}, $NR_{11}R_{12}$, $NR_{12}(CO)OR_{11}$, $NH(CO)NR_{11}R_{12}$, $NR_{12}(CO)R_{11}$, $0(CO)R_{11}$, $0(CO)OR_{11}$, $0(CS)R_{11}$, $NR_{12}(CS)R_{11}$, $NH(CS)NR_{11}R_{12}$, $NR_{12}(CS)OR_{11}$, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, haloalkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, acetamido, methanesulfonamido, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3- trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-(l,l- dimethylethoxy)carbonyl)- 1 -piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyethoxycarbonyl-substituted alkyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, wherein R_{11} and R_{12} are independently hydrogen, aryl, aralkyl, substituted aralkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, or substituted cycloalkyl, or R_{11} and R_{12} can be connected to form a cycle which can be heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic, cycloalkyl, or substituted cycloalkyl.

41. The compound of claim 40, wherein the compound has substantial androgen receptor antagonist activity and no substantial agonist activity on hormone refractory prostate cancer cells.

42. A method comprising: providing at least one compound according to claim 40; measuring inhibition of androgen receptor activity for the compound and determining if the inhibition is above a first predetermined level, measuring stimulation of androgen receptor activity in hormone refractory cancer cells for the compound and determining if the stimulation is below a second predetermined level, selecting the compound if the inhibition is above the first predetermined level and the stimulation is below the second predetermined level.

43. The method of claim 42, wherein the predetermined levels are those of bicalutamide.

44. The method of claim 42, wherein the step of measuring inhibition comprises measuring inhibitory concentration (IC50) in an AR response reporter system or a prostate specific antigen secreting system.

45. The method of claim 42, wherein the step of measuring stimulation comprises measuring fold induction by increasing concentrations in an AR response reporter system or a prostate specific antigen secreting system.

46. The method of claim 42, wherein the steps of measuring inhibition and/or stimulation comprise measuring an effect of the compound on tumor growth in an animal.

Dated this day 13th day of December 2007

Archana Shanker
Of Anand and Anand
Advocates for the Applicants

Abstract:

DIARYLHYDANTOIN COMPOUNDS

The present invention relates to diarylhydantoin compounds, including diarylthiohydantoins, and methods for syntheszing them and using them in the treatment of hormone refractory prostate cancer.

Annexure II

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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(54) Title: DIARYLHYDANTOIN COMPOUNDS

(57) Abstract: The present invention relates to diarylhydantoin compounds, including diarylthiohydantoins, and methods for syntheszing them and using them in the treatment of hormone refractory prostate cancer.

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DIARYLHYDANTOIN COMPOUNDS

FIELD OF THE INVENTION

[0001] The present invention relates to diarylhydantoin compounds including diarylthiohydantoins, and methods for synthesizing them and using them in the treatment of hormone refractory prostate cancer. This application claims priority from U.S. provisional applications bearing serial numbers 60/756,552, 60/750,351, and 60/680,835, the specifications of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] Prostate cancer is the most common incidence of cancer and the second leading cause of cancer death in Western men. When the cancer is confined locally, the disease can be cured by surgery or radiation. However, 30% of such cancer relapses with distant metastatic disease and others have advanced disease at diagnoses. Advanced disease is treated by castration and/or administration of antiandrogens, the so-called androgen deprivation therapy. Castration lowers the circulating levels of androgens and reduces the activity of androgen receptor (AR). Administration of antiandrogens blocks AR function by competing away androgen binding, therefore, reducing the AR activity. Although initially effective, these treatments quickly fail and the cancer becomes hormone refractory.

[0003] Recently, overexpression of AR has been identified and validated as a cause of hormone refractory prostate cancer. See Chen, C.D., Welsbie, D.S., Tran, C., Baek, S.H., Chen, R., Vessella, R., Rosenfeld, M.G., and Sawyers, C.L., Molecular determinants of resistance to antiandrogen therapy, Nat. Med., 10: 33-39, 2004, which is hereby incorporated by reference. Overexpression of AR is sufficient to cause progression from hormone sensitive to hormone refractory prostate cancer, suggesting that better AR inhibitors than the current drugs can slow the progression of prostate cancer. It was demonstrated that AR and its ligand binding are necessary for growth of hormone refractory prostate cancer, indicating that AR is still a target for this disease. It was also demonstrated that overexpression of AR converts anti-androgens from antagonists to agonists in hormone refractory prostate cancer (an AR antagonist inhibits AR activity and an AR agonist stimulates AR activity). Data from this work explains why castration and anti-androgens fail to prevent prostate cancer progression and reveals unrecognized properties of hormone refractory prostate cancer.

[0004] Bicalutamide (brand name: Casodex) is the most commonly used anti-androgen. While it has an inhibitory effect on AR in hormone sensitive prostate cancer, it fails to suppress AR when

cancer becomes hormone refractory. Two weaknesses of current antiandrogens are blamed for the failure to prevent prostate cancer progression from the hormone sensitive stage to the hormone refractory disease and to effectively treat hormone refractory prostate cancer. One is their weak antagonistic activities and the other is their strong agonistic activities when AR is overexpressed in hormone refractory prostate cancer. Therefore, better AR inhibitors with more potent antagonistic activities and minimal agonistic activities are needed to delay disease progression and to treat the fatal hormone refractory prostate cancer.

[0005] Nonsteroidal anti-androgens, such as bicalutamide, have been preferred over steroidal compounds for prostate cancer because they are more selective and have fewer side effects. This class of compounds has been described in many patents such as U.S. Patent Number 4,097,578, U.S. Pat. No. 5,411,981, U.S. Pat. No. 5,705,654, PCT International Applications WO 97/00071 and WO 00/17163, and U.S. Published Patent Application Number 2004/0009969, all of which are hereby incorporated by reference.

[0006] U.S. Patent No. 5,434,176 includes broad claims which encompass a very large number of compounds, but synthetic routes are only presented for a small fraction of these compounds and pharmacological data are only presented for two of them, and one skilled in the art could not readily envision other specific compounds.

[0007] Because the mechanism of hormone refractory prostate cancer was not known, there was no biological system to test these compounds described in these patents for their effect on hormone refractory prostate cancer. Particularly, the ability of AR overexpression in hormone refractory prostate cancer to switch inhibitors from antagonists to agonists was not recognized. Some new properties of hormone refractory prostate cancer are reported in PCT applications US04/42221 and US05/05529, which are hereby incorporated by reference. PCT International Application US05/05529 presented a methodology for identifying androgen receptor antagonist and agonist characteristics of compounds. However, for each compound produced, the time consuming process of determining the antagonist and agonist characteristics of a compound must be determined. That is, there is no method to accurately predict characteristics relevant to treating prostate cancer from the chemical structure of a compound alone.

[0008] There is a need for new thiohydantoin compounds having desirable pharmacological properties, and synthetic pathways for preparing them. Because activities are sensitive to small structural changes, one compound may be effective in treating prostate cancer, whereas a second compound may be

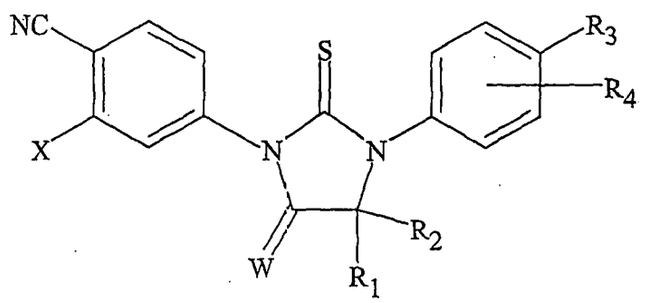
ineffective, even if it differs from the first compound only slightly, say by the replacement of a single substituent.

[0009] Identification of compounds which have high potency to antagonize the androgen activity, and which have minimal agonistic activity should overcome hormone refractory prostate cancer (HRPC) and avoid or slow down the progression of hormone sensitive prostate cancer (HSPC). Therefore, there is a need in the art for the identification of selective modulators of the androgen receptor, such as modulators which are non-steroidal, non-toxic, and tissue selective.

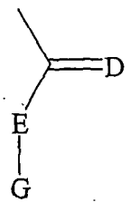
SUMMARY OF THE INVENTION

[0010] The invention provides a series of compounds having strong antagonistic activities with minimal agonistic activities against AR. These compounds inhibit the growth of hormone refractory prostate cancer.

[0011] The invention includes a compound having the formula



wherein X is selected from the group consisting of trifluoromethyl and iodo, wherein W is selected from the group consisting of O and NR5, wherein R5 is selected from the group consisting of H, methyl, and



wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or D is S or O and E-G together are C1-C4 lower alkyl,

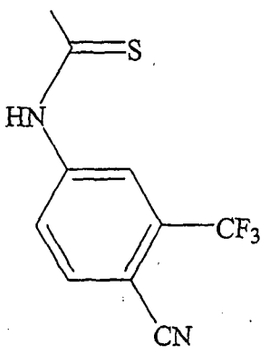
[0012] wherein R1 and R2 together comprise eight or fewer carbon atoms and are selected from the group consisting of alkyl, substituted alkyl including haloalkyl, and, together with the carbon to which they are linked, a cycloalkyl or substituted cycloalkyl group,

[0013] wherein R3 is selected from the group consisting of hydrogen, halogen, methyl, C1-C4 alkoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methoxycarbonyl, acetamido, methanesulfonamino, methanesulfonyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, and C1-C6 alkyl or alkenyl optionally substituted with hydroxyl, methoxycarbonyl, cyano, amino, amido, nitro, carbamoyl, or substituted carbamoyl including methylcarbamoyl, dimethylcarbamoyl, and hydroxyethylcarbamoyl,

[0014] wherein R4 is selected from the group consisting of hydrogen, halogen, alkyl, and haloalkyl, and

[0015] wherein R3 is not methylaminomethyl or dimethylaminomethyl.

[0016] R5 may be



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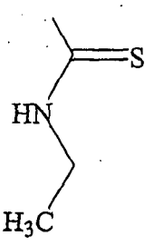

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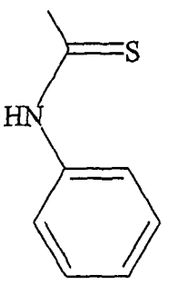
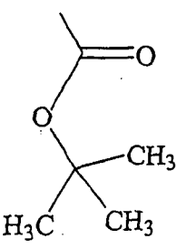
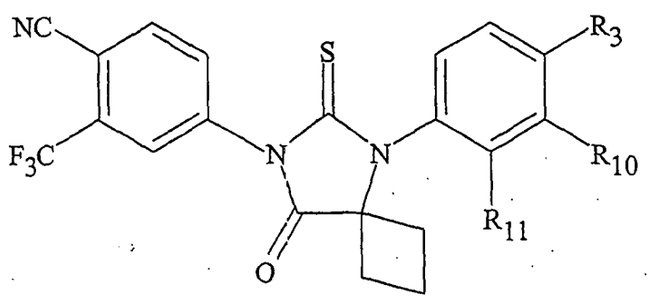


, or


[0017] The compound may have the formula



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164

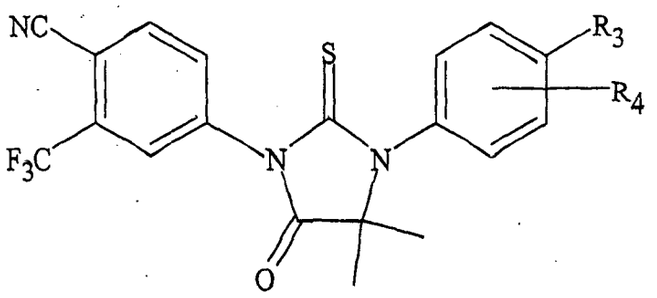
wherein R3 is selected from the group consisting of hydroxy, methylcarbamoyl, methylcarbamoylpropyl, methylcarbamoylethyl, methylcarbamoylmethyl, methylsulfonecarbamoylpropyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, carbamoylmethyl, carbamoylethyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoylpropyl, carboxypropyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, methoxycarbonyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, hydroxyethylcarbamoylethyl, and hydroxyethoxycarbonylethyl, and

[0018] wherein R10 and R11 are both H or, respectively, F and H, or H and F. In certain embodiments, R10 and R11 may both be H or, respectively, F and H. R3 may be methylcarbamoyl.

[0019] In some embodiments, R1 and R2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms, and R3 is selected from the group consisting of carbamoyl, alkylcarbamoyl, carbamoylalkyl, and alkylcarbamoylalkyl, and R4 is H or F or R4 is 3-fluoro.

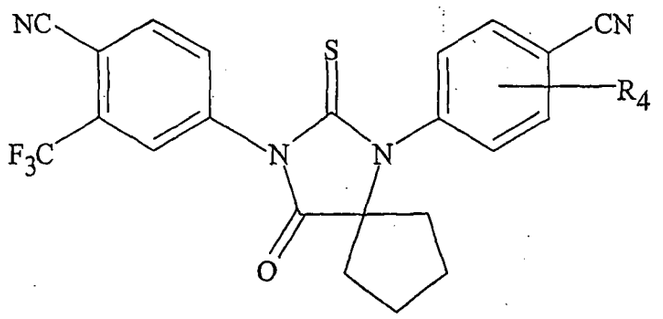
[0020] In other embodiments, R1 and R2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms, R3 is selected from the group consisting of cyano, hydroxy, methylcarbamoyl, methylcarbamoyl-substituted alkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, acetamido, methanesulfonamido, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-(1,1-dimethylethoxy)carbonyl)-1-piperazinyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyethoxycarbonyl-substituted alkyl, and 3-cyano-4-trifluoromethylphenylcarbamoyl, and R4 is F.

[0021] Compounds of the invention may have the formula



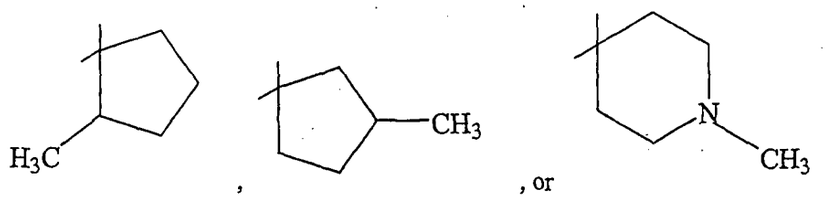
wherein R3 is selected from the group consisting of methylcarbonyl, methoxycarbonyl, acetamido, and methanesulfonamido, and R4 is selected from the group consisting of F and H.

[0022] Compounds of the invention may have the formula

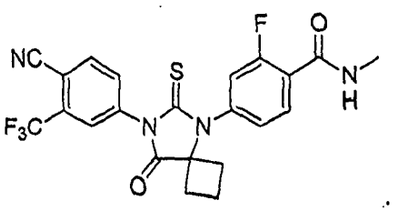


wherein R4 is selected from the group consisting of F and H.

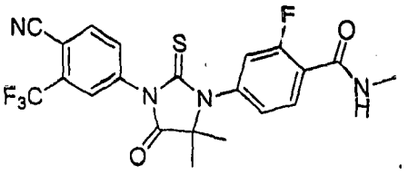
[0023] In embodiments of the invention, wherein R1 and R2 together with the carbon to which they are linked are



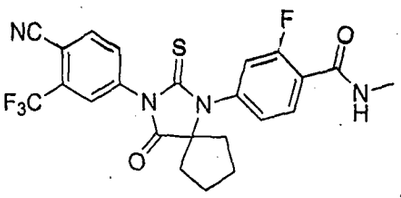
[0024] Compounds of the invention may be those listed in Tier 1, Tier 2, Tier 3, and/or Tier 4, below. Particular compounds of the invention include



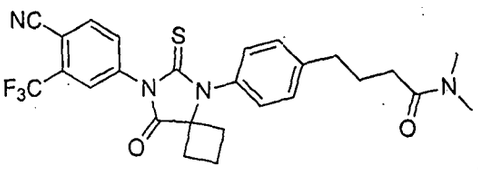
[RD162]



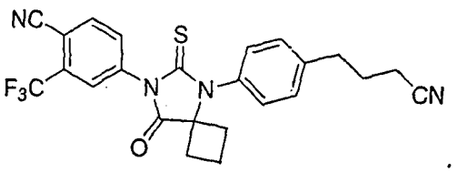
[RD162']



[RD162"]



[RD169]



[RD170]

[0025] The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of the preceding compounds or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

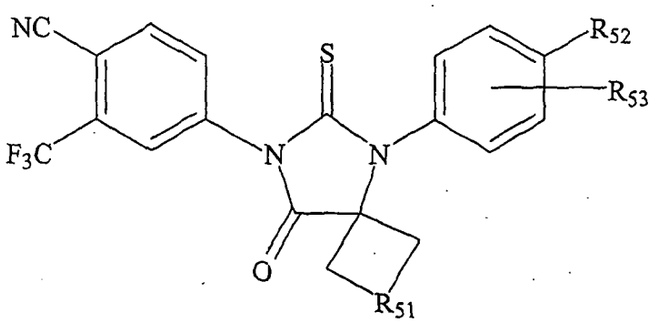
[0026] The invention encompasses a method for treating a hyperproliferative disorder

comprising administering such a pharmaceutical composition to a subject in need of such treatment, thereby treating the hyperproliferative disorder. The hyperproliferative disorder may be hormone refractory prostate cancer. The dosage may be in the range of from about 0.001 mg per kg body weight per day to about 100 mg per kg body weight per day, about 0.01 mg per kg body weight per day to about 100 mg per kg body weight per day, about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day, or about 1 mg per kg body weight per day.

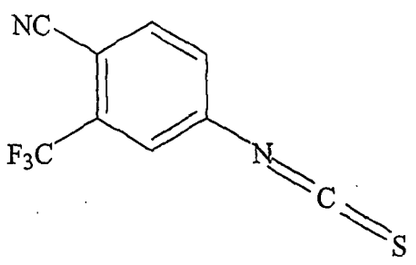
[0027] The compound may be administered by intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally. The composition may have a form selected from the group consisting of a solution, dispersion, suspension, powder, capsule, tablet, pill, time release capsule, time release tablet, and time release pill.

[0028] The administered compound may be selected from the group consisting of RD162', RD162", RD 169, or RD170, or a pharmaceutically acceptable salt thereof. The administered compound may be RD162 or a pharmaceutically acceptable salt thereof.

[0029] The invention provides a method of synthesizing a diaryl compound of formula:

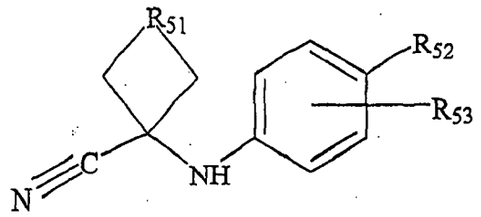


comprising mixing Compound I



Compound I

with Compound II

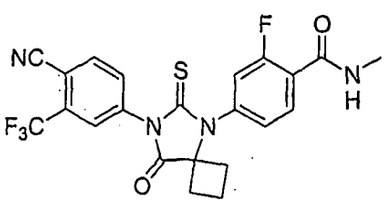


Compound II

in a first polar solvent to form a mixture, heating the mixture, adding a second polar solvent, the same as or different from the first polar solvent, and an aqueous acid to the mixture, refluxing the mixture, cooling the mixture and combining with water, and separating the diaryl compound from the mixture, wherein R51 comprises an alkyl chain of from 1 to 4 carbon atoms, R52 is selected from the group consisting of cyano, hydroxy, methylcarbamoyl, methylcarbamoyl-substituted alkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, and hydroxyethoxycarbonyl-substituted alkyl, and R53 is selected from the group consisting of F and H.

[0030] R51 may comprise an alkyl chain of from 1 to 2 carbon atoms, R52 may be selected from the group consisting of carbamoyl and methylcarbamoyl, and R53 may be F.

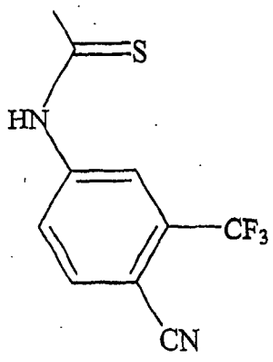
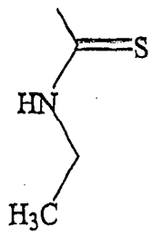
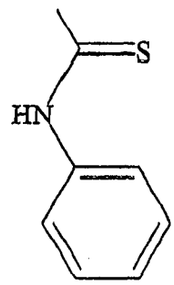
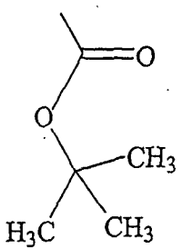
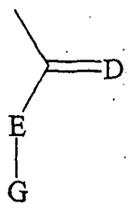
[0031] The invention provides methods of synthesizing a compound of formula:



[RD162]

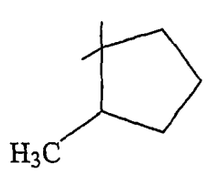
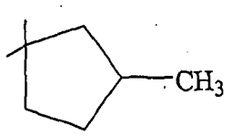
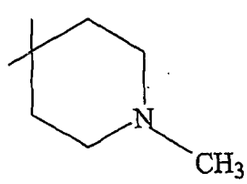
comprising mixing 4-isothiocyanato-2-trifluoromethylbenzonitrile and *N*-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide in dimethylformamide to form a first mixture, heating the

NR11R12, (CO)OR11, (CO)NR11R12, (CO)R11, (CS)R11, (CS)NR11R12, (CS)OR11,

[0037]  ,  ,  , and  , and 

wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or D is S or O and E-G together are C1-C4 lower alkyl,

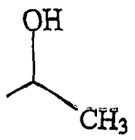
[0038] wherein R1 and R2 are independently alkyl, haloalkyl, hydrogen, aryl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkenyl, halogenated akynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocylic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, or R1 and R2 are connected to form a cycle which can be heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl,

[0039]  ,  , or  ,

[0040] wherein X is carbon or nitrogen and can be at any position in the ring, and

[0041] wherein R3, R4, and R7 are independently selected from the group consisting of hydrogen, halogen, methyl, methoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methylcarbamoyl-substituted alkyl, dimethylcarbamoyl-substituted

alkyl, methoxycarbonyl, acetamido, methanesulfonamino, carbamoyl-substituted alkyl, methanesulfonyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyl-substituted alkyl, hydroxyl-substituted alkenyl, carbamoyl-substituted alkenyl, methoxycarbonyl-



substituted alkyl, cyano-substituted alkyl, , aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkenyl, halogenated alkynyl, SO2R11, NR11R12, NR12(CO)OR11, NH(CO)NR11R12, NR12 (CO)R11, O(CO)R11, O(CO)OR11, O(CS)R11, NR12 (CS)R11, NH(CS)NR11R12, NR12 (CS)OR11, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, haloalkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, acetamido, methanesulfonamido, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-(1,1-dimethylethoxy)carbonyl)-1-piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyethoxycarbonyl-substituted alkyl, 3-cyano-4-trifluoromethylphenylcarbamoyl,

[0042] wherein R11 and R12 are independently hydrogen, aryl, aralkyl, substituted aralkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, or substituted cycloalkyl, or R11 and R12 can be connected to form a cycle which can be heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic, cycloalkyl, or substituted cycloalkyl.

[0043] Such compounds have substantial androgen receptor antagonist activity and no substantial agonist activity on hormone refractory prostate cancer cells.

[0044] The invention encompasses a method comprising providing at least one such compound, measuring inhibition of androgen receptor activity for the compound and determining if the inhibition is above a first predetermined level, measuring stimulation of androgen receptor activity in hormone refractory cancer cells for the compound and determining if the stimulation is below a second predetermined level, and selecting the compound if the inhibition is above the first predetermined level and the stimulation is below the second predetermined level. The predetermined levels may be those of bicalutamide. The step of measuring inhibition may comprise measuring inhibitory concentration (IC50) in an AR response reporter system or a prostate specific antigen secreting system. The step of measuring

stimulation may comprise measuring fold induction by increasing concentrations in an AR response reporter system or a prostate specific antigen secreting system. The method of measuring inhibition and/or stimulation may comprise measuring an effect of the compound on tumor growth in an animal.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] The following Figures present the results of pharmacological examination of certain compounds.

[0046] Figure 1 is a graph depicting that bicalutamide displays an agonistic effect on LNCaP-AR. Agonistic activities of bicalutamide in AR-overexpressed hormone refractory prostate cancer. LNCaP cells with overexpressed AR were treated with increasing concentrations of DMSO as vehicle or bicalutamide in the absence of R1881. Activities of AR response reporter were measured.

[0047] Figure 2 is a graph depicting an antagonistic assay of bicalutamide on LNCaP-AR. Agonistic activities of bicalutamide in hormone sensitive prostate cancer. LNCaP cells were treated with increasing concentrations of DMSO as vehicle or bicalutamide in the absence of R1881. Activities of AR response reporter were measured.

[0048] Figure 3 is a graph depicting the effect of compounds on LNCaP-AR.

[0049] Figure 4 is a graph depicting the effect of compounds on LNCaP-AR.

[0050] Figure 5 is a graph depicting the inhibition effect on LNCaP-AR.

[0051] In Figures 6-10, example 5-3b is RD7 and example 7-3b is RD37.

[0052] Figure 6. Inhibition on growth of AR-overexpressed LNCaP cells. Androgen starved LNCaP cells with overexpressed AR were treated with increasing concentrations of DMSO as vehicle or test substances in the presence of 100 pM of R1881. After 4 days of incubation, cell growth was measured by MTS assay.

[0053] Figure 7. Inhibitory effect on growth of AR-overexpressed LNCaP xenograft model. Mice with established LN-AR xenograft tumors were randomized and treated with indicated compounds orally once daily. Tumor size was measured by caliber. (A), mice were treated with 1 mg per kg of bicalutamide, example 7-3b, or vehicle for 44 days. (B), mice were treated with vehicle, 0.1, 1, or 10 mg per kg of example 7-3b for 44 days.

[0054] Figure 8. Inhibitory effect on PSA expression of AR-overexpressed LNCaP xenograft model. Mice were treated with vehicle, 0.1, 1, or 10 mg per kg of example 7-3b for 44 days orally once daily. The tumors were taken out from the mice after 44 days of treatment, tumor lysate was extracted, and PSA level in tissue lysate was determined by ELISA.

[0055] Figure 9. Inhibitory effect on growth and PSA of hormone refractory LAPC4 xenograft model. Mice with established tumors were randomized and treated with 1 mg per kg of bicalutamide, example 7-3b, or vehicle for 17 days orally once daily. (A), tumor size was measured by caliber. (B), the tumors were taken out from the mice after 17 days of treatment, tumor lysate was extracted, and PSA level in tissue lysate was determined by ELISA.

[0056] Figure 10. Inhibitory effect on growth of hormone sensitive prostate cancer cells. Androgen starved LNCaP cells were treated with increasing concentrations of DMSO as vehicle or test substances in the presence of 1 pM of R1881. After 4 days of incubation, cell growth was measured by MTS assay.

[0057] Figure 11 is a graph of tumor size. AR overexpressing LNCaP cells were injected in the flanks of castrated SCID mice, subcutaneously. When tumors reached about 100 cubic mm, they were randomized into five groups. Each group had nine animals. After they reached this tumor volume, they were given orally with either vehicle, bicalutamide or RD162 at 10 or 50 mg/kg everyday. The tumors were measured three-dimensionally, width, length and depth, using a caliper.

[0058] Figure 12 depicts experimental results of tumor size. At day 18, the animals were imaged via an optical CCD camera, 3 hours after last dose of treatment. A ROI was drawn over the tumor for luciferase activity measurement in photon/second. The right panels is a representation of the ROIs measurements.

[0059] Figure 13 is a graph depicting the pharmacokinetic curves of RD162 from intravenous (upper curve) and oral administration (lower curve).

[0060] Figure 14 is a graph depicting PSA absorbance measured for LN-AR cells after treatment with various doses of several compounds.

[0061] Figure 15 presents a table providing several characteristics of compounds. Figure 15 also presents a graph providing the pharmacokinetic characteristics of several compounds in terms of compound serum concentration as a function of time.

[0062] Figure 16 is a chart depicting prostate weight after treatment with various compounds.

10, 25, or 50 mg of compound per kilogram body weight were administered per day, as indicated by the label of a bar. The compounds were administered to healthy FVB mice. After treatment with compound for 14 days, the urogenital tract weight was determined by removing and weighing the semi-vesicles, prostate, and bladder. Three mice were administered a given compound to obtain the data presented by a bar in the chart. A set of mice was not treated with a compound: data are presented in the bar labeled "untreated". Another set of mice was treated only with vehicle solution: data are presented in the bar labeled "vehicle".

[0063] Figure 17 is a graph presenting a PSA assay performed along with the experimental protocol presented in Fig. 6.

[0064] Figure 18 is a graph presenting the effect of various dose regimens of RD162 on tumor volume.

[0065] Figure 19 is a graph presenting the rate of photon emission associated with luciferase activity at day 17 relative to the rate at day 0 after treatment with RD162 at doses of 0.1, 1, and 10 mg per kilogram body weight per day and without treatment with RD162.

[0066] Figure 20 presents the results of an experiment in which SCID mice were injected with the LN-AR (HR) cell line to induce tumor growth. One set of mice were treated with the compound RD162 at a dose of 10 mg per kilogram body weight per day; the other set of mice were treated only with vehicle solution. (A) The relative tumor volume as a function of time shown for each set of mice. (B) Images of each set of mice with photon emission associated with luciferase activity at day 31 shown as color contours. (C) Rate of photon emission associated with luciferase activity shown at several times for each set of mice.

[0067] Figure 21 is a graph presenting PSA absorbance associated with LN-AR cells treated with various concentrations of RD162, RD162', RD162", and RD170 and vehicle solution.

[0068] Figure 22 is a graph presenting PSA absorbance associated with LN-CaP cells treated with various concentrations of RD37, RD131, RD162, bicalutamide, and DMSO.

[0069] Figure 23 presents results of an experiment conducted with wild type nontransgenic mice (WT), castrated luciferase transgenic mice (Cast), and non-castrated luciferase transgenic mice (Intact). Data are shown for castrated luciferase transgenic mice treated with an implanted testosterone pellet yielding 12.5 mg per kilogram body weight with a 90 day release period (T/Cast), and data are shown for non-castrated luciferase transgenic mice treated with an implanted testosterone pellet yielding 12.5 mg per kilogram body weight with a 90 day release period (Intact+T). Data are shown for castrated

luciferase transgenic mice treated with the implanted testosterone pellet and with bicalutamide (BIC+T/Cast) or with RD162 (RD162+T/Cast) at 10 mg per kilogram body weight per day. (A) Urogenital tract weight at 14 days. (B) Photon emission rate at 14 days. In all cases, a hormone refractory disease state was not induced.

[0070] Figure 24 is a graph of luciferase activity of the L1AR cell line dosed with various compounds administered at concentrations ranging from 125 nmol to 1000 nmol.

[0071] Figure 25 is a graph of luciferase activity for the LN/AR cell line for various compounds administered at concentrations ranging from 1.25 to 10 μmol.

[0072] Figure 26 is a graph of luciferase activity for the 4AR cell line for various compounds administered at concentrations ranging from 1.25 to 10 μmol.

[0073] Figure 27 is a graph of PSA levels for the 1AR cell line for various compounds administered at concentrations ranging from 1.25 to 10 μmol.

[0074] Figure 28 is a graph of PSA levels for the LN/AR cell line for various compounds administered at concentrations ranging from 125 nmol to 1000 nmol.

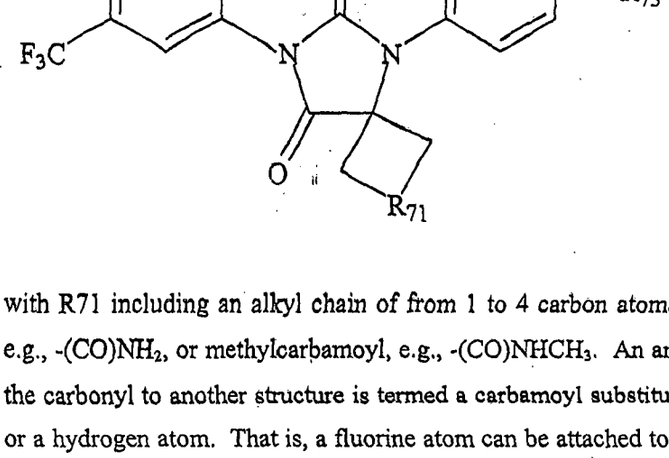
[0075] Figure 29 is a graph of luciferase activity for various compounds administered at concentrations ranging from 125 nmol to 1000 nmol.

DETAILED DESCRIPTION

[0076] Embodiments of the invention are discussed in detail below. In describing embodiments, specific terminology is employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology so selected. A person skilled in the relevant art will recognize that other equivalent parts can be employed and other methods developed without parting from the spirit and scope of the invention. All references cited herein are incorporated by reference as if each had been individually incorporated.

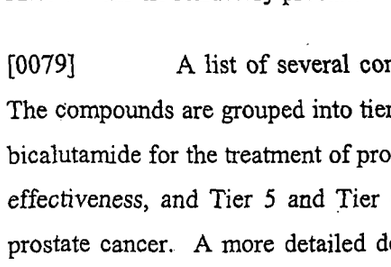
Synthesis of Diarylhydantoin Compounds

[0077] The invention provides for synthesis of diarylthiohydantoin compound having the formula



with R71 including an alkyl chain of from 1 to 4 carbon atoms. For example, R72 can be carbamoyl, e.g., -(CO)NH_2, or methylcarbamoyl, e.g., -(CO)$NHCH_3$. An amide group bonded at the carbon atom of the carbonyl to another structure is termed a carbamoyl substituent. For example, R73 can be a fluorine or a hydrogen atom. That is, a fluorine atom can be attached to any one of the carbons of the right-hand aryl ring which are not bonded to the R72 substituent or the nitrogen atom. Alternatively, no fluorine atom can be attached to the carbons of the right-hand aryl ring which are not bonded to the R72 substituent or the nitrogen atom. For example, a hydrogen atom can be attached to each of the carbons of the right-hand aryl ring which are not bonded to the R72 substituent or the nitrogen atom.

[0078] For example, as further presented below (see, for example, Figs. 3, 5, 11-13), the compound having the formula



[RD162]

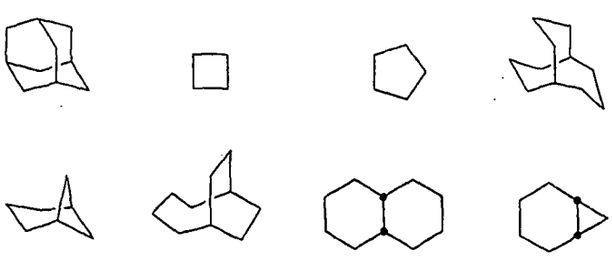
exhibited surprisingly potent antagonistic activities with minimal agonistic activities for overexpressed AR in hormone refractory prostate cancer.

[0079] A list of several compounds according to this invention is presented in Tables 5 - 11. The compounds are grouped into tiers, with Tier 1 to Tier 3 compounds being expected to be superior to bicalutamide for the treatment of prostate cancer, Tier 4 compounds being comparable to bicalutamide in effectiveness, and Tier 5 and Tier 6 compounds being worse than bicalutamide for the treatment of prostate cancer. A more detailed description of the protocol used to rank the compounds into tiers is presented below.

Definitions

[0080] As used herein, the term "alkyl" denotes branched or unbranched hydrocarbon chains, preferably having about 1 to about 8 carbons, such as, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, 2-methylpentyl pentyl, hexyl, isohexyl, heptyl, 4,4-dimethyl pentyl, octyl, 2,2,4-trimethylpentyl and the like. "Substituted alkyl" includes an alkyl group optionally substituted with one or more functional groups which may be attached to such chains, such as, hydroxyl, bromo, fluoro, chloro, iodo, mercapto or thio, cyano, alkylthio, heterocyclyl, aryl, heteroaryl, carboxyl, carbalkoyl, alkyl, alkenyl, nitro, amino, alkoxyl, amido, and the like to form alkyl groups such as trifluoro methyl, 3-hydroxyhexyl, 2-carboxypropyl, 2-fluoroethyl, carboxymethyl, cyanobutyl and the like.

[0081] Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or more double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl. "Substituted cycloalkyl" includes a cycloalkyl group optionally substituted with 1 or more substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the substituents included in the definition of "substituted alkyl." For example,



and the like.

[0082] Unless otherwise indicated, the term "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 2 to 8 carbons in the normal chain, which include one or more double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-

hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like. "Substituted alkenyl" includes an alkenyl group optionally substituted with one or more substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl."

[0083] Unless otherwise indicated, the term "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one or more triple bonds in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like. "Substituted alkynyl" includes an alkynyl group optionally substituted with one or more substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl."

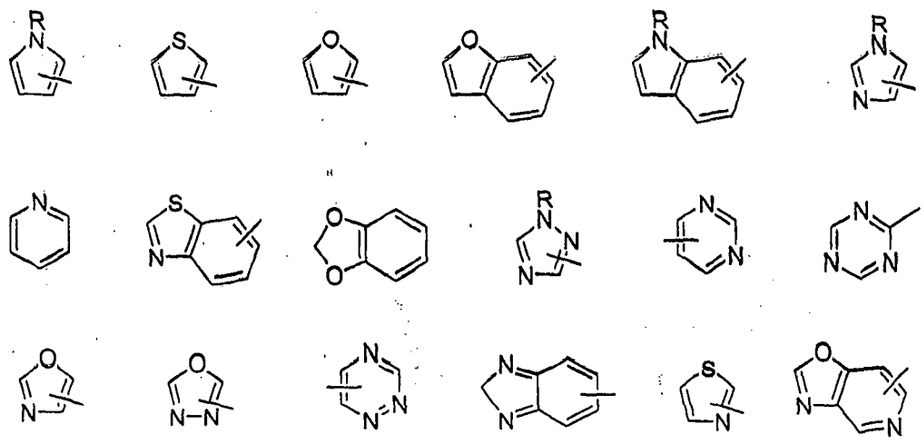
[0084] The terms "arylalkyl", "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkyl, alkenyl and alkynyl groups as described above having an aryl substituent. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, phenethyl, benzhydryl and naphthylmethyl and the like. "Substituted arylalkyl" includes arylalkyl groups wherein the aryl portion is optionally substituted with one or more substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl."

[0085] The terms "arylalkyl", "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkyl, alkenyl and alkynyl groups as described above having an aryl substituent. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, phenethyl, benzhydryl and naphthylmethyl and the like. "Substituted arylalkyl" includes arylalkyl groups wherein the aryl portion is optionally substituted with one or more substituents, such as the substituents included above in the definition of "substituted alkyl" and "substituted cycloalkyl."

[0086] The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine.

[0087] The terms "halogenated alkyl", "halogenated alkenyl" and "alkynyl" as used herein alone or as part of another group refers to "alkyl", "alkenyl" and "alkynyl" which are substituted by one or more atoms selected from fluorine, chlorine, bromine, fluorine, and iodine.

[0088] Unless otherwise indicated, the term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and polycyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include



and the like.

Example 1

4-isothiocyanato-2-trifluoromethylbenzonitrile, (1a)

[0091] 4-Amino-2-trifluoromethylbenzonitrile, (2.23 g, 12 mmol) was added portionwise over 15 minutes into the well-stirred heterogeneous mixture of thiophosgene (1 ml, 13 mmol) in water (22 ml) at room temperature. Stirring was continued for an additional 1 h. The reaction medium was extracted with chloroform (3 × 15 ml). The combined organic phase was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to yield desired product, 4-isothiocyanato-2-trifluoromethylbenzonitrile, **(1a)**, as brownish solid and was used as such for the next step (2.72 g, 11.9 mmol, 99%).

Example 2

2-1). (4-aminophenyl)carbamic acid *tert*-butyl ester, (2a)

[0092] An aqueous solution of potassium carbonate (1.52 g, 11 mmol in 5 ml of water) was added to a solution of 1,4-diaminobenzene (3.24 g, 30 mmol) in THF (30 ml) and DMF (10 ml). To this mixture was added di-*tert*-butyl pyrocarbonate, Boc_2O (2.18 g, 10 mmol), dropwise over 0.5 h. The reaction mixture was stirred for an additional 4 h at room temperature. The mixture was then poured into cold water (40 ml) and extracted with chloroform (3 × 50 ml). The combined organic phase was dried over $MgSO_4$ and concentrated to yield a brown residue which was subjected to flash chromatography (dichloromethane/acetone, 4:1) to afford (4-aminophenyl)carbamic acid *tert*-butyl ester, **(2a)** as a yellow solid (1.98 g, 9.5 mmol, 95%) (yield based on Boc_2O).

2-2). {4-[(1-cyano-1-methylethyl)amino]phenyl}carbamic acid *tert*-butyl ester, 2b

[0093] The mixture of **2a** (0.83 g, 4 mmol), acetone cyanohydrin (4 ml) and $MgSO_4$ (2 g) was

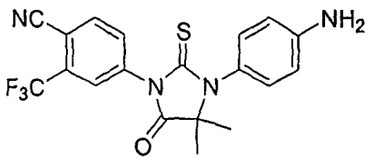
heated to 80 °C and stirred over 2.5 h. After cooling down to room temperature, compound **2b** was crystallized into water (30 ml). The solid was filtered and dried to yield {4-[(1-cyano-1-methylethyl)amino]phenyl}carbamic acid *tert*-butyl ester, **2b** (1.08 g, 3.9 mmol, 98%).

2-3). {4-[3-(4-cyano-3-trifluoromethylphenyl)-4-imino-5,5-dimethyl-2-thioxo-imidazolidin-1-yl]phenyl}carbamic acid *tert*-butyl ester, (2c)

[0094] Triethylamine (0.202 g, 2 mmol) was added to a solution of **1a** (0.456 g, 2 mmol) and **2b** (0.57 g, 2 mmol) in dry THF (5 ml). The reaction mixture was stirred at room temperature for 15 h and then concentrated to yield a dark residue which was subjected to flash chromatography (ethyl ether/acetone, 97:3) to afford {4-[3-(4-cyano-3-trifluoromethylphenyl)-4-imino-5,5-dimethyl-2-thioxo-imidazolidin-1-yl]phenyl}carbamic acid *tert*-butyl ester, (**2c**) (0.15 g, 0.3 mmol, 15%).

2-4). 4-[3-(4-aminophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 2d, [RD9]

[0095] The mixture of **2c** (0.15 g, 0.3 mmol) in HCl aq, 3N. (1 ml) and methanol (4 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (5 ml) and extracted with dichloromethane (8 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane/acetone, 9:1) to yield 4-[3-(4-aminophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, **2d**, [RD9] (0.118 g, 0.29 mmol, 97%) as a yellow solid.

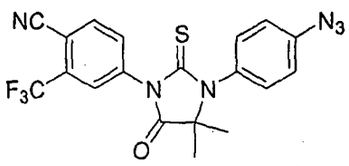


^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 6H), 6.73-6.75 (m, 2H), 7.00-7.03 (m, 2H), 8.02 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 66.2, 109.1, 114.3, 114.9, 120.4, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 130.4, 132.5 (q, J = 33.0 Hz), 133.4, 135.6, 138.5, 149.2, 175.3, 180.4.

2-5). 4-[3-(4-azidophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 2e, [RD10]

[0096] An aqueous solution of sulfuric acid (25% wt, 1 ml) was added to a solution of **2d** (0.10

g, 0.25 mmol) in acetone (1 ml) at -5 °C. An aqueous solution of $NaNO_2$ (0.024 g, 0.35 mmol, in 0.5 ml of water) was added slowly the above mixture over 0.1 h. The reaction mixture was allowed to stir at -5 °C for an additional 1 h and then an aqueous solution of NaN_3 (0.02 g, 0.3 mmol in 0.3 ml of water) was added dropwise. Upon completion of the addition, the reaction medium was warmed to room temperature and stirred for an additional 3 h. The product was extracted with dichloromethane (3 × 5 ml). The combined organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-[3-(4-azidophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, **2e**, [RD10] (0.08 g, 0.18 mmol, 72%) as a yellowish solid.



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 6H), 7.17-7.20 (m, 2H), 7.27-7.30 (m, 2H), 7.84 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 66.4, 110.1, 114.8, 120.4, 122.1 (q, J = 272.5 Hz), 127.0 (q, J = 4.7 Hz), 131.1, 131.5, 132.3, 133.3 (q, J = 33.0 Hz), 135.3, 137.1, 141.7, 174.8, 180.1. MS for $C_{19}H_{13}F_3N_6OS$, calculated 430.4, found 430.1.

Example 3

3-1). 2-(4-hydroxyphenylamino)-2-methylpropanenitrile, 3a

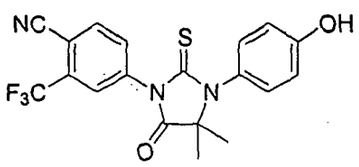
[0097] A mixture of 4-aminophenol (1.09 g, 10 mmol), acetone cyanohydrin (10 ml) and MgSO4 (2 g) was heated to 80 °C and stirred for 4 h. After concentration of the medium under vacuum, compound **3a** was crystallized from water (20 ml). The solid was filtered and dried to yield 2-(4-hydroxyphenylamino)-2-methylpropanenitrile, **3a** (1.69 g, 9.6 mmol, 96%).

3-2). 4-[3-(4-hydroxyphenyl)-5-imino-4,4-dimethyl-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 3b

[0098] Triethylamine (0.101 g, 1 mmol) was added to a solution of **1a** (0.456 g, 2 mmol) and **3a** (0.352 g, 2 mmol) in dry THF (5 ml). The reaction mixture was stirred at 0 °C for 48 h and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 85:15) to afford 4-[3-(4-hydroxyphenyl)-5-imino-4,4-dimethyl-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, **3b** (0.274 g, 0.68 mmol, 34%).

3-3). **4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 3c, [RD8]**

A mixture of **3b** (0.202 g, 0.5 mmol) in HCl aq., 2N (2 ml) and methanol (5 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane/acetone, 9:1) to yield 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, **3c**, [RD8] (0.198 g, 0.49 mmol, 98%) as a white powder.

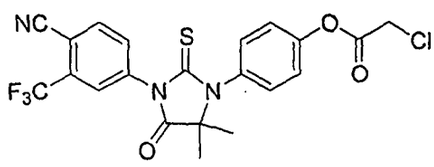


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57 (s, 6H), 6.26 (s, OH), 6.90-6.93 (m, 2H), 7.11-7.14 (m, 2H), 7.84 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 23.6, 66.5, 109.9, 114.9, 115.7, 116.8, 121.9 (q, J = 272.7 Hz), 127.2 (q, J = 4.7 Hz), 130.6, 132.3, 133.5 (q, J = 33.2 Hz), 135.3, 137.2, 157.0, 175.3, 180.2.

Example 4

Chloroacetic acid 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]phenyl ester, 4a, [RD13]

Chloroacetyl chloride (0.045 g, 0.4 mmol) was added to a mixture of **3c** (0.101g, 0.25 mmol) and triethylamine (0.041g, 0.41 mmol) in dry THF (1.5 ml). The mixture was stirred at room temperature for 4 h. Triethylamine hydrochloride was filtered off. The filtrate was concentrated and chromatographed (dichloromethane/acetone, 95:5) to yield 84% of Chloroacetic acid 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]phenyl ester, **4a**, [RD13] (0.101 g, 0.21 mmol) as white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58 (s, 6H), 4.32 (s, 2H), 7.33 (s, 4H), 7.83 (dd, J_1 = 8.3 Hz, J_2 = 1.9 Hz, 1H), 7.95-7.97 (m, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 23.7, 40.8, 66.5, 110.1, 114.8, 121.9 (q, J = 272.5 Hz), 122.7, 127.1 (q, J = 4.7 Hz), 130.9, 132.3, 132.9, 133.5 (q, J = 33.2 Hz), 135.3, 137.1, 150.9, 165.5, 174.8, 180.0.

Example 5

5-1a). 2-methyl-2-(4-methylphenyl)aminopropanenitrile, 5a

A mixture of *p*-toluidine (1.07 g, 10 mmol) and acetone cyanohydrin (10 ml) was heated to 80 °C and stirred for 4 h. The medium was concentrated and dried under vacuum to yield 2-methyl-2-(4-methylphenyl)aminopropanenitrile, **5a** (1.72g, 9.9 mmol, 99%) as brown solid.

5-1b). 2-methyl-2-(4-methylphenyl)aminopropanenitrile, 5a

Sodium cyanide (0.735g, 15 mmol) was added to a mixture of *p*-toluidine (1.07 g, 10 mmol) and acetone (1.16 g, 20 mmol) in 90% acetic acid (10 ml). The reaction mixture was stirred at room temperature for 12 h and then ethyl acetate (50 ml) was added. The organic layer was washed with water (4 × 30 ml), dried over magnesium sulfate and concentrated under vacuum to dryness to yield 2-methyl-2-(4-methylphenyl)aminopropanenitrile, **5a** (1.65g, 9.5 mmol, 95%) as a brown solid.

5-2). 4-[3-(4-methylphenyl)-5-imino-4,4-dimethyl-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 5b

Triethylamine (0.101 g, 1 mmol) was added to a solution of **1a** (0.456 g, 2 mmol) and **5a** (0.348 g, 2 mmol) in dry THF (3 ml). The reaction mixture was stirred at 0 °C for 2 days and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 95:5) to afford 4-[3-(4-methylphenyl)-5-imino-4,4-dimethyl-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, **5b** (0.136 g, 0.34 mmol, 17%).

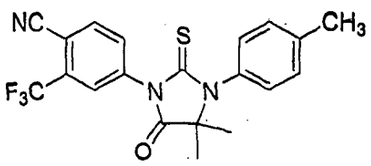
5-3a). 4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 5c

A mixture of **5b** (0.121 g, 0.3 mmol) in HCl aq., 2N (2 ml) and methanol (5 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, **5c** (0.118 g, 0.294 mmol, 98%) as a white powder.

5-3b). 4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile, 5c , [RD7]

A mixture of **1a** (0.547 g, 2.4 mmol) and **5a** (0.348 g, 2 mmol) in dry DMF (0.6 ml) was stirred for 36 h. To this mixture were added methanol (20 ml) and 2N HCl (5 ml). The second mixture was refluxed for 6

h. After being cooled to room temperature, the reaction mixture was poured into cold water (30 ml) and extracted with ethyl acetate (40 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile, **5c**, [RD7] (0.596 g, 1.48 mmol, 74%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 6H), 2.44 (s, 3H), 7.17-7.20 (m, 2H), 7.33-7.36 (m, 2H), 7.86 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 23.6, 66.4, 110.0, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.2, 130.6, 132.2, 132.3, 133.4 (q, J = 33.2 Hz), 135.2, 137.2, 140.1, 175.1, 179.9.

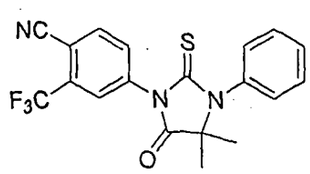
Example 6

6-1. 2-methyl-2-phenylaminopropanenitrile, 6a

A mixture of aminobenzene (0.931 g, 10 mmol) and acetone cyanohydrin (2 ml) was heated to reflux and stirred for 20 h. After being cold to room temperature, the reaction mixture was poured into ethyl acetate (40 ml) and washed with cold water (2 × 30 ml). The organic layer was dried over $MgSO_4$, concentrated under vacuum to dryness to yield 2-methyl-2-phenylaminopropanenitrile, **6a** (1.51g, 9.4 mmol, 94%) as slurry brown liquid.

6-2). 4-[3-phenyl-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 6b, [RD10]

A mixture of **1a** (0.274 g, 1.2 mmol) and **6a** (0.160 g, 1 mmol) in dry DMF (0.2 ml) was stirred for 48 h. To this mixture were added methanol (10 ml) and 2N HCl (3 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (20 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-[3-phenyl-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, **6b**, [RD10] (0.276 g, 0.71 mmol, 71%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60 (s, 6H), 7.28-7.31 (m, 2H), 7.50-7.58 (m, 3H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96-7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 66.4, 110.2, 114.8, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.5, 129.8, 129.9, 132.2, 133.4 (q, J = 33.2 Hz), 135.1, 135.2, 137.2, 175.0, 179.9.

Example 7

7-1a). 1-(4-methylphenyl)aminocyclobutanenitrile, 7a

Sodium cyanide (0.147g, 3 mmol) was added to a mixture of *p*-toluidine (0.214 g, 2 mmol) and cyclobutanone (0.21 g, 3 mmol) in 90% acetic acid (3 ml). The reaction mixture was stirred at room temperature for 12 h and then 20 ml of ethyl acetate was added. The organic layer was washed with water (3 × 10 ml), dried over magnesium sulfate and concentrated under vacuum to dryness to yield 1-(4-methylphenyl)aminocyclobutanenitrile, **7a** (0.343 g, 1.84 mmol, 92%) as a brown solid.

7-1b). 1-(4-methylphenyl)aminocyclobutanenitrile, 7a

Trimethylsilyl cyanide (0.93 ml, 7 mmol) was added dropwise to a mixture of *p*-toluidine (0.535 g, 5 mmol) and cyclobutanone (0.42 g, 6 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield 1-(4-methylphenyl)aminocyclobutanenitrile, **7a** (0.912 g, 4.9 mmol, 98%) as a yellowish solid.

7-2). 4-(8-imino-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 7b

To a solution of **1a** (2.28 g, 10 mmol) in dry DMF (3 ml) was added progressively, over 20 hours, a solution of **7a** (1.764 g, 9 mmol) in dry DMF (3 ml) at room temperature. The medium was stirred for an additional 4 h. After DMF being evaporated, the residue was chromatographed (dichloromethane/acetone, 95:5) to afford 4-(8-imino-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, **7b** (1.937 g, 4.68 mmol, 52%).

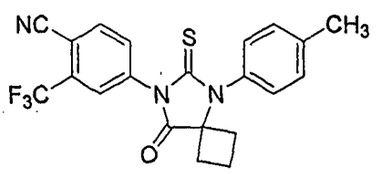
7-3a). 4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 7c [RD37]

A mixture of **7b** (0.041 g, 0.1 mmol) in HCl aq., 2N (3 ml) and methanol (1 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (5 ml) and extracted with ethyl acetate (6 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-

diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, **7c** (0.04 g, 0.096 mmol, 96%) as a white powder.

7-3b). 4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 7c, [RD37]

A mixture of **1a** (0.912 g, 4 mmol) and **7a** (0.558 g, 3 mmol) in dry DMF (0.5 ml) was stirred at room temperature for 24 h. To this mixture were added methanol (30 ml) and HCl aq. 2N (6 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 ml) and extracted with ethyl acetate (60 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, **7c** (0.959 g, 2.31 mmol, 77%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62-1.69 (m, 1H), 2.16-2.22 (m, 1H), 2.46 (s, 3H), 2.55-2.66 (m, 4H), 7.19-7.26 (m, 2H), 7.36-7.42 (m, 2H), 7.86 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 21.3, 31.4, 67.4, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.5, 130.8, 132.2, 132.4, 133.3 (q, J = 33.2 Hz), 135.2, 137.3, 140.1, 175.0, 180.0.

Example 8

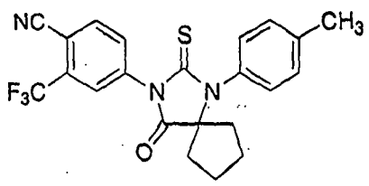
8-1). 1-(4-methylphenyl)aminocyclopentanenitrile, 8a

Trimethylsilyl cyanide (0.865 ml, 7 mmol) was added dropwise to a mixture of *p*-toluidine (0.535 g, 5 mmol) and cyclopentanone (0.589 g, 7 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield 1-(4-methylphenyl)aminocyclopentanenitrile, **8a** (0.981 g, 4.9 mmol, 98%) as a yellowish solid.

8-2). 4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 8b, [RD35]

A mixture of **1a** (0.296 g, 1.3 mmol) and **8a** (0.2 g, 1 mmol) in dry DMF (0.2 ml) was stirred for 48 h. To this mixture were added methanol (10 ml) and HCl aq. 2N (3 ml). The second mixture was refluxed for 6

h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, **8b**, [RD35] (0.3 g, 0.7 mmol, 70%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47-1.57 (m, 2H), 1.81-1.92 (m, 2H), 2.20-2.24 (m, 2H), 2.27-2.34 (m, 2H), 2.43 (s, 3H), 7.18-7.22 (m, 2H), 7.33-7.36 (m, 2H), 7.86 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 25.2, 36.3, 75.1, 110.0, 114.9, 121.9 (q, J = 272.5 Hz), 127.1 (q, J = 4.7 Hz), 129.5, 130.7, 123.2, 133.0, 133.4 (q, J = 33.2 Hz), 135.1, 137.4, 140.0, 176.3, 180.2.

Example 9

9-1). 1-(4-methylphenyl)aminocyclohexanenitrile, 9a

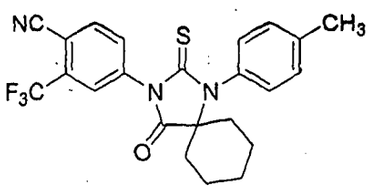
Sodium cyanide (0.147g, 3 mmol) was added to a mixture of *p*-toluidine (0.214 g, 2 mmol) and cyclohexanone (0.294 g, 3 mmol) in acetic acid 90% (3 ml). The reaction mixture was stirred at room temperature for 12 h and then 20 ml of ethyl acetate was added. The organic layer was washed with water (3 × 10 ml), dried over magnesium sulfate and concentrated under vacuum to dryness to yield 1-(4-methylphenyl)aminocyclohexanenitrile, **9a** (0.398 g, 1.86 mmol, 93%) as a brown solid.

9-2). 4-(4-imino-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 9b

Triethylamine (0.05 g, 0.5 mmol) was added to a solution of **1a** (0.228 g, 1 mmol) and **9a** (0.214 g, 1 mmol) in dry THF (2 ml). The reaction mixture was stirred at room temperature for 2 days and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 95:5) to afford 4-(4-imino-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, **9b** (0.035 g, 0.08 mmol, 8%).

9-3). 4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 9c, [RD48]

A mixture of **9b** (0.035 g, 0.08 mmol) in HCl aq., 2N (1 ml) and methanol (3 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (5 ml) and extracted with ethyl acetate (6 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield 4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, **9c**, [RD48] (0.034 g, 0.076 mmol, 95%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02-1.05 (m, 1H), 1.64-1.76 (m, 4H), 2.03-2.12 (m, 5H), 2.44 (s, 3H), 7.12-7.15 (m, 2H), 7.33-7.36 (m, 2H), 7.85 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 21.3, 24.0, 32.6, 67.4, 109.9, 114.9, 122.0 (q, J = 272.5 Hz), 127.3 (q, J = 4.6 Hz), 130.0, 130.5, 132.0, 132.5, 133.3 (q, J = 33.2 Hz), 135.2, 137.3, 140.1, 174.1, 180.1.

Example 10

10-1). 1-(4-methylphenyl)aminocyclohexanenitrile, 10a

Sodium cyanide (0.147g, 3 mmol) was added to a mixture of *p*-toluidine (0.214 g, 2 mmol) and cycloheptanone (0.337 g, 3 mmol) in acetic acid 90% (3 ml). The reaction mixture was stirred at room temperature for 12 h and then 20 ml of ethyl acetate was added. The organic layer was washed with water (3 × 10 ml), dried over magnesium sulfate and concentrated under vacuum to dryness to yield 1-(4-methylphenyl)aminocyclohexanenitrile, **10a** (0.438 g, 1.92 mmol, 96%) as a brown solid.

10-2). 4-(4-imino-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]undec-3-yl)-2-trifluoromethylbenzonitrile, 10b

Triethylamine (0.05 g, 0.5 mmol) was added to a solution of **1a** (0.228 g, 1 mmol) and **9a** (0.228 g, 1 mmol) in dry THF (2 ml). The reaction mixture was stirred at room temperature for 2 days and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 95:5) to afford 4-(4-imino-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]undec-3-yl)-2-trifluoromethylbenzonitrile, **10b** (0.036 g, 0.08 mmol, 8%).

10-3). 4-(4-oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]undec-3-yl)-2-trifluoromethylbenzonitrile, 10c, [RD49]

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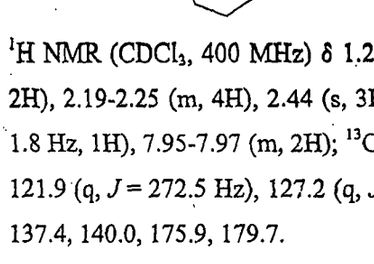
A mixture of **9b** (0.036 g, 0.08 mmol) in HCl aq., 2N (1 ml) and methanol (3 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (5 ml) and extracted with ethyl acetate (6 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **10c** (0.034 g, 0.075 mmol, 94%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24-134 (m, 2H), 1.37-1.43 (m, 2H), 1.53-1.60 (m, 2H), 1.74-1.82 (m, 2H), 2.19-2.25 (m, 4H), 2.44 (s, 3H), 7.16-7.19 (m, 2H), 7.32-7.35 (m, 2H), 7.83 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.95-7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 22.2, 30.9, 36.3, 71.1, 110.0, 114.9, 121.9 (q, J = 272.5 Hz), 127.2 (q, J = 4.6 Hz), 129.6, 130.5, 132.3, 133.0, 133.2 (q, J = 33.2 Hz), 135.1, 137.4, 140.0, 175.9, 179.7.

Example 11

11-1). 1-(4-hydroxyphenyl)aminocyclobutanenitrile, 11a

Trimethylsilyl cyanide (0.93 ml, 7 mmol) was added dropwise to a mixture of 4-hydroxyaniline (0.545 g, 5 mmol) and cyclobutanone (0.42 g, 6 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane:acetone, 98:2) to yield **11a** (0.903 g, 4.8 mmol, 96%) as a yellowish solid.

11-2). 4-(8-oxo-6-thioxo-5-(4-hydroxyphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 11b , [RD58]

A mixture of **1a** (0.57 g, 2.5 mmol) and **7a** (0.376 g, 2 mmol) in dry DMF (0.5 ml) was stirred at room temperature for 40 h. To this mixture were added methanol (30 ml) and HCl aq. (5 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (40 ml) and extracted with ethyl acetate (50 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 98:2) to yield **11b** (0.659 g, 1.58 mmol, 79%) as a white powder.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55-1.63 (m, 1H), 2.01-2.09 (m, 1H), 2.50-2.65 (m, 4H), 6.97-7.01 (m, 2H), 7.20-7.24 (m, 2H), 8.02 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 13.4, 31.3, 67.5, 108.9, 114.8, 116.1, 123.5 (q, J = 271.5 Hz), 127.4 (q, J = 4.9 Hz), 131.3, 131.8 (q, J = 32.7 Hz), 133.3, 135.5, 136.2, 138.5, 158.1, 175.1, 180.7.

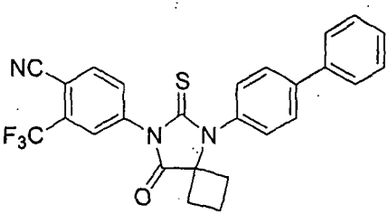
Example 12

12-1). 1-(4-biphenylamino)cyclobutanecarbonitrile, 12a

Trimethylsilyl cyanide (0.2 ml, 1.5 mmol) was added dropwise to a mixture of 4-biphenylamine (0.169 g, 1 mmol) and cyclobutanone (0.098 g, 1.4 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **12a** (0.24 g, 0.97 mmol, 97%) as a white solid.

12-2). 4-(8-oxo-6-thioxo-5-(4-biphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 12b [RD57]

A mixture of **1a** (0.137 g, 0.6 mmol) and **12a** (0.124 g, 0.5 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 3 days. To this mixture were added methanol (5 ml) and HCl aq. 2N (1 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (15 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **12b** (0.162 g, 0.34 mmol, 68%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67-1.76 (m, 1H), 2.19-2.31 (m, 1H), 2.59-2.74 (m, 4H), 7.40-7.44 (m, 3H), 7.47-7.53 (m, 2H), 7.64-7.67 (m, 2H), 7.79-7.82 (m, 2H), 7.88 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 67.5, 110.0, 114.9, 122.0 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 127.3, 128.1, 128.7, 129.0, 130.2, 132.3, 133.5 (q, J = 33.2 Hz), 134.2, 135.2, 137.2, 139.6, 142.8, 174.9, 179.9.

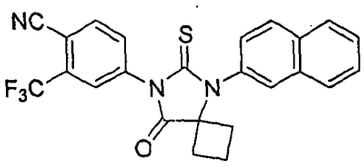
Example 13

13-1). 1-(2-naphthylamino)cyclobutanecarbonitrile, 13a

Trimethylsilyl cyanide (0.27 ml, 2 mmol) was added dropwise to a mixture of 2-aminonaphthalene (0.143 g, 1 mmol) and cyclobutanone (0.098 g, 1.4 mmol). The reaction mixture was stirred at room temperature for 12 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **13a** (0.209 g, 0.94 mmol, 94%) as a yellow solid.

13-2). 4-(8-oxo-6-thioxo-5-(4-biphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 12b, [RD85]

A mixture of **1a** (0.137 g, 0.6 mmol) and **13a** (0.111 g, 0.5 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 3 days. To this mixture were added methanol (5 ml) and HCl aq. (1 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (15 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **12b** (0.146 g, 0.325 mmol, 65%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 158-1.68 (m, 1H), 2.17-2.29 (m, 1H), 2.61-2.75 (m, 4H), 7.40 (dd, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 1H), 7.58-7.65 (m, 2H), 7.86-8.00 (m, 5H), 8.04 (J = 1.8 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.6, 67.7, 110.0, 114.9, 122.0 (q, J = 272.6 Hz), 126.8, 127.1 (q, J = 4.8 Hz), 127.2, 127.7, 128.0, 128.3, 129.1, 130.2, 132.2, 132.5, 133.4, 133.5 (q, J = 33.1 Hz), 133.6, 135.2, 137.2, 175.0, 180.1.

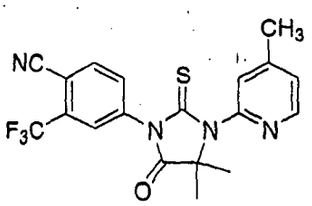
Example 14

14-1). 2-(4-methyl-2-pyridinamino)-2-methylpropanenitrile, 14a

Trimethylsilyl cyanide (0.27 ml, 2 mmol) was added dropwise to a mixture of 2-amino-4-methylpyridine (0.108 g, 1 mmol) and acetone (0.58 g, 10 mmol). The reaction mixture was stirred at room temperature for 6 days and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane: acetone, 60:40) to yield **14a** (0.133 g, 0.76 mmol, 76%) as a white solid.

14-2). 4-[4,4-dimethyl-3-(4-methylpyridin-2-yl)-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 14b, [RD83]

A mixture of **1a** (0.91 g, 0.4 mmol) and **14a** (0.053 g, 0.3 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 6 days. To this mixture were added methanol (5 ml) and HCl aq. (1ml). The second mixture was refluxed for 5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (15 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **14b** (0.07 g, 0.174 mmol, 58%) as a white powder.



^1H NMR ($CDCl_3$, 400 MHz) δ 1.70 (s, 6H), 2.44 (s, 3H), 7.19 (d, J = 4.4 Hz, 1H), 7.45 (t, J = 0.6 Hz, 1H), 7.82 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 8.47 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 24.1, 67.1, 110.2, 114.8, 121.9 (q, J = 272.6 Hz), 124.4, 125.1, 127.3 (q, J = 4.8 Hz), 132.4, 133.5 (q, J = 33.2 Hz), 135.3, 137.1, 149.2, 149.5, 150.0, 175.2, 179.0.

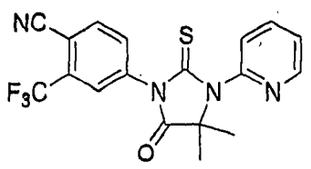
Example 15

15-1). 2-(2-pyridinamino)-2-methylpropanenitrile, 15a

Trimethylsilyl cyanide (0.27 ml, 2 mmol) was added dropwise to a mixture of 2-aminopyridine (0.094 g, 1 mmol) and acetone (0.58 g, 10 mmol). The reaction mixture was stirred at room temperature for 6 days and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane: acetone, 60:40) to yield **15a** (0.131 g, 0.81 mmol, 81%) as a white solid.

15-2). 4-[4,4-dimethyl-3-(4-pyridin-2-yl)-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 15b, [RD82]

A mixture of **1a** (0.91 g, 0.4 mmol) and **15a** (0.048 g, 0.3 mmol) in dry DMF (0.3 ml) was stirred at room temperature for 10 days. To this mixture were added methanol (5 ml) and of HCl aq. (1 ml). The second mixture was refluxed for 5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (15 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **15b** (0.059 g, 0.153 mmol, 51%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (s, 6H), 7.38 (dd, J_1 = 7.3 Hz, J_2 = 5.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.87 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.95 (td, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 1.3 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 8.62 (dd, J_1 = 4.7 Hz, J_2 = 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 67.1, 110.3, 114.8, 121.9 (q, J = 272.6 Hz), 123.7, 123.8, 127.3 (q, J = 4.8 Hz), 132.4, 133.6 (q, J = 33.2 Hz), 135.3, 137.1, 138.2, 149.5, 149.6, 175.1, 179.0.

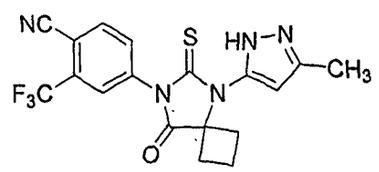
Example 16

16-1). 1-(5-methyl-2H-pyrazol-3-ylamino)-cyclobutanecarbonitrile, 16a

Trimethylsilyl cyanide (0.532 ml, 4.0 mmol) was added dropwise to the mixture of 3-amino-5-methylpyrazole (0.194 g, 2.0 mmol) and cyclobutanone (0.154 g, 2.2 mmol). The reaction mixture was stirred at room temperature for 40 h and then concentrated under vacuum to obtain a dark liquid which was subjected to chromatography (dichloromethane) to yield **16a** (0.267 g, 1.52 mmol, 76%) as a off-white powder.

16-2). 4-[5-(5-methyl-2H-pyrazol-3-yl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-7-yl]-2-trifluoromethyl-benzonitrile, 16b, [RD84]

A mixture of **1a** (0.0684 g, 0.3 mmol) and **16a** (0.053 g, 0.3 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 4 days. To this mixture were added methanol (10 ml) and HCl aq. 2N (2 ml). The second mixture was refluxed for 5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (30 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 97:3) to yield **16b** (0.0826 g, 0.2 mmol, 67%) as a white powder.

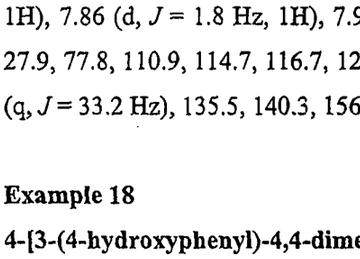


^{1}H NMR (acetone d_6, 400 MHz) δ δ 1.66-1.76 (m, 1H), 2.00-2.07 (m, 1H), 3.35 (s, 3H), 2.56-2.63 (m, 2H), 2.85-2.93 (m, 2H), 8.04 (dd, J_1 = 8.2 Hz, J_2 = 1.6 Hz, 1H), 8.18 (d, J = 1.6 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 11.99 (s, 1H); ^{13}C NMR (acetone d_6, 100 MHz) δ 10.2, 13.1, 31.1, 67.4, 102.5, 109.1, 114.8, 122.5 (q, J = 271.4 Hz), 127.8 (q, J = 4.8 Hz), 131.9 (q, J = 33.6 Hz), 133.6, 135.6, 138.4, 139.9, 145.0, 175.0, 179.6.

Example 17

4-[3-(4-hydroxyphenyl)-4,4-dimethyl-2,5-dithioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 17a, [RD59]

A mixture of **3c** (0.081 g, 0.2 mmol) and Lawesson reagent (0.097 g, 0.24 mmol) in toluene (3 ml) was heated to reflux for 15 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:pentane, 9:1) to yield **17a** (0.0185 g, 0.044 mmol, 22%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65 (s, 6H), 6.95-6.97 (m, 2H), 7.15-7.18 (m, 2H), 7.75 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H), 7.98 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 77.8, 110.9, 114.7, 116.7, 121.9 (q, J = 272.6 Hz), 128.1 (q, J = 4.8 Hz), 129.1, 130.7, 133.3, 133.5 (q, J = 33.2 Hz), 135.5, 140.3, 156.8, 179.9, 207.9.

Example 18

4-[3-(4-hydroxyphenyl)-4,4-dimethyl-2,5-dioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 18a, [RD60]

Hydrogen peroxide, 30% (3 ml, 26 mmol) was added dropwise to a solution of of **3c** (0.121 g, 0.4 mmol) in glacial acetic acid (3 ml). The mixture was stirred at room temperature for 12 h and then 20 ml of ethyl acetate was added. The organic layer was washed with water (3 × 15 ml), dried over magnesium sulfate, concentrated and chromatographed (dichloromethane) to yield **18a** (0.102 g, 0.261 mmol, 87%) as a white powder.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52 (s, 6H), 6.70-6.73 (m, 2H), 7.01-7.04 (m, 2H), 7.92 (d, J = 8.4 Hz, 1H), 8.00 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1H), 8.15 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 63.7, 108.4, 115.0, 116.7, 121.9 (q, J = 272.6 Hz), 123.5 (q, J = 4.8 Hz), 124.0, 128.5, 130.5, 133.6 (q, J = 33.2 Hz), 135.5, 136.2, 153.4, 157.2, 174.5.

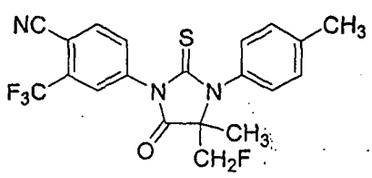
Example 19

19-1). 3-fluoro-2-methyl-2-(4-methylphenyl)aminopropionitrile, 19a

Trimethylsilyl cyanide (0.146 ml, 1.1 mmol) was added dropwise to the mixture of *p*-toluidine (0.107 g, 1 mmol) and fluoroacetone (0.082 g, 1.1 mmol). The reaction mixture was stirred at room temperature for 12 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **19a** (0.179 g, 0.93 mmol, 93%) as a yellowish solid.

19-2). 4-(4-fluoromethyl-4-methyl-5-oxo-2-thioxo-3-(4-methylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile, 19b, [RD68]

A mixture of **1a** (0.16 g, 0.7 mmol) and **19a** (0.096 g, 0.5 mmol) in dry DMF (0.3 ml) was stirred at room temperature for 48 h. To this mixture were added methanol (10 ml) and HCl aq. 2N (2 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (30 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **19b** (0.168 g, 0.4 mmol, 80%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 3H), 2.44 (s, 3H), 4.35 (dd, J_1 = 47.2 Hz, J_2 = 10.0 Hz, 1H), 4.71 (dd, J_1 = 45.2 Hz, J_2 = 10 Hz, 1H), 7.22-7.26 (m, 2H), 7.35-7.39 (m, 2H), 7.82 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.93 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.0 (d, J = 4.6 Hz), 21.3, 69.3 (d, J = 18.3 Hz), 81.9 (d, J = 179.5 Hz), 109.9, 114.8, 121.8 (q, J = 272.6 Hz), 127.2 (q, J = 4.7 Hz), 129.3, 130.9, 131.6, 132.3, 133.3 (q, J = 33.2 Hz), 135.3, 137.0, 140.5, 174.1, 181.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -62.5, 110.9.

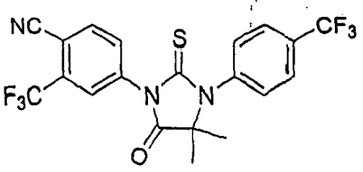
Example 20

20-1). 2-methyl-2-(4-trifluoromethylphenyl)aminopropanenitrile, 20a

A mixture of 4-trifluoromethylaniline (1.61 g, 10 mmol), acetone cyanohydrin (5 ml) and magnesium sulfate (2 g) was heated to 80 °C and stirred for 12 h. To the medium was added ethyl acetate (50 ml) and then washed with water (3 × 30 ml). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to dryness to yield **20a** (2.166 g, 9.5 mmol, 95%) as brown solid.

20-2). 4-(4,4-dimethyl-5-oxo-2-thioxo-3-(4-trifluoromethylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile, 20b, [RD66]

A mixture of **1a** (0.114 g, 0.5 mmol) and **20a** (0.092 g, 0.4 mmol) in dry DMF (0.3 ml) was stirred at room temperature for 48 h. To this mixture were added methanol (10 ml) and HCl aq. (3 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (20 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **20b** (0.117 g, 0.256 mmol, 64%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 6H), 7.45-7.49 (m, 2H), 7.80-7.83 (m, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 66.6, 110.3, 114.8, 121.8 (q, J = 272.6 Hz), 123.5 (q, J = 271.1 Hz), 127.0 (q, J = 4.6 Hz), 127.1 (q, J = 4.7 Hz), 130.3, 131.9 (q, J = 32.9 Hz),, 132.2, 133.5 (q, J = 33.3 Hz), 135.3, 136.9, 138.4, 174.6, 179.9.

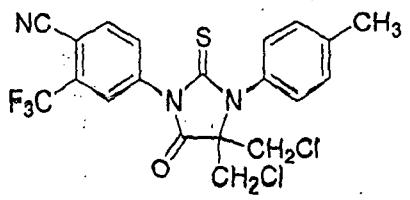
Example 21

21-1). 3-chloro-2-chloromethyl-2-(4-methylphenyl)aminopropanenitrile, 21a

Trimethylsilyl cyanide (0.27 ml, 2 mmol) was added dropwise to a mixture of *p*-toluidine (0.107 g, 1 mmol) and 1,3-dichloroacetone (0.254 g, 2 mmol). The reaction mixture was heat to 80 °C and stirred for 6 h. To the mixture was added 20 ml of ethyl acetate and then wash with water (2 × 20 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **21a** (0.192 g, 0.79 mmol, 79%) as a brown powder.

21-2). 4-(4,4-bischloromethyl-5-oxo-2-thioxo-3-(4-methylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile, 21b, [RD67]

A mixture of **1a** (0.16 g, 0.7 mmol) and **21a** (0.122 g, 0.5 mmol) in dry DMF (0.5 ml) was stirred at room temperature for 10 days. To this mixture were added methanol (10 ml) and of HCl aq. 2N (2 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **21b** (0.09 g, 0.19 mmol, 38%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.44 (s, 3H), 3.54 (d, J = 11.8 Hz, 2H), 3.93 (d, J = 11.8 Hz, 2H), 7.37-7.40 (m, 2H), 7.48-7.51 (m, 2H), 7.79 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 42.8, 74.3, 110.7, 114.7, 121.7 (q, J = 272.6 Hz), 127.2 (q, J = 4.7 Hz), 128.8, 131.0, 131.1, 132.4, 133.8 (q, J = 33.2 Hz), 135.5, 136.9, 140.9, 169.5, 182.5.

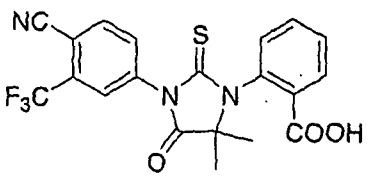
Example 22

22-1). 1-(4-methylphenyl)aminocyclohexanenitrile, 22a

Sodium cyanide (0.245g, *5 mmol*) was added to a mixture of anthranilic acid (0.411 g, 3 mmol) and acetone (1 ml, 13.6 mmol) in acetic acid 90% (3 ml). The reaction mixture was stirred at room temperature for 12 h and then 50 ml of ethyl acetate was added. The organic layer was washed with brine (3 × 30 ml). The organic layer was dried over magnesium sulfate, concentrated and chromatographed (dichloromethane:acetone, 90:10) to yield **22a** (0.551 g, 2.7 mmol, 90%) as a brown solid.

22-2). 2-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]benzoic acid, 22b, [RD65]

A mixture of **1a** (0.114 g, 0. mmol) and **22a** (0.103 g, 0.5 mmol) in dry DMF (0.5 ml) was stirred at room temperature for 3 days. To this mixture were added methanol (10 ml) and HCl aq. 2N, (3 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (ethyl acetate:pentane, 2:1) to yield **22b** (0.143 g, 0.33 mmol, 66%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 3H), 1.78 (s, 3H), 7.39 (d, J = 7.7 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H) 7.76-7.82 (m, 2H), 7.90-7.98 (m, 2H), 8.22 (d, J = 6.8 Hz, 1H), 8.96 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 26.2, 67.6, 110.1, 114.8, 121.9 (q, J = 272.6 Hz), 127.2 (q, J = 4.7 Hz), 128.9, 131.0, 130.2, 132.5, 133.2 (q, J = 33.3 Hz), 133.7, 134.7, 135.4, 135.8, 137.3, 169.8, 175.3, 180.7.

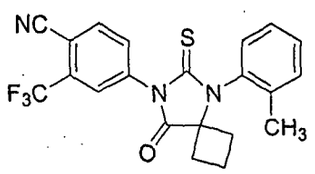
Example 23

23-1). 1-(2-methylphenyl)aminocyclobutanenitrile, 23a

Trimethylsilyl cyanide (0.66 ml, 5 mmol) was added dropwise to the mixture of *p*-toluidine (0.321 g, 3 mmol) and cyclobutanone (0.28 g, 4 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **23a** (0.541 g, 2.91 mmol, 97%) as a yellowish solid.

23-2). 4-(8-oxo-6-thioxo-5-(2-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 23b, [RD71]

A mixture of **1a** (0.114 g, 0.5 mmol) and **23a** (0.093 g, 0.5 mmol) in dry DMF (0.3 ml) was stirred at room temperature for 3 days. To this mixture were added methanol (10 ml) and HCl aq. 2N, (3 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **23b** (0.116 g, 0.28 mmol, 56%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63-1.69 (m, 1H), 2.26 (s, 3H), 2.28-2.41 (m, 2H), 2.58-2.76 (m, 3H), 7.21 (d, J = 7.6 Hz, 1H), 7.39-7.49 (m, 3H), 7.89 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 18.0, 30.7, 32.2, 67.6, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 127.5, 129.8, 130.2, 131.9, 132.3, 133.4, 133.5 (q, J = 34.3 Hz), 135.2, 135.8, 137.1, 138.0, 175.3, 178.7.

Example 24

24-1). 1-aminocyclopentanecarbonitrile, 24a

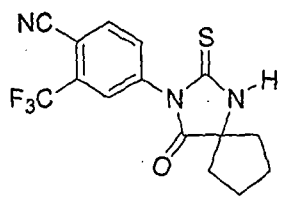
Ammonia anhydrous was bubble into a mixture of cyclopentanone (0.452 g) and trimethylsilyl cyanide (0.66 ml, 5 mmol). The excess of ammonia was refluxed by a dry ice-acetone condenser. After 1 h of reflux, the ammonia was allowed to degas form the medium and then the remaining mixture was concentrated under vacuum to yield **24a** (0.522 g, 4.75 mmol, 95%) as a colorless liquid.

24-2). 4-(4-imino-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 24b

Triethylamine (0.101 g, 0.1 mmol) was added to a solution of **1a** (0.684 g, 3 mmol) and **24a** (0.33 g, 3 mmol) in dry THF (5 ml). The reaction mixture was stirred at room temperature for 5 h and then concentrated to yield a brown residue which was subjected to flash chromatography (dichloromethane/acetone, 93:7) to afford **24b** (0.741 g, 2.19 mmol, 73%).

24-3). 4-(4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 24c, [RD77]

A mixture of **24b** (0.741 g, 2.19 mmol) in HCl aq., 2N (4 ml) and methanol (20 ml) was heated to reflux for 1 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (40 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **24c** (0.72 g, 2.12 mmol, 97%) as a white powder.

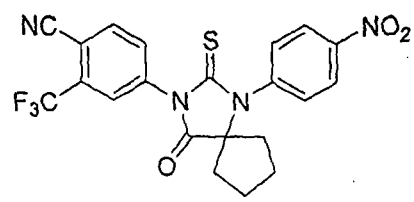


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.86-190 (m, 2H), 1.96-2.05 (m, 4H), 2.26-2.30 (m, 2H), 7.80 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H) 8.20 (bs, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3, 38.1, 71.0, 110.1, 114.8, 121.8 (q, J = 272.7 Hz), 126.8 (q, J = 4.7 Hz), 131.9, 133.6 (q, J = 34.3 Hz), 135.3, 136.7, 176.1, 179.8.

Example 25

25). 4-[1-(4-nitrophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl]-2-trifluoromethylbenzonitrile, 25a, [RD55]

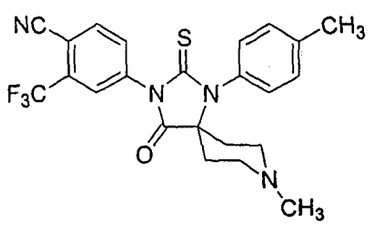
A mixture of **25c** (0.0678 g, 0.2 mmol), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.05 g, 0.33 mmol) and 4-fluoronitrobenzene (0.056 g, 0.4 mmol) in dimethylformamide (0.5 ml) was placed under argon in a sealed-tube and heated to 130 °C for 40 h. The reaction mixture was poured into ethyl acetate (5 ml) and washed with water (2 × 10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **25a** (0.038 g, 0.084 mmol, 42%) as a white powder.



Triethylamine (0.02, 0.2 mmol) was added to a solution of **1a** (0.228 g, 1 mmol) and **27a** (0.114 g, 0.5 mmol) in dry THF (2 ml). The reaction mixture was stirred at room temperature for 20 h and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 90:10, and then acetone) to afford **27b** (0.059 g, 0.13 mmol, 26%).

27-3). 4-(8-methyl-4-oxo-2-thioxo-1-(4-methylphenyl)-1,3,8-triazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 27c, [RD53]

A mixture of **27b** (0.059 g, 0.13 mmol) in HCl aq., 2N (1 ml) and methanol (3 ml) was heated to reflux for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (5 ml) and extracted with ethyl acetate (10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 60:40) to yield **27c** (0.055 g, 0.012 mmol, 92%) as a white powder.

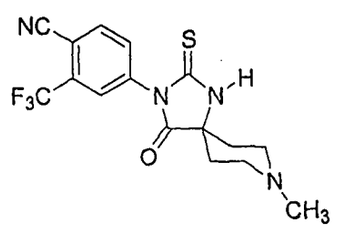


^{1}H NMR (Acetone-d_6, 400 MHz) δ 1.93-1.99 (m, 1H), 2.00-2.04 (m, 1H), 2.18 (s, 3H), 2.24-2.28 (m, 2H), 2.38 (s, 3H), 2.61-2.72 (m, 4H), 7.18-7-20 (m, 2H), 7.32-7.35 (m, 2H), 8.03 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 20.3, 31.4, 45.1, 49.8, 65.1, 109.1, 114.8, 122.4 (q, J = 275.1 Hz), 127.7 (q, J = 4.8 Hz), 130.0, 130.5, 131.9 (q, J = 32.6 Hz), 132.6, 133.5, 135.6, 138.3, 139.4, 174.0, 180.6.

Example 28

4-(8-methyl-4-oxo-2-thioxo-1,3,8-triazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 28a, [RD52]

Compound **28a** was synthesized according to the procedure described in patent US 5958936.

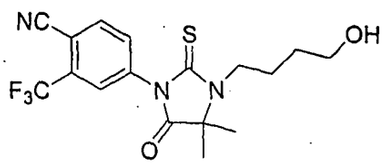


^{1}H NMR (Acetone-d_6, 400 MHz) δ 1.93-2.00 (m, 2H), 2.09-2.16 (m, 2H), 2.25 (s, 3H), 2.42-2.49 (m, 2H), 2.75-2.80 (m, 2H), 7.97 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 8.11 (d, J = 1.8 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 9.80 (bs, NH); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 32.9, 45.4, 50.1, 62.3, 109.1, 114.8, 122.4 (q, J = 271.6 Hz), 127.5 (q, J = 4.8 Hz), 131.8 (q, J = 32.7 Hz), 133.2, 135.6, 135.6, 138.0, 175.2, 180.4.

Example 29

4-[3-(4-hydroxybutyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, RU 59063

Compound **RU 59063** was synthesized according to the procedure described by Teutsch *et al* [*J. Steroid. Biochem. Molec. Biol.* **1994**, *48(1)*, 111-119].



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55 (s, 6H), 1.58-1.62 (m, 2H), 1.86-1.89 (m, 2H), 2.25 (bs, OH), 3.65-3.71 (m, 4H), 7.74 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1, 24.7, 29.6, 43.9, 61.7, 65.2, 109.7, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.8 Hz), 132.2, 133.7 (q, J = 34.3 Hz), 135.2, 137.2, 175.3, 178.2.

Example 30

30-1). 1-methylaminocyclobutanecarbonitrile, 30a

Methylamine was bubbled into a refrigerated mixture of cyclobutanone (0.21 g, 3 mmol) and trimethylsilyl cyanide (0.396 g, 4 mmol) until the volume doubled. The mixture was stirred 3 h and then concentrated to dryness to obtain **30a** (0.33 g, quantitative).

30-2). 4-(5-methyl-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylenzonitrile, 30b, [RD73]

A mixture of **1a** (0.114 g, 0.5 mmol) and **30a** (0.055 g, 0.5 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 0.5 h. To this mixture were added 10 ml of methanol and 2 ml of 2N HCl. The second mixture was refluxed for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **30b** (0.148 g, 0.435 mmol, 87%) as a white powder.

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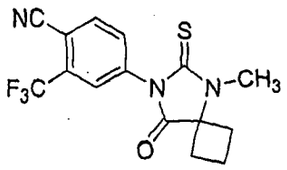
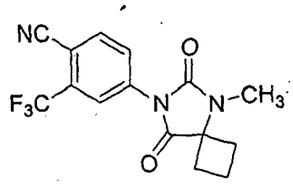


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95-2.06 (m, 1H), 2.21-2.32 (m, 1H), 2.58-2.71 (m, 4H), 3.44 (s, 3H), 7.77 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 30.3, 30.4, 66.1, 109.7, 114.9, 121.9 (q, J = 272.6 Hz), 126.9 (q, J = 4.8 Hz), 132.1, 133.2 (q, J = 34.3 Hz), 135.2, 137.3, 175.1, 178.7.

30-3). 4-(5-methyl-6,8-dioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 30c, [RD74]

Hydrogen peroxide (2 ml, 30%) was added to the mixture of **30b** (0.068 g, 0.2 mmol) in glacial acetic acid (3 ml). After being stirred at room temperature for 10 h, the reaction mixture was poured into ethyl acetate (20 ml) and then washed with water (2 × 20 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone) to yield **30c** (0.057 g, 0.176 mmol, 88%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91-2.35 (m, 1H), 2.21-2.31 (m, 1H), 2.50-2.61 (m, 4H), 3.12 (s, 3H), 7.89 (d, J = 8.2 Hz, 1H), 7.97 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1H), 8.12 (d, J = 2.0 Hz, 1H),; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 25.4, 29.3, 63.4, 108.1, 115.1, 121.6 (q, J = 272.6 Hz), 122.9 (q, J = 4.8 Hz), 127.9, 133.5 (q, J = 34.3 Hz), 135.3, 136.5, 152.7, 174.4.

Example 31

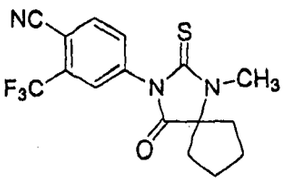
31-1). 1-methylaminocyclopentanecarbonitrile, 31a

Methylamine was bubbled into a refrigerated mixture of cyclopentanone (0.252 g, 3 mmol) and trimethylsilyl cyanide (0.396 g, 4 mmol) until the volume doubled. The mixture was stirred 3 h and then concentrated to dryness to obtain **31a** (0.372 g, quantitative).

31-2). 4-(1-methyl-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 31b, [RD75]

A mixture of **1a** (0.114 g, 0.5 mmol) and **31a** (0.062 g, 0.5 mmol) in dry DMF (0.2 ml) was stirred at room temperature for 0.5 h. To this mixture were added 10 ml of methanol and 2 ml of 2N HCl. The

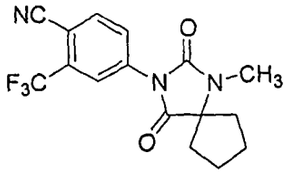
second mixture was refluxed for 2 h. After being cooled to room temperature, the reaction mixture was poured into cold water (20 ml) and extracted with ethyl acetate (30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **31b** (0.159 g, 0.45 mmol, 90%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91-2.05 (m, 6H), 2.16-2.21 (m, 2H), 3.27 (s, 3H), 7.77 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.89 (d, J = 1.8 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 30.3, 35.4, 73.2, 109.5, 114.9, 121.9 (q, J = 272.6 Hz), 126.9 (q, J = 4.8 Hz), 132.2, 133.2 (q, J = 34.3 Hz), 135.2, 137.5, 176.8, 178.5.

31-3). 4-(1-methyl-2,4-dioxo-1,3-diaza-spiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 31c, [RD76]

Hydrogen peroxide (2 ml, 30%) was added to the mixture of **31b** (0.07 g, 0.2 mmol) in glacial acetic acid (3 ml). After being stirred at room temperature for 10 h, the reaction mixture was poured into ethyl acetate (20 ml) and then washed with water (2 × 20 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone) to yield **31c** (0.057 g, 0.168 mmol, 84%) as a white powder.

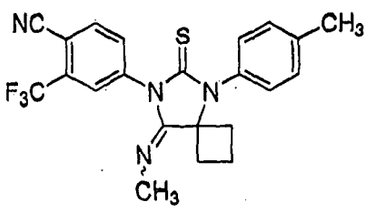


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88-1.99 (m, 6H), 2.12-2.17 (m, 2H), 2.98 (s, 3H), 7.88 (d, J = 8.2 Hz, 1H), 7.97 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 8.12 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 26.5, 34.8, 70.1, 108.0, 115.1, 122.0 (q, J = 272.5 Hz), 122.9 (q, J = 4.9 Hz), 127.9, 133.5 (q, J = 32.9 Hz), 135.3, 136.6, 152.7, 176.1.

Example 32

4-(8-methylimino-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-7-yl)-2-trifluoromethyl-benzonitrile, 32a, [RD90]

A mixture of **7b** (0.042 g, 0.1 mmol), DBU (0.023 g, 0.15 mmol) and iodomethane (0.073 g, 0.5 mmol) in DMF (0.3 ml) was stirred for 15 h at room temperature. After DMF being evaporated, the medium was chromatographed (dichloromethane) to yield **32a** (0.011g, 0.026 mmol, 26%) as white powder.

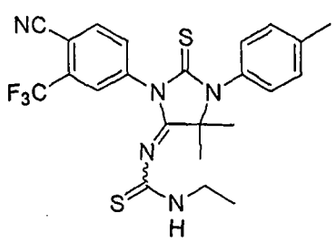


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58-1.65 (m, 1H), 2.04-2.13 (m, 1H), 2.45 (s, 3H), 2.70-2.77 (m, 2H), 3.06-3.10 (m, 2H), 3.58 (s, CH_3-N, major isomer) [2.70 (s, CH_3-N, minor isomer)], 7.20-7.34 (m, 4H), 7.75-7.91 (m, 3H); ($CDCl_3$, 100 MHz) δ 12.6, 21.4, 30.2, 33.7 (35.3 for the other isomer), 66.9, 109.1, 115.2, 122.1 (q, J = 272.5 Hz), 128.5 (q, J = 4.9 Hz), 129.8, 130.4, 130.6, 132.8, 133.2 (q, J = 32.9 Hz), 133.5, 134.9, 139.8, 157.0, 180.2.

Example 33

1-[3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene]-3-ethyl-thiourea, 33a, [RD91]

A mixture of **5b** (0.06 g, 0.149 mmol), ethylthioisocyanate (0.087 g, 1 mmol) and CuI (0.01 g, 0.05 mmol) in DMF (0.1 ml) was heated under microwave for 45 minutes. Then the medium was washed with brine and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and chrpmatographed (HPLC, alumina column) to yield **33a** (0.054 g, 0.108 mmol, 72%) as white powder.

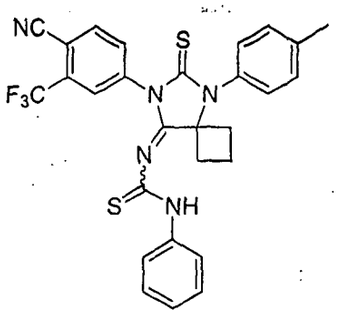


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, J = 7.23 Hz, 3H), 1.70 [1.75 minor isomer] (s, 6H), 2.42 (s, 3H), 3.28-3.39 (m, 2H) [3.15-3.22 (m, 2H), minor isomer], 6.50 (bs, 1H) [6.93 (bs, 1H), minor isomer], 7.14-7.18 (m, 2H), 7.32-7.35 (m, 2H), 7.77-7.94 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.31 (13.83 minor), 21.3, 25.22 (24.89 minor), 40.31 (40.67 minor), 68.1, 109.9, 114.9, 122.3 (q, J = 272.5 Hz), 127.6 (q, J = 4.9 Hz), 129.1, 129.59 (129.55 minor), 130.52 (130.57 minor), 132.27 (132.15 minor), 132.9 (q, J = 32.9 Hz), 134.27 (134.15 minor), 134.9, 135.2, 156.33 (156.06 minor), 180.28 (180.06 minor), 187.24 (186.63 minor).

Example 34

1-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-3-phenyl-thiourea, 34a, [RD92]

A mixture of **7b** (0.021 g, 0.05 mmol) and phenylthioisocyante (0.027 g, 0.2 mmol) in DMF (0.3 ml) was stirred for 2 days at 60°C. After DMF being evaporated, the medium was chromatographed (dichloromethane) to yield **34a** (0.015 g, 0.028 mmol, 57%) as white powder.

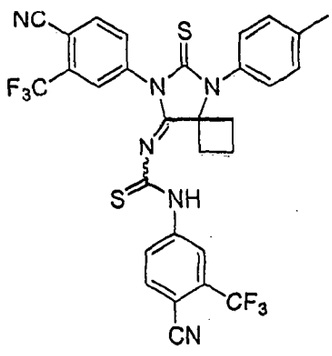


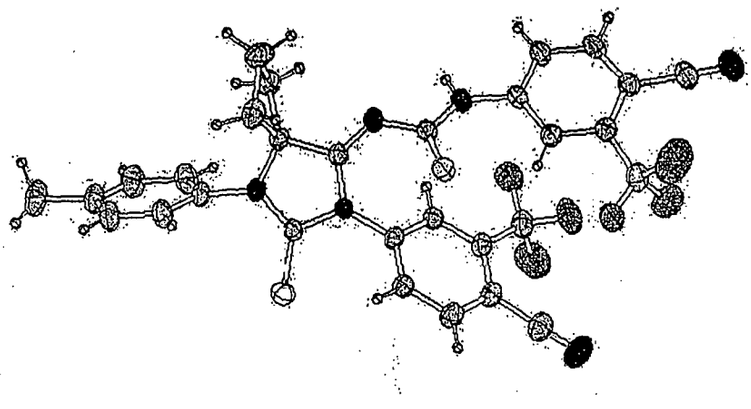
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.59-1.67 (m, 1H), 2.12-2.22 (m, 1H), 2.45 (s, 3H), 2.61-2.71 (m, 2H), 2.81-2.87 (m, 2H), 7.18-7.27 (m, 6H), 7.33-7.41 (m, 5H), 7.60-7.62 (m, 1H), 8.40 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 21.4, 32.3, 69.6, 110.7, 114.8, 121.6, 122.0 (q, J = 272.5 Hz), 126.3, 128.0 (q, J = 4.9 Hz), 128.9, 129.4, 130.7, 132.5, 133.2 (q, J = 32.9 Hz), 134.1, 134.9, 137.7, 139.2, 140.2, 154.8, 180.3, 185.5.

Example 35

1-(4-Cyano-3-trifluoromethyl-phenyl)-3-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-thiourea, 35a, [RD93]

A mixture of **1a** (0.5.02 g, 2.2 mmol) and **7a** (0.186 g, 1 mmol) in DMF (1 ml) was stirred at room temperature. After 20 hours of stirring, the mixture was concentrated under reduced pressure to yield an orange viscous liquid, which was chromatographed (dichloromethane:acetone, 99:1) to yield **35a** (0.269 g, 0.42 mmol, 42%) as a yellow powder.





X-ray structure of **35a**

Example 36

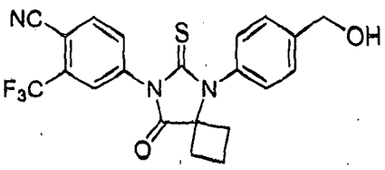
36-1). 1-(4-hydroxymethylphenylamino)-cyclobutanecarbonitrile, 36a

Trimethylsilyl cyanide (0.66 ml, 5 mmol) was added dropwise to a mixture of 4-aminobenzoic acid (0.492 g, 4 mmol) and cyclobutanone (0.35 g, 5 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **36a** (0.677 g, 3.36 mmol, 84%) as a brown solid.

36-2). 4-[8-(4-hydroxymethylphenyl)-5-oxo-7-thioxo-6-azaspiro[3.4]oct-6-yl]-2-trifluoromethyl-benzonitrile, 36b, [RD110]

A mixture of **1a** (0.342 g, 1.5 mmol) and **36a** (0.21 g, 1 mmol) in dry DMF (0.5 ml) was stirred at room temperature for 24 h. To this mixture were added methanol (20 ml) and HCl aq. 2N (5 ml). The second mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into cold water (40 ml) and extracted with ethyl acetate (60 ml). The organic layer was dried over

$MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 90:10) to yield **36b** (0.296 g, 0.69 mmol, 69%) as a white powder.

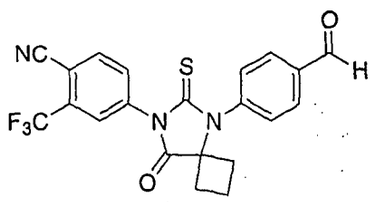


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63-1.68 (m, 1H), 2.17-2.26 (m, 1H), 2.52-2.68 (m, 4H), 4.75 (s, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.88 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 64.4, 67.5, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 128.3, 130.0, 132.2, 133.3, 133.4 (q, J = 33.2 Hz), 134.2, 137.2, 142.9, 174.9, 179.9.

Example 37

4-[5-(4-formylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethyl-benzonitrile, 37a, [RD114]

To a mixture of **36b** (0.303 g, 0.7 mmol) and Dess-Martin periodinane (0.417g, 1 mmol) in dichloromethane (5 ml) was added pyridine (1.01g, 1 mmol). The mixture was stirred for 2 hours at room temperature and then ethyl ether (10 ml) was added to precipitate the by-product of the reaction. After filtration and concentration under reduced pressure, the mixture was chromatographed (dichloromethane:acetone, 95:5) to yield **37a** (0.24 g, 0.56 mmol, 80%) as white powder.

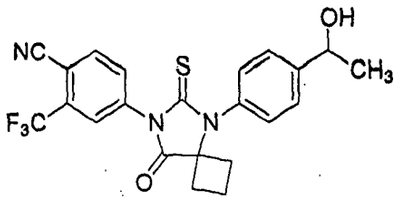


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62-1.73 (m, 1H), 2.24-2.30 (m, 1H), 2.50-2.58 (m, 2H), 2.69-2.75 (m, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.97-7.99 (m, 2H), 8.11 (d, J = 8.1 Hz, 2H), 10.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.7, 67.5, 110.2, 114.8, 121.9 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 129.1, 131.0, 131.2, 132.2, 133.3 (q, J = 33.2 Hz), 135.3, 136.9, 140.5, 174.5, 179.8, 190.8.

Example 38

4-{5-[4-(1-hydroxyethyl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethyl-benzonitrile, 38a [RD116]

The mixture of **37a** (0.043 g, 0.1 mmol) and dry THF (1 ml) in a flamed-dried flash was placed under argon and cooled to -78°C. Then, methylmagnesium iodide (1.1 ml, 0.1 M) was added. The mixture was stirred at -78°C for 30 minutes and warmed slowly to room temperature. The medium was washed with water (3 ml) and extracted with ethyl acetate (10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield **38a** (0.037 g, 0.082 mmol, 82%) as a white powder.

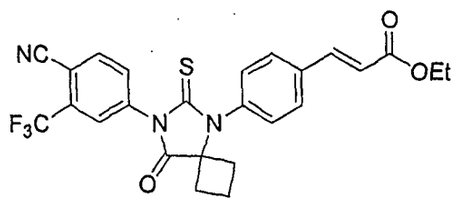


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57 (d, J = 6.5 Hz, 3H), 1.61-1.71 (m, 1H), 2.09 (d, J = 3.2 Hz, OH), 2.16-2.28 (m, 1H), 2.52-2.60 (m, 2H), 2.63-2.69 (m, 2H), 5.00 (dd, J_1 = 6.5 Hz, q, J_2 = 3.1 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 25.3, 31.5, 67.4, 69.8, 110.0, 114.9, 121.9 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 127.1, 129.9, 132.2, 133.4 (q, J = 33.2 Hz), 134.1, 135.2, 137.1, 147.6, 174.9, 179.9.

Example 39

3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-acrylic acid ethyl ester, 39a [RD117]

A mixture of **37a** (0.043 g, 0.1 mmol) and (carbethoxyethylidene)triphenylphosphorane (0.039 g, 0.12 mmol) in dichloromethane (2 ml) was stirred at room temperature for 10 hours. The medium was concentrated and chromatographed (dichloromethane) to yield **39a** (0.048 g, 0.096 mmol, 96%) as white powder.

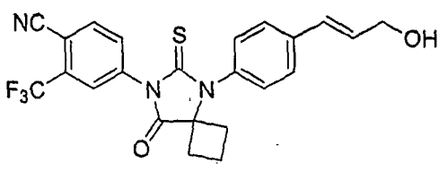


^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, J = 7.1 Hz, 3H), 1.66-1.70 (m, 1H), 2.19-2.65 (m, 1H), 2.51-2.69 (m, 2H), 2.66-2.72 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 6.51 (d, J = 16.1 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 16.1 Hz, 1H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 14.3, 31.6, 60.8, 67.5, 110.0, 114.9, 120.5, 121.8 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 129.5, 130.5, 132.2, 133.4 (q, J = 33.2 Hz), 135.2, 136.0, 136.5, 137.0, 142.7, 166.5, 174.7, 179.8.

Example 40

4-{5-[4-(3-hydroxypropenyl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethylbenzonitrile, 40a [RD120]

To a mixture of **39a** (0.05 g, 0.1 mmol) in dichloromethane (2 ml) at -78°C was added a solution of diisobutylaluminum hydride in THF (0.11 ml, 1M, 0.11 mmol). The mixture was stirred at -78°C for 3 hours. After being warmed to room temperature, the mixture was washed with an aqueous solution of sodium thiosulfate and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield **40a** (0.040 g, 0.089 mmol, 89%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57-1.68 (m, 1H), 2.17-2.39 (m, 1H), 2.55-2.61 (m, 2H), 2.61-2.67 (m, 2H), 4.39 (d, J = 4.7 Hz, 2H), 6.47 (dt, J_1 = 16.0 Hz, J_2 = 5.3 Hz, 1H), 6.70 (d, J = 16.0 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 63.4, 67.4, 110.0, 114.8, 120.5, 121.8 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 127.9, 129.2, 130.1, 131.1, 132.1, 133.4 (q, J = 33.2 Hz), 135.2, 137.1, 138.4, 174.8, 179.9.

Example 41

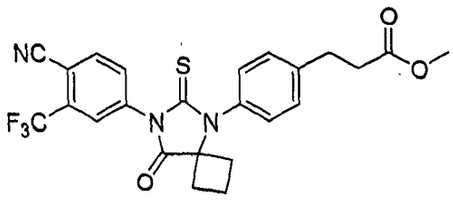
41-1) 3-[4-(1-cyanocyclobutylamino)-phenyl]-propionic acid, 41a (41-1)

Trimethylsilyl cyanide (0.4 g, 4 mmol) was added dropwise to a mixture of 3-(4-aminophenyl)-propionic acid (0.33 g, 2 mmol), cyclobutanone (0.35 g, 5 mmol) and sodium sulfate (1 g) in 1,4-dioxane (5 ml). The mixture was stirred for 15 hours. After filtration to eliminate sodium sulfate, the medium was concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane:acetone, 50:50) to yield **41a** (0.472 g, 1.93 mmol, 97%) as a yellowish solid.

41-2) 3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-propionic acid methyl ester, 41b (41-2) [RD128]

A mixture of **1a** (0.661 g, 2.9 mmol) and **41a** (0.472 g, 1.93 mmol) in dry DMF (2 ml) was stirred at room temperature for 15 hours. To this mixture were added methanol (10 ml) and HCl aq. (5 ml, 2M). The second mixture was refluxed for 3 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (3 × 30 ml). The organic layer was

dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **41b** (0.582 g, 1.19 mmol, 62%) as a white powder.



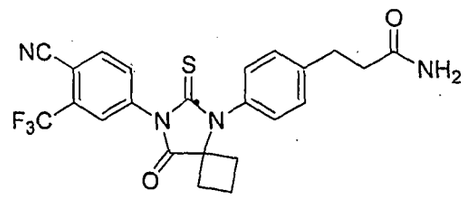
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.70 (m, 1H), 2.14-2.26 (m, 1H), 2.51-2.56 (m, 2H), 2.58-2.67 (m, 2H), 2.71 (t, J = 7.8 Hz, 2H), 3.05 (t, J = 7.8 Hz, 2H), 3.69 (s, 3H), 7.23 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 30.5, 31.4, 35.1, 51.8, 67.5, 109.9, 114.9, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.9, 130.0, 133.2, 132.3, 133.3 (q, J = 33.2 Hz), 135.7, 137.2, 142.5, 173.1, 174.9, 179.9.

41-3) 3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-propionic acid, 41c (41-3) [RD132]

A mixture of **41b** (0.487 g, 1 mmol) in methanol (10 ml) and solution of sodium hydroxide (10 ml, 2M) was stirred at room temperature for 5 hours. Methanol was evaporated. The residue was adjusted to pH = 5 by HCl aq. (2M) and then extracted with ethyl acetate (3 ×50 ml). The organic layer was dried over $MgSO_4$ and concentrated to dryness to obtain **41c** (0.472 g, 0.99 mmol, 99%).

41-4) 3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-propionamide, 41d (41-4) [RD133]

To a suspension of **41c** (0.094 g, 0.2 mmol) in THF (10 ml) at -5°C was added thionyl chloride (0.019 ml, 0.26 mmol). The medium was stirred at -5°C for one hour. Then ammonia was bubbled into the mixture. The excess of ammonia was condensed by reflux condenser at -78°C for 30 minutes and then was allowed to evaporate. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield **41d** (0.09 g, 0.19 mmol, 95%) as an off-white powder.

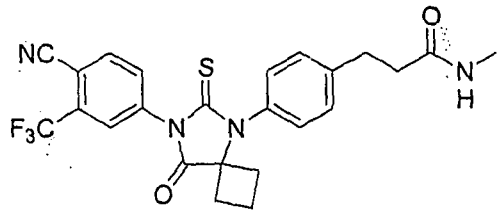


^{1}H NMR (acetone-d_6, 400 MHz) δ 1.52-160 (m, 1H), 2.01-2.09 (m, 1H), 2.49-2.58 (m, 4H), 2.61-2.67 (m, 2H), 2.98 (t, J = 7.5 Hz, 2H), 6.20 (bs, 1H), 6.78 (bs, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 8.03 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 8.15 (d, J = 1.8 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H); ^{13}C

NMR (acetone-d_6, 100 MHz) δ 13.4, 30.7, 31.2, 36.4, 67.5, 109.0, 114.8, 122.5 (q, J = 271.5 Hz), 127.5 (q, J = 4.7 Hz), 129.5, 130.0, 131.8 (q, J = 32.5 Hz), 133.3, 133.8, 135.6, 138.4, 143.2, 171.6, 174.9, 178.0.

41-5) 3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-N-methyl-propionamide, 41e (41-5) [RD134]

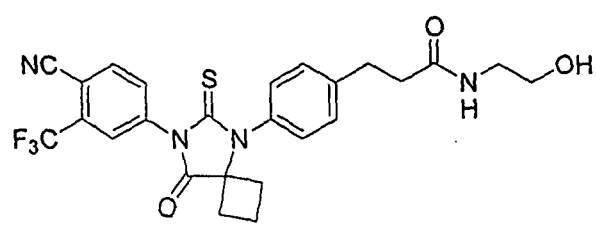
To a suspension of **41c** (0.094 g, 0.2 mmol) in THF (10 ml) at -5°C was added thionyl chloride (0.019 ml, 0.26 mmol). The medium was stirred at -5°C for one hour. Then methylamine was bubbled into the mixture at -5°C for 30 minutes. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 75:25) to yield **41e** (0.092 g, 0.19 mmol, 95%) as an off-white powder.



^{1}H NMR (acetone-d_6, 400 MHz) δ 1.51-1.60 (m, 1H), 2.01-2.11 (m, 1H), 2.48-2.58 (m, 4H), 2.61-2.67 (m, 2H), 2.77 (d, J = 4.6 Hz, 3H), 2.98 (t, J = 7.5 Hz, 2H), 7.03 (bs, NH), 7.33 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 8.01 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 8.13 (d, J = 1.8 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 13.4, 25.3, 30.0, 31.2, 37.0, 67.6, 109.0, 114.8, 122.5 (q, J = 271.5 Hz), 127.4 (q, J = 4.7 Hz), 129.5, 130.0, 131.9 (q, J = 32.5 Hz), 133.3, 133.8, 135.6, 138.4, 143.1, 171.7, 175.0, 178.0.

41-6) 3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-N-(2-hydroxyethyl)-propionamide, 41f (41-6) [RD135]

To a suspension of **41c** (0.094 g, 0.2 mmol) in THF (10 ml) at -5°C was added thionyl chloride (0.019 ml, 0.26 mmol). The medium was stirred at -5°C for one hour. Then 2-aminoethanol (0.0183 g, 0.03 mmol) was added into the mixture at -5°C. After stirring of an additional 30 minutes, the medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 50:50) to yield **41f** (0.093 g, 0.18 mmol, 90%) as an off-white powder.



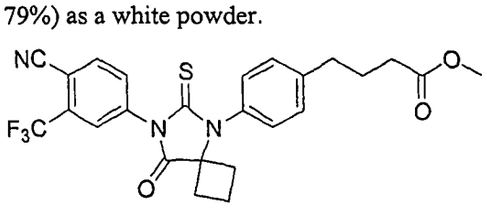
^{1}H NMR (acetone-d_6, 400 MHz) δ 1.51-161 (m, 1H), 2.01-2.11 (m, 1H), 2.49-2.66 (m, 6H), 2.99 (t, J = 7.5 Hz, 2H), 3.27 (dd, J_1 = 11.2 Hz, J_2 = 5.6 Hz, 3H), 3.51 (dd, J_1 = 11.2 Hz, J_2 = 5.6 Hz, 2H), 3.87 (bs, OH), 7.20 (bs, NH), 7.33 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 8.02 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 13.4, 31.0, 31.2, 37.1, 42.0, 61.2, 67.6, 109.0, 114.8, 122.5 (q, J = 271.5 Hz), 127.4 (q, J = 4.7 Hz), 129.6, 130.0, 131.9 (q, J = 32.5 Hz), 133.3, 133.8, 135.6, 138.4, 143.0, 171.9, 175.0, 178.1.

42-1) 4-[4-(1-Cyanocyclobutylamino)-phenyl]-butyric acid, 42a

Trimethylsilyl cyanide (0.50 g, 5 mmol) was added dropwise to a mixture of 4-(4-aminophenyl)-butyric acid (0.537 g, 3 mmol), cyclobutanone (0.35 g, 5 mmol) and sodium sulfate (1 g) in 1,4-dioxane (10 ml). The mixture was stirred for 15 hours. After filtration to eliminate sodium sulfate, the medium was concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane:acetone, 50:50) to yield **42a** (0.665 g, 2.58 mmol, 86%) as a yellowish solid.

42-2) 4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-butyric acid methyl ester, 42b [RD129]

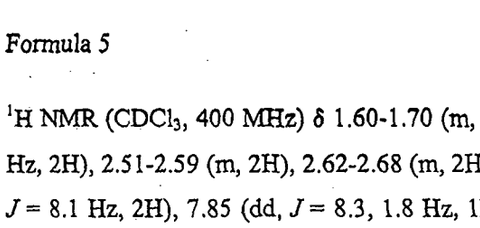
A mixture of **1a** (0.547 g, 2.4 mmol) and **42a** (0.342 g, 1.5 mmol) in dry DMF (2 ml) was stirred at room temperature for 15 hours. To this mixture were added methanol (10 ml) and HCl aq. (5 ml, 2M). The second mixture was refluxed for 3 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (3 × 30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane) to yield **42b** (0.594 g, 1.18 mmol, 79%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.70 (m, 1H), 1.98-2.07 (m, 2H), 2.14-2.26 (m, 1H), 2.40 (t, J = 7.4 Hz, 2H), 2.52-2.60 (m, 2H), 2.62-2.68 (m, 2H), 2.74 (t, J = 7.4 Hz, 2H), 3.68 (s, 3H), 7.22 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.86 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 26.1, 31.4, 33.5, 34.8, 51.7, 67.5, 109.9, 114.9, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.7, 130.1, 132.3, 133.0, 133.3 (q, J = 33.2 Hz), 135.2, 137.2, 143.5, 173.8, 175.0, 179.9.

42-3) 4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-butyric acid, 42c [RD141]

A mixture of **42b** (0.501 g, 1 mmol) in methanol (10 ml) and solution of sodium hydroxide (10 ml, 2M) was stirred at room temperature for 5 hours. The methanol was evaporated. The residue was adjusted to pH = 5 by HCl aq. (2M) and then, the medium was extracted with ethyl acetate (3 ×50 ml). The organic layer was dried over $MgSO_4$ and concentrated to dryness to obtain **42c** (0.482 g, 0.99 mmol, 99%), the structure of which is illustrated in Formula 5.



Formula 5

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.70 (m, 1H), 1.98-2.07 (m, 2H), 2.14-2.26 (m, 1H), 2.45 (t, J = 7.3 Hz, 2H), 2.51-2.59 (m, 2H), 2.62-2.68 (m, 2H), 2.77 (t, J = 7.3 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 25.9, 31.4, 33.4, 34.7, 67.5, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.8, 130.1, 132.3, 133.0, 133.4 (q, J = 33.1 Hz), 135.2, 137.2, 143.3, 174.9, 178.9, 179.9.

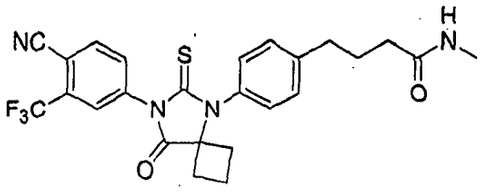
42-4) 4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-butyramide, 42d [RD130]

To a suspension of **42c** (0.097 g, 0.2 mmol) in THF (10 ml) at -5°C was added thionyl chloride (0.019 ml, 0.26 mmol). The medium was stirred at -5°C for one hour. Then ammonia was bubbled into the mixture. The excess of ammonia was condensed by reflux condenser at -78°C for 30 minutes and then was allowed to evaporate. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield **42d** (0.093 g, 0.19 mmol, 95%) as an off-white powder.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57-1.70 (m, 1H), 2.00-2.08 (m, 2H), 2.16-2.25 (m, 1H), 2.31 (t, J = 7.3 Hz, 2H), 2.51-2.59 (m, 2H), 2.62-2.68 (m, 2H), 2.77 (t, J = 7.3 Hz, 2H), 5.56 (bs, 1H), 5.65 (bs, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 26.5, 31.4, 34.8, 35.0, 67.5, 109.9, 114.9, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.8, 130.1, 132.2, 133.0, 133.3 (q, J = 33.2 Hz), 135.2, 137.2, 143.5, 173.8, 174.9, 179.9.

42-5) 4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-N-methyl-butyramide, 42e [RD131]

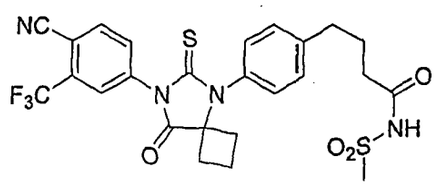
To a suspension of **42c** (0.097 g, 0.2 mmol) in THF (10 ml) at -5°C was added thionyl chloride (0.019 ml, 0.26 mmol). The medium was stirred at -5°C for one hour. Then methylamine was bubbled into the mixture at -5°C for 30 minutes. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 75:25) to yield **42e** (0.095 g, 0.19 mmol, 95%) as an off-white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52-1.64 (m, 1H), 1.94-2.01 (m, 2H), 2.10-2.17 (m, 1H), 2.20 (t, J = 7.3 Hz, 2H), 2.46-2.62 (m, 4H), 2.69 (t, J = 7.3 Hz, 2H), 2.73 (d, J = 4.7 Hz, 3H), 6.09 (bs, 1H), 7.16 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.82 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 26.2, 26.8, 31.4, 35.0, 35.7, 67.5, 109.7, 114.9, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.7, 130.0, 132.3, 133.8, 133.3 (q, J = 33.2 Hz), 135.2, 137.3, 143.7, 173.3, 174.9, 179.8.

42-6) *N*-(4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}-butanoyl)-methanesulfonamide, 42f [RD157]

[0099] A mixture of 4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}butanoic acid (42c) (0.049 g, 0.1 mmol), 2,4,6-trichlorobenzoyl chloride (0.244 g, 1 mmol), 4-dimethylaminopyridine (0.122 g, 1 mmol) and methanesulfonamide (0.019 g, 0.2 mmol) in dichloromethane was stirred at room temperature for 20 hours. The mixture was concentrated and chromatographed (dichloromethane:acetone, 80:20) to yield *N*-(4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}-butanoyl)-methanesulfonamide (42f) [RD157] (0.053 g, 0.094 mmol, 94%), the structure of which is illustrated in Formula 8, as a white powder.



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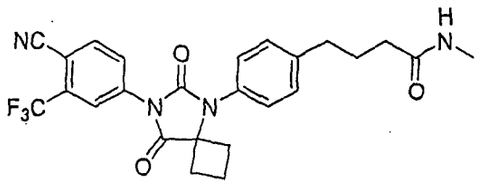
Formula 8

^{1}H NMR (acetone-d_6, 400 MHz) δ 1.51-160 (m, 1H), 1.96-2.11 (m, 3H), 2.49 (t, J = 7.3 Hz, 2H), 2.51-2.57 (m, 2H), 2.61-2.67 (m, 2H), 2.75 (t, J = 7.5 Hz, 2H), 2.94 (bs, 1H), 3.24 (s, 3H), 7.33 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 8.02 (dd, J = 8.3, 1.6 Hz, 1H), 8.02 (d, J = 1.6 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 13.4, 25.8, 31.2, 34.3, 35.2, 40.6, 67.6, 109.0, 114.8, 122.5 (q, J = 271.5 Hz), 127.5 (q, J = 4.9 Hz), 129.6, 130.1, 131.9 (q, J = 33.6 Hz), 133.3, 133.9, 135.6, 138.4, 143.1, 171.9, 175.0, 180.5.

42-7). *N*-methyl-4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-6,8-dioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}butyramide, 42g [RD158]

[00100] Hydrogen peroxide (30%, 0.4) was added dropwise to a solution of *N*-methyl-4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}butanamide (42e) (0.032 g, 0.064 mmol) in glacial acetic acid (0.5 ml). The mixture was stirred at room temperature for 5 hours and then washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated and chromatographed (dichloromethane:acetone, 80:20) to yield *N*-methyl-4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-6,8-dioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}butyramide (42g) [RD158] (0.029 g, 0.06 mmol, 94%), the structure of which is illustrated in Formula 9, as a white powder.



Formula 9

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63-1.71 (m, 1H), 1.93-2.04 (m, 2H), 2.18-2.27 (m, 3H), 2.44-2.53 (m, 2H), 2.57-2.65 (m, 2H), 2.70 (t, J = 7.3 Hz, 2H), 2.79 (d, J = 4.8 Hz, 3H), 5.79 (bs, 1H), 7.21 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H), 8.03 (dd, J = 8.3, 1.8 Hz, 1H), 8.18 (d, J = 1.8 Hz, 1H).

Example 43

43-1) 4-(4-aminophenyl)-piperazine-1-carboxylic acid *tert*-butyl ester, 43a

A mixture of 4-iodoaniline (0.654 g, 3 mmol), piperazine-1-carboxylic acid *tert*-butyl ester (0.67 g, 3.6 mmol), potassium phosphate (1.272 g, 6 mmol), ethylene glycol (0.33 ml) and copper iodide (0.03 g, 0.15 mmol) in 2-propanol (3 ml) was placed under argon in a sealed-tube and heated to 80°C for 30 hours. After being cooled to room temperature, the medium was washed with water (50 ml) and extracted with ethyl acetate (100 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield **43a** (0.36 g, 1.3 mmol, 43%) as a yellow powder.

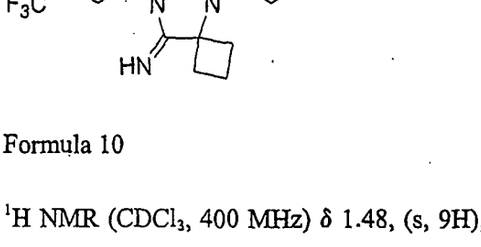
43-2) 4-[4-(1-cyanocyclobutylamino)phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester, 43b

Trimethylsilyl cyanide (0.3 g, 3 mmol) was added dropwise to a mixture of **43a** (0.415 g, 1.5 mmol), cyclobutanone (0.21 g, 3 mmol) and sodium sulfate (1 g) in dichloromethane (5 ml). The mixture was stirred for 15 hours. After filtration to eliminate sodium sulfate, the medium was concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane:acetone, 75:25) to yield **43b** (0.448 g, 1.26 mmol, 84%) as a yellow solid.

43-3) 4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-imino-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester, 43c [RD139]

and 4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-(4-cyano-3-trifluoromethyl-phenylthiocarbamoylimino)-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester, 43d [RD140]

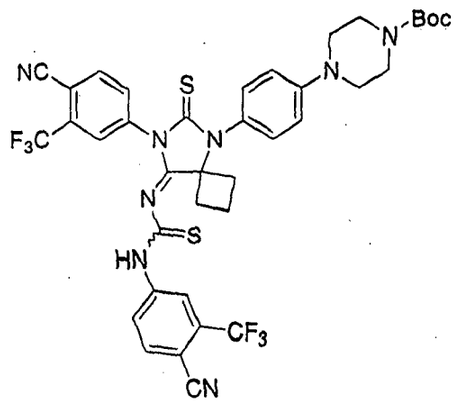
A mixture of **1a** (0.228 g, 1 mmol) and **43b** (0.472 g, 0.63 mmol) in dry DMF (1 ml) was stirred at room temperature for 20 hours. The mixture was concentrated and chromatographed (dichloromethane:acetone, 90:10) to yield **43c** (0.173 g, 0.296 mmol, 47%), the structure of which is illustrated in Formula 10, as a off-white powder and **43d** (0.169 g, 0.21 mmol, 33%), the structure of which is illustrated in Formula 11, as a yellow powder.



Formula 10

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48, (s, 9H), 1.57-1.67 (m, 1H), 2.01-2.09 (m, 1H), 2.59-2.70 (m, 4H), 3.25 (t, J = 5.1 Hz, 4H), 3.59 (t, J = 4.9 Hz, 4H), 7.02 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 7.81

(d, J = 7.4 Hz, 1H), 7.93 (s, 1H), 7.97 (d, J = 8.1 Hz, 1H).

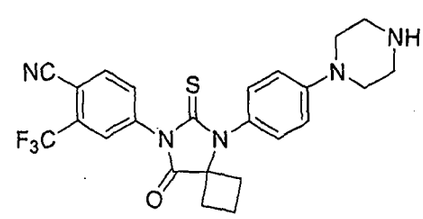


Formula 11

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48, (s, 9H), 1.57-1.64 (m, 1H), 2.01-2.10 (m, 1H), 2.60-2.89 (m, 4H), 3.24 (t, J = 5.1 Hz, 4H), 3.57 (t, J = 4.9 Hz, 4H), 7.02 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 7.54-7.98 (m, 4H), 7.97 (d, J = 8.1 Hz, 1H).

43-4) 4-[8-Oxo-5-(4-piperazin-1-yl-phenyl)-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile, 43e [RD137]

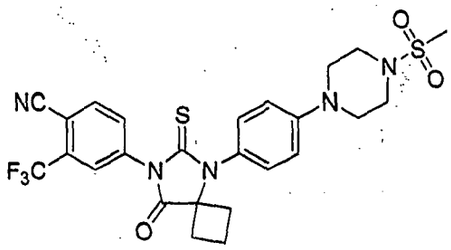
A mixture of **43c** (0.117 g, 0.2 mmol), methanol (5 ml) and HCl aq. (2 ml, 2M) was refluxed for 2 hours. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (3 × 30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 50:50 and then methanol:acetone, 50:50) to yield **43e** (0.089 g, 0.184 mmol, 92%) as a white powder.



^{1}H NMR (CD_3OD, 400 MHz) δ 1.51-1.61 (m, 1H), 2.01-2.11 (m, 1H), 2.48-2.59 (m, 4H), 2.90-2.97 (m, 4H), 3.25-3.30 (m, 4H), 7.03 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.9 Hz, 2H), 7.86 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 8.02 (d, J = 8.3 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 13.2, 30.9, 45.1, 48.9, 67.5, 108.9, 114.8, 115.9, 122.3 (q, J = 271.7 Hz), 126.4, 127.3 (q, J = 4.7 Hz), 130.4, 132.2 (q, J = 33.2 Hz), 133.0, 135.4, 138.1, 152.1, 175.4, 180.4.

43-5) 4-{5-[4-(4-methanesulfonylpiperazin-1-yl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethylbenzonitrile, 43f [RD138]

A mixture of **43e** (0.049g, 0.1 mmol), methanesulfonyl chloride (0.012 ml, 0.15 mmol) and triethylamine (0.15 ml) in dichloromethane was stirred at room temperature for 5 hours. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane: acetone, 95:5) to yield **43f** (0.042 g, 0.074 mmol, 74%) as a white powder.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62-1.70 (m, 1H), 2.14-2.23 (m, 1H), 2.51-2.58 (m, 2H), 2.61-2.67 (m, 2H), 2.84 (s, 3H), 3.39 (s, 8H), 7.05 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 7.84 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.4, 34.6, 45.7, 48.4, 67.5, 109.8, 114.9, 117.0, 121.9 (q, J = 272.7 Hz), 126.8, 127.1 (q, J = 4.7 Hz), 130.7, 132.3, 133.4 (q, J = 33.2 Hz), 135.2, 137.3, 151.1, 175.0, 180.2.

Example 44

44-1) 3-{4-[7-(4-Cyano-3-trifluoromethyl-phenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-acrylic acid, 44a

A mixture of **39a** (0.025 g, 0.05 mmol) in methanol (2 ml) and solution of sodium hydroxide (2 ml, 2M) was stirred at room temperature for 5 hours. Methanol was evaporated. The residue was adjusted to pH = 5 by HCl aq. (2M) and then extracted with ethyl acetate (3 ×50 ml). The organic layer was dried over $MgSO_4$ and concentrated to dryness to obtain **44a** (0.02 g, 0.042 mmol, 85%).

44-2) 3-{4-[7-(4-Cyano-3-trifluoromethyl-phenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-acrylamide, 44b [RD119]

To a suspension of **44b** (0.02 g, 0.042 mmol) in THF (1 ml) at -5°C was added thionyl chloride (0.007 ml, 0.1 mmol). The medium was stirred at -5°C for one hour. Then ammonia was bubbled into the mixture. The excess of ammonia was condensed by reflux condenser at -78°C for 30 minutes and then was allowed to evaporate. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield **44b** (0.014 g, 0.03 mmol, 71%) as an off-white powder.

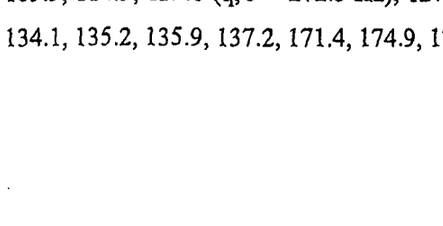
2H), 3.16 (s, 3H), 7.57 (d, J = 8.3 Hz, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 8.17 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 31.8, 44.4, 67.5, 110.2, 114.8, 122.4 (q, J = 271.5 Hz), 127.0 (q, J = 4.9 Hz), 129.4, 131.4, 132.1, 133.6 (q, J = 33.3 Hz), 135.3, 136.8, 140.3, 141.8, 174.4, 179.9.

Example 46

[00103] Trimethylsilyl cyanide (0.69 g, 7 mmol) was added dropwise to a mixture of 4-aminophenylacetic acid (0.755 g, 5 mmol) and cyclobutanone (0.49 g, 7 mmol) in dioxane (20 ml). The mixture was stirred for 8 hours at 80 °C. The mixture was concentrated and chromatographed (dichloromethane:acetone, 60:40) to yield [4-(1-cyanocyclobutylamino)phenyl]acetic acid (46a) (1.138 g, 4.95 mmol, 99%) as a white solid.

46-1) **RD146**

[00104] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (0.638 g, 2.8 mmol) and [4-(1-cyanocyclobutylamino)phenyl]acetic acid (46a) (0.46 g, 2.0 mmol) in DMF (5 ml) was stirred at room temperature for 15 hours. To this mixture were added methanol (20 ml) and aq. 2N HCl (10 ml). The second mixture was refluxed for 1 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (3 × 50 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane pure and then dichloromethane:acetone, 95:5) to yield {4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetic acid methyl ester (46b) [RD146] (0.532 g, 1.124 mmol, 56%), the structure of which is illustrated in Formula 15, as a white powder.

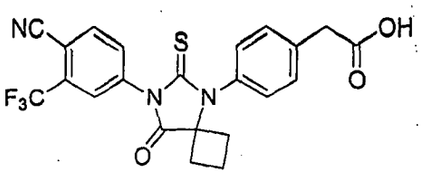


Formula 15

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.69 (m, 1H), 2.15-2.25 (m, 1H), 2.50-2.58 (m, 2H), 2.61-2.66 (m, 2H), 3.72 (bs, 5H), 7.27 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.4, 44.7, 52.3, 67.4, 109.9, 114.9, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 130.0, 131.1, 132.3, 133.0 (q, J = 33.3 Hz), 134.1, 135.2, 135.9, 137.2, 171.4, 174.9, 179.9.

46-2) **RD147**

[00105] A mixture of {4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetic acid methyl ester (46b) (0.095 g, 0.2 mmol) and a solution of sodium hydroxide (1 ml, 2M) in methanol (2 ml) was stirred at room temperature for 2 hours. The methanol was evaporated. The residue was adjusted to pH 5 by aq. 2M HCl and then the mixture was extracted with ethyl acetate (3 ×10 ml). The organic layer was dried over $MgSO_4$ and concentrated to dryness to obtain {4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetic acid (46c) **[RD147]** (0.087 g, 0.19 mmol, 95%), the structure of which is illustrated in Formula 16.

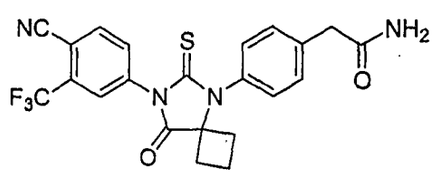


Formula 16

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.69 (m, 1H), 2.15-2.25 (m, 1H), 2.50-2.64 (m, 4H), 3.73 (s, 2H), 7.26 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.4, 40.2, 40.8, 67.4, 109.9, 114.9, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 129.9, 131.2, 132.3, 133.3 (q, J = 33.3 Hz), 133.9, 135.2, 136.1, 137.2, 174.1, 174.9, 179.9.

46-3) **RD148**

[00106] Thionyl chloride (0.238 g, 2 mmol) was added dropwise to a mixture of {4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetic acid (46c) (0.357 g, 0.777 mmol) in THF (5 ml) cooled to 0 °C. The mixture was stirred for 1 hour at room temperature and then ammonia was bubbled into the mixture. The excess ammonia was condensed by a reflux condenser at -78 °C for 30 minutes and then was allowed to evaporate. The medium was filtered and the filtrate was concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield 2-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetamide (46d) **[RD148]** (0.345 g, 0.75 mmol, 97%), the structure of which is illustrated in Formula 17, as an off-white powder.

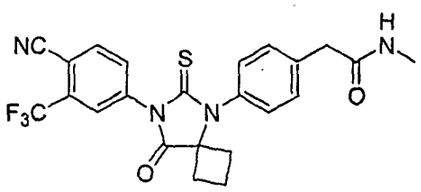


Formula 17

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62-1.66 (m, 1H), 2.18.2.23 (m, 1H), 2.49-2.55 (m, 2H), 2.61-2.66 (m, 2H), 3.63 (s, 2H), 5.91 (bs, 1H), 6.10 (bs, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.83 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 42.5, 67.4, 109.9, 114.9, 121.9 (q, J = 272.4 Hz), 127.1 (q, J = 4.9 Hz), 130.2, 131.1, 132.2, 133.3 (q, J = 33.3 Hz), 134.1, 135.2, 136.8, 137.2, 172.8, 174.8, 180.0.

46-4) RD149

[00107] Thionyl chloride (0.238 g, 2 mmol) was added dropwise to a mixture of {4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetic acid (46c) (0.357 g, 0.777 mmol) in THF (5 ml) cooled to 0 °C. The mixture was stirred for 1 hour at room temperature and then methylamine (0.5 ml) was added into the mixture. The mixture was stirred for an additional 2 hours. The medium was filtered and the filtrate was concentrated and chromatographed (dichloromethane:acetone, 80:20) to yield *N*-methyl-2-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}acetamide (46e) **[RD149]** (0.348 g, 0.738 mmol, 95%), the structure of which is illustrated in Formula 18, as an off-white powder.



Formula 18

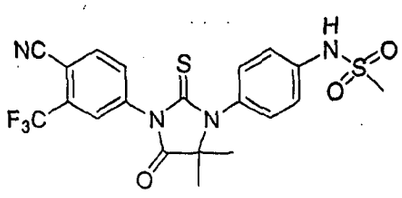
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61-1.70 (m, 1H), 2.17-2.31 (m, 1H), 2.50-2.56 (m, 2H), 2.61-2.68 (m, 2H), 2.82 (d, J = 4.8 Hz, 3H), 3.62 (s, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 26.6, 31.5, 43.1, 67.4, 110.0, 114.9, 122.0 (q, J = 272.5 Hz), 127.1 (q, J = 4.9 Hz), 130.2, 131.0, 132.2, 133.3 (q, J = 33.3 Hz), 134.1, 135.2, 137.0, 137.1, 170.1, 174.8, 179.9.

Example 47

***N*-{4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenyl}methanesulfonamide (47a) [RD150]**

[00108] A mixture of 4-[3-(4-aminophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-

trifluoromethylbenzonitrile (2d) (0.02 g, 0.05 mmol), methanesulfonyl chloride (0.009g, 0.075 mmol) and pyridine (0.006 g, 0.075 mmol) in dichloromethane (1 ml) was stirred at room temperature for 15 hours. The medium was washed with water (2 ml) and extracted with ethyl acetate (5 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (HPLC, alumina column) to yield *N*-{4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenyl}methanesulfonamide (47a) [RD150] (0.009 g, 0.018 mmol, 36%), the structure of which is illustrated in Formula 2, as a white powder.



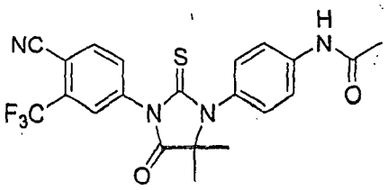
Formula 2

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.46 (s, 6H), 3.07 (s, 3H), 7.32 (s, 4H), 8.05 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.26 (d, *J* = 1.2 Hz, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 10.08 (bs, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.3, 40.4, 66.7, 109.0, 115.5, 119.9, 122.6 (q, *J* = 272.2 Hz), 128.5 (q, *J* = 4.7 Hz), 130.8, 131.2, 131.5 (q, *J* = 32.3 Hz), 134.5, 136.6, 138.6, 139.5, 175.4, 180.4.

Example 48

***N*-{4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenyl}acetamide, 48a, [RD151]**

[00109] A mixture of 4-[3-(4-aminophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile (2d) [RD9] (0.008 g, 0.02 mmol), acetyl chloride (0.004g, 0.03 mmol) and triethylamine (0.003 g, 0.03 mmol) in dichloromethane (1 ml) was stirred at 0 °C for 2 hours. The mixture was concentrated and chromatographed (dichloromethane:acetone, 90:10) to yield *N*-{4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenyl}acetamide, 48a, [RD151] (0.007 g, 0.016 mmol, 80%), the structure of which is illustrated in Formula 3, as a white powder.



Formula 3

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58 (s, 6H), 2.21 (s, 3H), 7.24 (d, J = 8.6 Hz, 2H), 7.48 (bs, 1H), 7.69 (d, J = 8.6 Hz, 2H), 7.83 (dd, J = 8.2, 1.9 Hz, 1H), 7.96 (d, J = 1.2 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6, 53.4, 66.4, 110.0, 114.8, 120.7, 122.6 (q, J = 272.2 Hz), 127.1 (q, J = 4.7 Hz), 129.1, 130.2, 132.2, 133.5 (q, J = 32.3 Hz), 135.2, 137.1, 139.2, 168.1, 175.0, 180.0.

Example 49

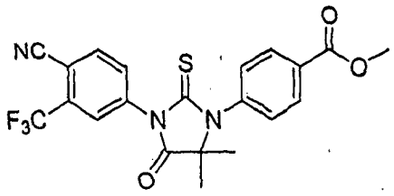
[00110] Concentrated sulfuric acid was slowly added to a mixture of 4-aminobenzoic acid (4 g, 29.2 mmol) in methanol cooled to 0 °C. After the addition, the mixture was stirred at room temperature for 5 hours. The mixture was washed with a saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to obtain 4-aminobenzoic acid methyl ester (49a) (4.22 g, 27.9 mmol, 96%) as an off-white solid.

[00111] A mixture of 4-aminobenzoic acid methyl ester (0.32 g, 2.12 mmol), acetonecyanohydrin (3ml) and sodium sulfate (1 g) was refluxed for 15 hours. After filtration to remove the sodium sulfate, the filtrate was washed with brine and extracted with ethyl acetate. The organic layer was concentrated and chromatographed (dichloromethane:acetone, 60:40) to yield 4-[(cyanodimethylmethyl)-amino]-benzoic acid methyl ester (49b) (0.398 g, 1.95 mmol, 92%) as a white solid.

49-1) RD152

[00112] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (0.228 g, 1 mmol) and 4-[(cyanodimethylmethyl)-amino]-benzoic acid methyl ester (49b) (0.14 g, 0.64 mmol) in DMF (2 ml) was heated under microwave irradiation at 60 °C for 12 hours. To this mixture were added methanol (6 ml) and aq. 2N HCl (2 ml). The second mixture was refluxed for 4 h. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (3 × 30 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane; dichloromethane:acetone, 75:25) to yield 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]benzoic acid methyl ester (49c) **[RD152]** (0.18 g, 0.4 mmol,

63%), the structure of which is illustrated in Formula 19, as a white powder.

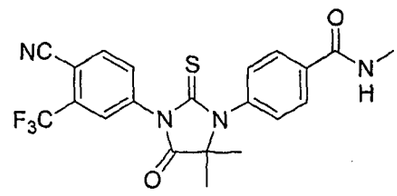


Formula 19

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60 (s, 6H), 3.95 (s, 3H), 7.40 (d, J = 8.6 Hz, 2H), 7.84 (dd, J = 8.2, 1.9 Hz, 1H), 7.96 (d, J = 1.2 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 8.21 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 52.6, 66.6, 110.3, 114.8, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.8, 131.2, 131.4, 132.2, 133.5 (q, J = 32.3 Hz), 135.3, 137.0, 139.2, 165.9, 174.7, 179.7.

49-2) RD153

[00113] A mixture of 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]benzoic acid methyl ester (49c) (0.02 g, 0.0435 mmol) and methylamine (2 ml distilled from its 40% aqueous solution) was kept at -20 °C for 15 hours. After evaporation of the methylamine, the mixture was chromatographed (dichloromethane:acetone, 80:20) to yield 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-N-methylbenzamide (49d) **[RD153]** (0.01 g, 0.0224, 51%), the structure of which is illustrated in Formula 20. The ester 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]benzoic acid methyl ester (49c) (0.08 g, 0.0179 mmol, 41%) was also recovered.



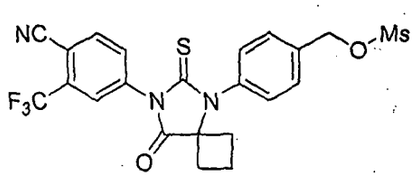
Formula 20

^{1}H NMR (Acetone-d_6, 400 MHz) δ 1.60 (s, 6H), 2.90 (d, J = 4.6 Hz, 3H), 7.48 (d, J = 8.6 Hz, 2H), 7.80 (bs, 1H), 7.99 (d, J = 8.6 Hz, 2H), 8.06 (dd, J = 8.2, 1.8 Hz, 1H), 8.18 (d, J = 1.8 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H); ^{13}C NMR (Acetone-d_6, 100 MHz) δ 23.8, 54.0, 66.5, 110.3, 114.8, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 128.2, 129.9, 133.5 (q, J = 32.3 Hz), 135.7, 135.8, 138.2, 138.3, 139.2, 166.0, 174.9, 179.7.

Example 50

50-1) RD154

[00114] A mixture of 4-[8-(4-hydroxymethylphenyl)-5-oxo-7-thioxo-6-azaspiro[3.4]oct-6-yl]-2-trifluoromethyl-benzonitrile (36b) (0.086 g, 0.2 mmol) and methanesulfonyl anhydride (0.07 g, 0.4 mmol) in dichloromethane (1 ml) was stirred at room temperature for 15 hours. The mixture was concentrated and chromatographed (dichloromethane:acetone, 98:2) to yield Methanesulfonic acid 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenylmethyl ester (50a) **[RD154]** (0.089 g, 0.175 mmol, 88%), the structure of which is illustrated in Formula 22, as a white powder.

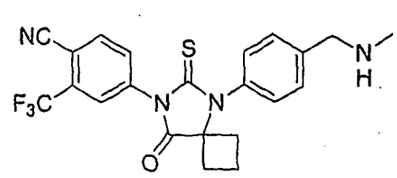


Formula 22

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63-1.70 (m, 1H), 2.17-2.31 (m, 1H), 2.48-2.57 (m, 2H), 2.64-2.70 (m, 2H), 3.04 (s, 3H), 5.30 (s, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 1.6 Hz, 1H).

50-2) RD155

[00115] Methylamine (0.5 ml) was bubbled into a mixture of Methanesulfonic acid 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenylmethyl ester (50a) (0.059 g, 0.115 mmol) in THF (3 ml) cooled to -78 °C. After 1 hour of reaction at -78 °C, the mixture was concentrated and chromatographed (dichloromethane:acetone, 95:5; methanol) to yield 4-[5-(4-methylaminomethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile (50b) **[RD155]** (0.042 g, 0.095 mmol, 82%), the structure of which is illustrated in Formula 23, as a white powder.

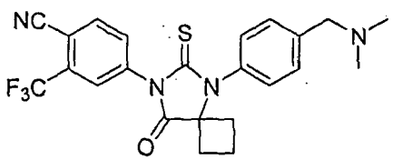


Formula 23

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57-1.70 (m, 1H), 2.16-2.24 (m, 1H), 2.52 (s, 3H), 2.53-2.57 (m, 2H), 2.60-2.68 (m, 2H), 3.85 (s, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 36.4, 55.6, 67.4, 110.0, 114.9, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 129.1, 129.6, 129.8, 132.2, 133.3 (q, J = 33.3 Hz), 133.7, 135.2, 142.4, 174.8, 179.9.

50-3) RD156

[00116] A mixture of Methanesulfonic acid 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenylmethyl ester (50a) (0.02 g, 0.039 mmol) and dimethylamine (0.5 ml; distilled from its 40% aqueous solution) in THF (1 ml) was stirred for 2 hours at -78 °C. The mixture was concentrated and chromatographed (dichloromethane:acetone, 95:5;acetone) to yield 4-[5-(4-dimethylaminomethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile (50c) **[RD156]** (0.017 g, 0.037 mmol, 95%), the structure of which is illustrated in Formula 24, as a white powder.



Formula 24

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57-1.70 (m, 1H), 2.16-2.24 (m, 1H), 2.32 (s, 6H), 2.55-2.60 (m, 2H), 2.63-2.69 (m, 2H), 3.53 (s, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 45.5, 63.7, 67.4, 110.0, 114.9, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 129.1, 129.6, 129.8, 132.2, 133.3 (q, J = 33.3 Hz), 133.7, 135.2, 142.4, 174.8, 179.9.

Example 51

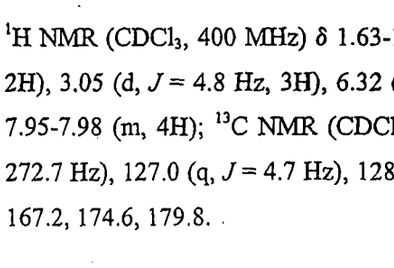
[00117] Sodium cyanide (0.245 g, 5 mmol) was added to a mixture of 4-aminobenzoic acid (0.274 g, 2 mmol) and cyclobutanone (0.21 g, 3 mmol) in 90% acetic acid (4.5 ml). The reaction mixture was stirred at room temperature for 15 hours. The mixture was washed with aqueous HCl (pH 2) and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to

Formula 26

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67-1.71 (m, 1H), 2.18-2.26 (m, 1H), 2.50-2.58 (m, 2H), 2.68-2.74 (m, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.7 Hz, 1H), 7.84 (dd, J = 8.3, 1.9 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 9.97 (d, J = 1.9 Hz, 1H), 8.10-8.14 (m, 3H), 8.21 (d, J = 1.9 Hz, 1H), 8.88, (s, 1H).

51 -2) RD161

[00119] A mixture of 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-benzoic acid methyl ester (51b) (0.046 g, 0.1 mmol) and methylamine (1 ml distilled from its 40% aqueous solution) was kept at -20 °C for 15 hours. After evaporation of the methylamine, the mixture was chromatographed (dichloromethane:acetone, 80:20) to yield *N*-methyl-4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]benzamide (51c) **[RD161]** (0.041 g, 0.085, 84%), the structure of which is illustrated in Formula 27.



Formula 27

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63-1.70 (m, 1H), 2.18-2.26 (m, 1H), 2.48-2.56 (m, 2H), 2.65-2.71 (m, 2H), 3.05 (d, J = 4.8 Hz, 3H), 6.32 (bs, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.7 Hz, 1H), 7.95-7.98 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 27.0, 31.6, 67.4, 110.3, 114.8, 121.8 (q, J = 272.7 Hz), 127.0 (q, J = 4.7 Hz), 128.7, 130.3, 132.1, 133.3 (q, J = 33.2 Hz), 135.2, 136.3, 137.0, 137.8, 167.2, 174.6, 179.8.

Example 52 [RD162]

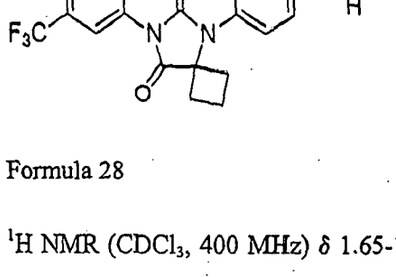
[00120] Thionyl chloride (2.38 g, 20 mmol) was added slowly to a solution of 2-fluoro-4-nitrobenzoic acid (2.97 g, 16 mmol) in DMF (50 ml) cooled at -5 °C. The mixture was stirred for an additional 1 hour at -5 °C. Methylamine (0.62 g, 20 mmol; freshly distilled from its 40% aqueous solution) was added to the reaction medium. The second mixture was stirred for an additional 1 hour. Ethyl acetate (300 ml) was added to the mixture, which was washed with brine (3 × 150 ml). The organic layer was dried over $MgSO_4$, and concentrated to yield *N*-methyl-2-fluoro-4-nitrobenzamide (52a) (2.89

g, 14.6 mmol, 91%) as a yellow solid. ^{1}H NMR (Acetone d6, 400 MHz) δ 3.05 (d, J = 4.3 Hz, 3H), 6.31 (dd, J = 13.5, 2.1 Hz, 1H), 6.40 (dd, J = 8.5, 2.1 Hz, 1H), 7.64 (dd, J = 8.6, 8.6 Hz, 1H).

[00121] A mixture of *N*-methyl-2-fluoro-4-nitrobenzamide (52a) (2.89 g, 14.6 mmol) and iron (5.04 g, 90 mmol) in ethyl acetate (40 ml) and acetic acid (40 ml) was refluxed for 1 hour. The solid particles were filtered off. The filtrate was washed with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield *N*-methyl-2-fluoro-4-aminobenzamide (52b) (2.3 g, 13.7 mmol, 94%) as an off-white solid. ^{1}H NMR (acetone-d_6, 400 MHz) δ 2.86 (d, J = 4.3 Hz, 3H), 5.50 (bs, 2H), 6.37 (dd, J_1 = 14.7 Hz, J_2 = 2.1 Hz, 1H), 6.50 (dd, J = 8.5, 2.1 Hz, 1H), 7.06 (bs, 1H), 7.68 (dd, J = 8.8 8.8 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 25.8, 99.6 (d, J = 13.8 Hz), 109.2 (d, J = 12.8 Hz), 110.0 (d, J = 1.6 Hz), 132.5 (d, J = 4.8 Hz), 153.5 (d, J = 12.6 Hz), 162.2 (d, J = 242.5 Hz), 164.0 (d, J = 3.1 Hz).

[00122] Sodium cyanide (1.47 g, 30 mmol) was added to a mixture of *N*-methyl-2-fluoro-4-aminobenzamide (52b) (1.68 g, 10 mmol) and cyclobutanone (1.4 g, 20 mmol) in 90% acetic acid (20 ml). The reaction mixture was stirred at 80 °C for 24 hours. The mixture was washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to dryness under vacuum. The solid was washed with a 50:50 mixture of ethyl ether and hexane (10 ml) to remove cyclobutanone cyanohydrin to afford after filtration *N*-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide (52c) (2.19 g, 8.87 mmol, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.87-1.95 (m, 1H), 2.16-2.27 (m, 1H), 2.35-2.41 (m, 2H), 2.76-2.83 (m, 2H), 2.97 (d, J = 4.4 Hz, 3H), 4.68 (bs, 1H), 6.29 (dd, J = 14.3, 1.8 Hz, 1H), 6.48 (dd, J = 8.3, 1.8 Hz, 1H), 6.75 (q, J = 4.4 Hz, 1H), 7.90 (dd, J = 8.3, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 26.7, 33.9, 49.4, 100.2 (d, J = 29.5 Hz), 110.6, 111.0 (d, J = 11.8 Hz), 133.1 (d, J = 4.2 Hz), 148.4 (d, J = 12.0 Hz), 162.0 (d, J = 244.1 Hz), 164.4 (d, J = 3.6 Hz).

[00123] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (2.16 g, 9.47 mmol) and *N*-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide (52c) (1.303 g, 5.27 mmol) in DMF (20 ml) was heated under microwave irradiation at 80 °C for 16 hours. To this mixture was added methanol (50 ml) and aq. 2N HCl (20 ml). The second mixture was refluxed for 3 hours. After being cooled to room temperature, the reaction mixture was poured into cold water (100 ml) and extracted with ethyl acetate (150 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield *N*-methyl-4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-2-fluorobenzamide (52d) **[RD162]** (1.43 g, 3.0 mmol, 57%), the structure of which is illustrated in Formula 28, as a yellow powder.



Formula 28

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65-1.75 (m, 1H), 2.18-2.30 (m, 1H), 2.49-2.57 (m, 2H), 2.67-2.73 (m, 2H), 3.07 (d, J = 4.4 Hz, 3H), 6.75 (q, J = 4.6 Hz, 1H), 7.17 (dd, J = 11.5, 1.9 Hz, 1H), 7.26 (dd, J = 8.3, 1.9 Hz, 1H), 7.83 (dd, J = 8.2, 2.0 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H) 8.30 (dd, J = 8.3, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 27.0, 31.7, 67.4, 110.3, 114.8, 118.2, 118.5, 121.9 (q, J = 272.7 Hz), 126.6, 127.0 (q, J = 4.8 Hz), 132.1, 133.3 (q, J = 33.2 Hz), 133.8, 135.3, 136.8, 139.1 (d, J = 10.9 Hz), 160.5 (d, J = 249.1 Hz), 162.7 (d, J = 3.3 Hz), 174.3, 179.8; ^{19}F NMR ($CDCl_3$, 100 MHz) δ -111.13, -62.58.

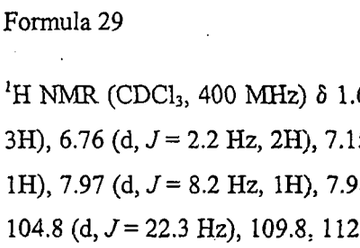
Example 53 [RD163]

[00124] A mixture of 4-nitro-3-fluorophenol (0.314 g, 2 mmol) and iron (0.56 g, 10 mmol) in ethyl acetate (4 ml) and acetic acid (2 ml) was refluxed for 3 hour. The solid particles were filtered off. The filtrate was washed with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated to yield 4-amino-3-fluorophenol (53a) (0.25 g, 19.6 mmol, 98%) as a brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.48-6.58 (m, 2H), 6.61-6.70 (m, 1H), 7.87 (bs, 3H).

[00125] Sodium cyanide (0.194 g, 4 mmol) was added to a mixture of 4-amino-3-fluorophenol (0.29 g, 2.28 mmol) and cyclobutanone (0.175 g, 2.5 mmol) in 90% acetic acid (3 ml). The reaction mixture was stirred at room temperature for 15 hours. The medium was washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated and chromatographed (dichloromethane:acetone, 90:10) to yield 1-(2-fluoro-4-hydroxyphenylamino)-cyclobutanecarbonitrile (53b) (0.271 g, 1.31 mmol, 58%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13-2.20 (m, 2H), 2.36-2.41 (m, 2H), 2.70.2.75 (m, 2H), 4.00 (bs, 1H), 6.46 (bs, 1H), 6.52 (ddd, J_1 = 2.2 Hz, J_2 = 0.65 Hz, J_3 = 0.22 Hz, 1H), 6.57 (d, J = 2.3 Hz), 6.62 (dd, J_1 = 3.0 Hz, J_2 = 0.67 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 34.1, 50.9, 104.0 (d, J = 21.9 Hz), 111.0 (d, J = 3.4 Hz), 115.8 (d, J =3.7 Hz), 121.8, 125.3 (d, J = 12.3 Hz), 150.1 (d, J = 10.4 Hz), 152.8 (d, J = 239.3 Hz).

[00126] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (0.228 g, 1.0 mmol) and 1-(2-fluoro-4-hydroxyphenylamino)-cyclobutanecarbonitrile (53b) (0.145 g, 0.7 mmol) in dry DMF (2 ml) was stirred at room temperature for 24 hours. To this mixture were added methanol (10 ml) and

aq. 2M HCl (2 ml). The second mixture was refluxed for 1 hour. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (50 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane pure and then dichloromethane:acetone, 90:10) to yield 4-[5-(2-fluoro-4-hydroxyphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile (53c) [RD163] (0.17 g, 0.39 mmol, 56%), the structure of which is illustrated in Formula 29, as a off-white powder.



Formula 29

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.66-1.75 (m, 1H), 2.18-2.28 (m, 1H), 2.42-2.50 (m, 1H), 2.54-2.67 (m, 3H), 6.76 (d, J = 2.2 Hz, 2H), 7.15 (t, J = 2.1 Hz, 1H), 7.35 (bs, 1H), 7.87 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 31.0, 67.6, 104.8 (d, J = 22.3 Hz), 109.8, 112.6, 114.4 (d, J = 13.1 Hz), 114.9, 121.9 (q, J = 272.8 Hz), 127.1 (q, J = 4.8 Hz), 132.0, 132.3, 133.5 (q, J = 33.3 Hz), 135.3, 137.2, 159.3 (d, J = 11.2 Hz), 159.6 (d, J = 249.7 Hz), 175.2, 180.5; ^{19}F NMR ($CDCl_3$, 100 MHz) δ -117.5, -62.49.

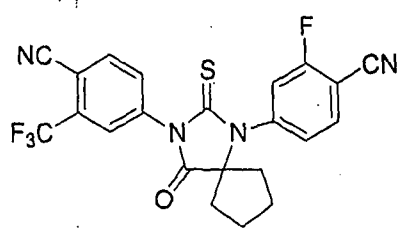
Example 54 [RD168]

[00127] A mixture of 4-nitro-2-fluorobenzonitrile (1.83 g, 5 mmol) and iron (1.68 g, 6 mmol) in a mixture of acetic acid (40 ml) and ethyl acetate (40 ml) was refluxed for 2 hours. The solid was filtered off and the filtrate was washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield 4-amino-2-fluorobenzonitrile (54a) (0.653 g, 4.8 mmol, 96%).

[00128] Sodium cyanide (0.74 g, 15 mmol) was added to a mixture of 4-amino-2-fluorobenzonitrile (1.36 g, 10 mmol) and cyclopentanone (1.26 g, 15 mmol) in 90% acetic acid (10 ml). The reaction mixture was stirred at room temperature for 3 hours and then the medium was hearted to 80 °C and stirred for an additional 5 hours. The medium was washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated and chromatographed (dichloromethane:acetone, 97:3) to yield 4-(1-cyanocyclopentylamino)-2-fluorobenzonitrile (54b) (2.07 g, 9.03 mmol, 90%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.69-1.91 (m, 4H), 2.13-2.18 (m,

2H), 2.37-2.42 (m, 2H), 5.08 (bs, 1H), 6.54-6.62 (m, 2H), 7.39 (t, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 39.8, 56.8, 89.6 (d, J = 15.8 Hz), 101.2 (d, J = 23.8 Hz), 110.9, 115.2, 120.8, 134.1 (d, J = 2.4 Hz), 150.3 (d, J = 11.2 Hz), 164.5 (d, J = 254.1 Hz).

[00129] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (0.171 g, 0.75 mmol) and 4-(1-cyanocyclopentylamino)-2-fluorobenzonitrile (54b) (0.115 g, 0.5 mmol) in dry DMF (1 ml) was heated under microwave irradiation at 60 °C for 48 hours. To this mixture were added methanol (3 ml) and aq 2M HCl (2 ml). The second mixture was refluxed for 1 hour. After being cooled to room temperature, the reaction mixture was poured into cold water (10 ml) and extracted with ethyl acetate (15 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 98:2) to yield 4-[1-(4-cyano-3-fluorophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl]-2-trifluoromethylbenzonitrile (54c) **[RD168]** (0.017 g, 0.037 mmol, 7%), of which the structure is illustrated in Formula 30, as an off-white powder.

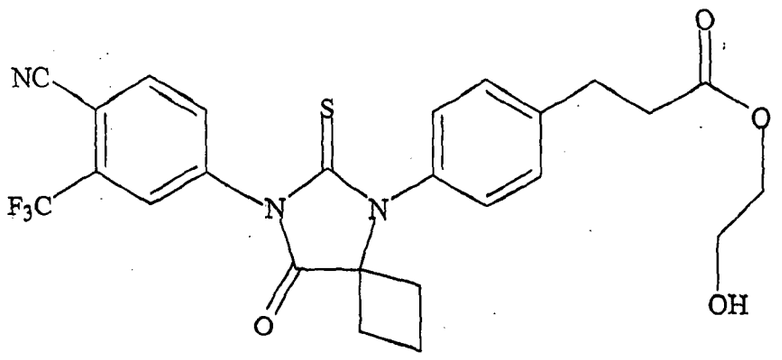


Formula 30

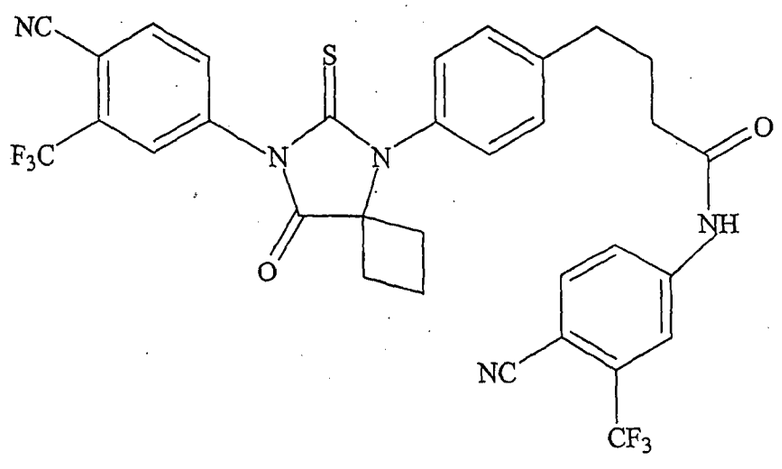
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53-1.63 (m, 2H), 1.89-2.00 (m, 2H), 2.09-2.16 (m, 2H), 2.35-2.42 (m, 2H), 7.27-7.37 (m, 2H), 7.78-7.90 (m, 3H), 7.95 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 36.5, 75.3, 103.2 (d, J = 15.3 Hz), 110.4, 112.8, 114.7, 119.2 (d, J = 20.7 Hz), 121.9 (q, J = 272.8 Hz), 127.0 (q, J = 4.8 Hz), 132.1, 133.7 (q, J = 33.2 Hz), 134.6, 135.3, 135.8, 136.8, 141.8 (d, J = 9.5 Hz), 163.4 (d, J = 261.5 Hz), 175.3, 180.1.

Example 55 [RD136 and RD142]

[00130] Additional diarylhydantoin compounds can be synthesized, including the following compounds illustrated in Formulas 35 and 36.



Formula 35 **[RD136]**

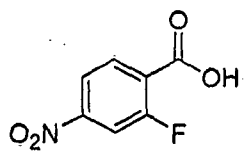


Formula 36 **[RD142]**

Example 56 [RD162']

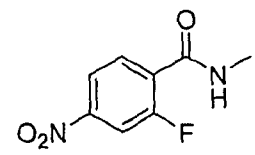
[00131] In the following, air or moisture sensitive reactions were conducted under argon atmosphere using oven-dried glassware and standard syringe/septa techniques. The reactions were monitored with a SiO_2 TLC plate under UV light (254 nm) followed by visualization with a *p*-anisaldehyde or ninhydrin staining solution. Column chromatography was performed on silica gel 60. ^1H NMR spectra were measured at 400 MHz in $CDCl_3$ unless stated otherwise and data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration,

coupling constant in Hz.).



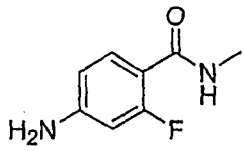
Formula 37

[00132] Periodic acid (1.69 g, 7.41 mmol) was dissolved in acetonitrile (25 mL) by vigorous stirring, and then chromium trioxide (0.16 g, 1.60 mmol) was dissolved into the solution. 2-Fluoro-4-nitrotoluene (0.33 g, 2.13 mmol) was added to the above solution with stirring. A white precipitate formed immediately with exothermic reaction. After 1 h of stirring, the supernatant liquid of the reaction mixture was decanted to a flask, and the solvent was removed by evaporation. The residues were extracted with methylene chloride (2×30 mL) and water (2×30 mL). The organic layer was dried over $MgSO_4$, and concentrated to give 2-Fluoro-4-nitrobenzoic acid (Formula 37) (0.32 mg, 81%) as a white solid. ^{1}H NMR δ 8.06 (ddd, 1 H, *J*=9.9, 2.2 and 0.3), 8.13 (ddd, 1 H, *J*=8.6, 2.2 and 0.9), 8.25 (ddd, 1 H, *J*=8.6, 7.0 and 0.3).



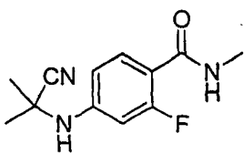
Formula 38

[00133] Thionyl chloride (0.15 g, 1.30 mmol) was added slowly to a solution of 2-fluoro-4-nitrobenzoic acid (Formula 37) (0.20 g, 1.10 mmol) in DMF (5 mL) cooled at -5 °C. The mixture was stirred for an additional 1 hour at -5 °C. Excess methylamine (freshly distilled from its 40% aqueous solution) was added to the reaction medium. The second mixture was stirred for an additional 1 hour. Ethyl acetate (50 mL) was added to the mixture, which was washed with brine (2 × 50 ml). The organic layer was dried over $MgSO_4$, and concentrated to yield *N*-Methyl-2-fluoro-4-nitrobenzamide (Formula 38) (0.18 g, 85%) as a yellowish solid. ^{1}H NMR (acetone-d_6) δ 3.05 (d, 3 H, *J*=4.3), 6.31 (dd, 1 H, *J*=13.5 and 2.1), 6.40 (dd, 1H, *J*=8.6 and 2.1), 7.64 (dd, 1H, *J* = 8.6 and 8.6).



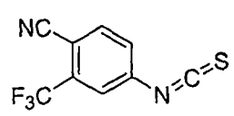
Formula 39

[00134] A mixture of *N*-Methyl-2-fluoro-4-nitrobenzamide (Formula 38) (0.18 g, 0.91 mmol) and iron (0.31 g, 5.60 mmol) in ethyl acetate (5 mL) and acetic acid (5 mL) was refluxed for 1 h. The solid particles were filtered off. The filtrate was washed with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane:acetone, 95:5) to give *N*-Methyl-2-fluoro-4-aminobenzamide (Formula 39) (0.14 g, 92%) as an off-white solid. ^{1}H NMR (acetone-d_6) δ 2.86 (d, 3 H, *J*=4.3), 5.50 (br s, 2 H), 6.37 (dd, 1 H, *J*=14.7 and 2.1), 6.50 (dd, 1H, *J*=8.6 and 2.1), 7.06 (br s, 1H), 7.68 (dd, 1H, *J*=8.8 and 8.8).



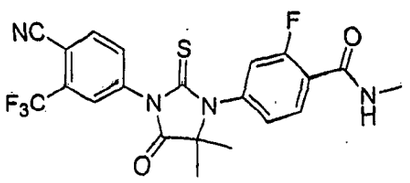
Formula 40

[00135] A mixture of *N*-Methyl-2-fluoro-4-aminobenzamide (Formula 39) (96 mg, 0.57 mmol), acetone cyanohydrin (0.3 mL, 3.14 mmol) and magnesium sulfate (50 mg) was heated to 80 °C and stirred for 12 h. To the medium was added ethyl acetate (25 mL) and then washed with water (2 × 25 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane:acetone, 95:5) to give *N*-Methyl-2-fluoro-4-(1,1-dimethyl-cyanomethyl)-aminobenzamide (Formula 40) (101 mg, 75%) as a white solid. ^{1}H NMR δ 1.74 (s, 6 H), 2.98 (dd, 3 H, *J*=4.8 and 1.1), 6.58 (dd, 1 H, *J*=14.6 and 2.3), 6.63 (dd, 1 H, *J*=8.7 and 2.3), 6.66 (br s, 1 H), 7.94 (dd, 1 H, *J*=8.7 and 8.7).



Formula 41

[00136] 4-Amino-2-trifluoromethylbenzonitrile (2.23 g, 12 mmol) was added portionwise over 15 min into a well-stirred heterogeneous mixture of thiophosgene (1 mL, 13 mmol) in water (22 mL) at room temperature. Stirring was continued for an additional 1 h. The reaction medium was extracted with chloroform (3 × 15 ml). The combined organic phase was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to yield desired product 4-Isothiocyanato-2-trifluoromethylbenzonitrile (Formula 41) as brownish solid and was used as such for the next step (2.72 g, 11.9 mmol, 99%). ^{1}H NMR δ 7.49 (dd, 1 H, *J*=8.3 and 2.1), 7.59 (d, 1 H, *J*=2.1), 7.84 (d, 1 H, *J*=8.3).

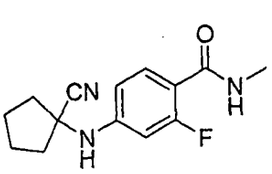


RD162' (Formula 42)

56-1) RD162'

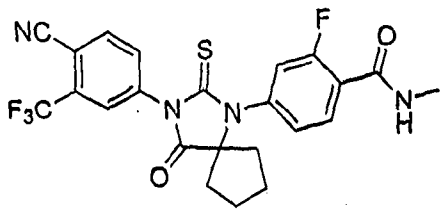
[00137] A mixture of *N*-Methyl-2-fluoro-4-(1,1-dimethyl-cyanomethyl)-aminobenzamide (Formula 40) (30 mg, 0.13 mmol) and 4-Isothiocyanato-2-trifluoromethylbenzonitrile (Formula 41) (58 mg, 0.26 mmol) in DMF (1 mL) was heated under microwave irradiation at 100 °C for 11 hours. To this mixture was added methanol (20 mL) and *aq*. 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane:acetone, 95:5) to give **RD162'** (Formula 42) (15 mg, 25%) as a colorless crystal. ^{1}H NMR δ 1.61 (s, 6 H), 3.07 (d, 3 H, *J*=4.1), 6.71 (m, 1 H), 7.15 (dd, 1H, *J*=11.7 and 2.0), 7.24 (dd, 1H, *J*=8.4 and 2.0), 7.83 (dd, 1H, *J*=8.2 and 2.1), 7.95 (d, 1H, *J*=2.1), 7.99 (d, 1H, *J*=8.2), 8.28 (dd, 1H, *J*=8.4 and 8.4).

Example 57



Formula 43

[00138] A mixture of N-Methyl-2-fluoro-4-aminobenzamide (Formula 39) (62 mg, 0.37 mmol), cyclopentanone (0.07 mL, 0.74 mmol) and TMSCN (0.1 mL, 0.74 mmol) was heated to 80 °C and stirred for 13 h. To the medium was added ethyl acetate (2 × 20 mL) and then washed with water (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 95:5) to give *N*-Methyl 2-fluoro-4-(1-cyanocyclopentyl)aminobenzamide (Formula 43) (61 mg, 63%) as a white solid. ^{1}H NMR δ 7.95 (dd, 1H, *J* = 8.8, 8.8 Hz), 6.65 (br s, 1H), 6.59 (dd, 1H, *J* = 8.8, 2.3 Hz), 6.50 (dd, 1H, *J* = 14.6, 2.3 Hz), 4.60 (br s, 1H), 2.99 (dd, 3H, *J* = 4.8, 1.1 Hz), 2.36-2.45 (m, 2H), 2.10-2.18 (m, 2H), 1.82-1.95 (m, 4H).

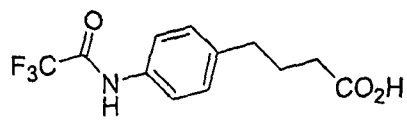


RD162" (Formula 44)

57-1) RD162"

[00139] A mixture of *N*-Methyl 2-fluoro-4-(1-cyanocyclopentyl)aminobenzamide (Formula 43) (57 mg, 0.22 mmol) and 4-isothiocyanato-2-trifluoromethyl benzonitrile (0.15 g, 0.65 mmol) in DMF (3 mL) was heated under microwave irradiation (open vessel) at 130 °C for 12 hours. To this mixture was added methanol (20 mL) and *aq*. 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 95:5) to give 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]nonan-1-yl)-2-fluoro-*N*-methylbenzamide, **RD162"** (Formula 44) (8 mg, 7%) as a pale yellowish solid. ^{1}H NMR δ 8.28 (dd, 1H, *J* = 8.4, 8.4 Hz), 7.98 (d, 1H, *J* = 8.3 Hz), 7.96 (d, 1H, *J* = 1.8 Hz), 7.84 (dd, 1H, *J* = 8.3, 1.8 Hz), 7.27 (dd, 1H, *J* = 8.4, 1.8 Hz), 7.17 (dd, 1H, *J* = 11.7, 1.8 Hz), 6.67-6.77 (m, 1H), 3.07 (d, 3H, *J* = 4.3 Hz), 2.32-2.41 (m, 2H), 2.13-2.21 (m, 2H), 1.85-1.96 (m, 2H), 1.49-1.59 (m, 2H).

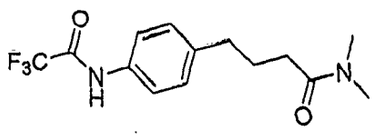
Example 58



Formula 45

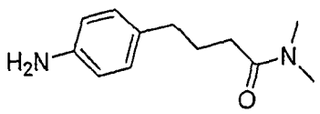
[00140] Trifluoroacetic anhydride (0.85 mL, 6.14 mmol) was added to a solution of 4-(4-aminophenyl)butyric acid (0.5 g, 2.79 mmol) in chloroform (10 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 3 hours. The mixture was partitioned with chloroform (20 mL) and water (20 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 9:1) to give 4-[4-(2,2,2-Trifluoroacetylamino)phenyl]butanoic acid (Formula 45) (0.53 g, 69%). ^{1}H NMR δ 7.81 (br s, 1H), 7.48

(d, 2H, J = 8.5 Hz), 7.22 (d, 2H, J = 8.5 Hz), 2.68 (t, 2H, J = 7.5 Hz), 2.38 (t, 2H, J = 7.5 Hz), 1.96 (p, 2H, J = 7.5 Hz).



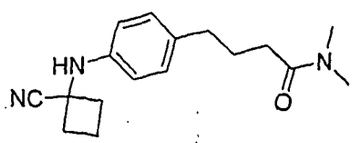
Formula 46

[00141] Thionyl chloride (71 mg, 0.60 mmol) was added slowly to a solution of 4-[4-(2,2,2-Trifluoroacetylamino)phenyl]butanoic acid (Formula 45) (0.15 g, 0.55 mmol) in DMF (5 mL) cooled at -5 °C. The mixture was stirred for an additional 1 hour at -5 °C. Excess dimethylamine (freshly distilled from its 40% aqueous solution) was added to the reaction medium. The second mixture was stirred for an additional 1 hour. Ethyl acetate (50 mL) was added to the mixture, which was washed with brine (2 × 50 ml). The organic layer was dried over $MgSO_4$, and concentrated to yield *N,N*-Dimethyl 4-[4-(2,2,2-Trifluoroacetylamino)phenyl]butanamide (Formula 46) (0.17 g, quant.) as a yellowish solid. ^{1}H NMR δ 9.70 (br s, 1H), 7.55 (d, 2H, J = 8.6 Hz), 7.11 (d, 2H, J = 8.6 Hz), 2.91 (s, 3H), 2.89 (s, 3H), 2.60 (t, 2H, J = 7.7 Hz), 2.27 (t, 2H, J = 7.7 Hz), 1.89 (p, 2H, J = 7.7 Hz).



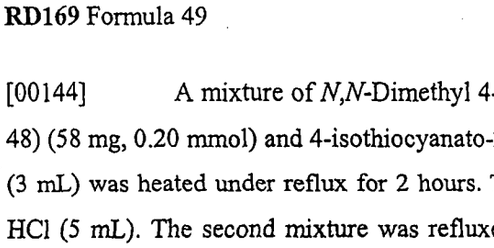
Formula 47

[00142] 1 N NaOH solution (3 mL) was added to a solution of *N,N*-Dimethyl 4-[4-(2,2,2-Trifluoroacetylamino)phenyl]butanamide (Formula 46) (0.17 g, 0.55 mmol) in methanol (2 mL) at room temperature. The mixture was stirred for 14 hour. The mixture was partitioned with chloroform (25 mL) and water (25 mL). The organic layer was dried over $MgSO_4$, and concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 9:1) to give *N,N*-Dimethyl 4-(4-aminophenyl)butanamide (Formula 47) (74 mg, 66%) as a white solid. ^{1}H NMR δ 6.97 (d, 2H, J = 8.3 Hz), 6.61 (d, 2H, J = 8.3 Hz), 3.56 (br s, 2H), 2.92 (s, 6 H), 2.56 (t, 2H, J = 7.7 Hz), 2.28 (t, 2H, J = 7.7 Hz), 1.91 (p, 2H, J = 7.7 Hz).



Formula 48

[00143] A mixture of *N,N*-Dimethyl 4-(4-aminophenyl)butanamide (Formula 47) (74 mg, 0.36 mmol), cyclobutanone (54 mg, 0.78 mmol) and TMSCN (77 mg, 0.78 mmol) was heated to 80 °C and stirred for 15 h. To the medium was added ethyl acetate (2 × 20 mL) and then washed with water (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 9:1) to give *N,N*-Dimethyl 4-[4-(1-cyanocyclobutylamino)phenyl]butanamide (Formula 48) (58 mg, 57%) as a white solid. ^{1}H NMR δ 7.07 (d, 2H, J = 8.5 Hz), 6.59 (d, 2H, J = 8.5 Hz), 3.94 (br s, 1H), 2.94 (s, 3H), 2.93 (s, 3H), 2.75-2.83 (m, 2H), 2.60 (t, 2H, J = 7.6 Hz), 2.33-2.42 (m, 2H), 2.30 (t, 2H, J = 7.6 Hz), 2.11-2.28 (m, 2H), 1.93 (p, 2H, J = 7.6 Hz).



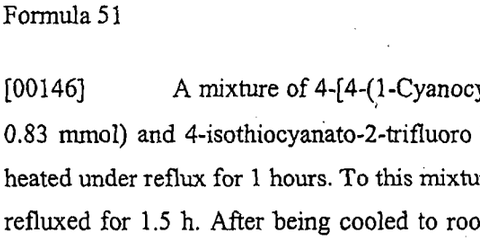
RD169 Formula 49

[00144] A mixture of *N,N*-Dimethyl 4-[4-(1-cyanocyclobutylamino)phenyl]butanamide (Formula 48) (58 mg, 0.20 mmol) and 4-isothiocyanato-2-trifluoromethyl benzonitrile (74 mg, 0.32 mmol) in DMF (3 mL) was heated under reflux for 2 hours. To this mixture was added methanol (20 mL) and *aq*. 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 95:5) to give 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)-*N,N*-dimethylbutanamide, **RD169** (Formula 49) (44 mg, 42%) as a pale yellowish solid. ^{1}H NMR δ 7.98 (s, 1H), 7.97 (d, 1H, J = 8.2 Hz), 7.86 (d, 1H, J = 8.2 Hz), 7.42 (d, 2H, J = 8.3 Hz), 7.22 (d, 2H, J = 8.3 Hz), 2.99 (s, 3H), 2.96 (s, 3H), 2.78 (t, 2H, J = 7.5 Hz), 2.62-2.70 (m, 2H), 2.52-2.63 (m, 2H), 2.40 (t, 2H, J = 7.5 Hz), 2.15-2.30 (m, 1H), 2.04 (p, 2H, J = 7.5 Hz), 1.62-1.73 (m, 1H).

Example 59

Formula 50

[00145] A mixture of 4-(4-aminophenyl)butyric acid (0.20 g, 1.12 mmol), cyclobutanone (0.17 mL, 2.23 mmol) and TMSCN (0.30 mL, 2.23 mmol) was heated to 80 °C and stirred for 13 h. To the medium was added ethyl acetate (2 × 30 mL) and then washed with water (2 × 30 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 9:1) to give 4-[4-(1-Cyanocyclobutylamino)phenyl]butanoic acid (Formula 50) (0.21 g, 74%) as a yellowish solid. ^{1}H NMR δ 7.06 (d, 2H, J = 8.6 Hz), 6.59 (d, 2H, J = 8.6 Hz), 2.75-2.83 (m, 2H), 2.59 (t, 2H, J = 7.5 Hz), 2.37 (t, 2H, J = 7.5 Hz), 2.33-2.42 (m, 2H), 2.11-2.28 (m, 2H), 1.92 (p, 2H, J = 7.5 Hz).



Formula 51

[00146] A mixture of 4-[4-(1-Cyanocyclobutylamino)phenyl]butanoic acid (Formula 50) (0.21 g, 0.83 mmol) and 4-isothiocyanato-2-trifluoro benzonitrile (0.25 g, 1.08 mmol) in toluene (10 mL) was heated under reflux for 1 hours. To this mixture was added *aq.* 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$, concentrated and the residue was purified with silica gel column chromatography (dichloromethane:acetone, 95:5) to give 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)butanoic acid, RD141 (Formula 51) (60 mg, 15%). ^{1}H NMR δ 7.98 (d, 1H, J = 1.8 Hz), 7.97 (d, 1H, J = 8.3 Hz), 7.86 (dd, 1H, J = 8.3, 1.8 Hz), 7.42 (d, 2H, J = 8.5 Hz), 7.24 (d, 2H, J = 8.5 Hz), 2.79 (t, 2H, J = 7.5 Hz), 2.62-2.68 (m, 2H), 2.51-2.59 (m, 2H), 2.47 (t, 2H, J = 7.5 Hz), 2.14-2.26 (m, 1H), 2.06 (p, 2H, J = 7.5 Hz), 1.60-1.70 (m, 1H).

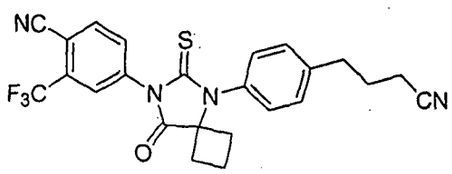
Example 60

RD130 Formula 52

[00147] To a solution of 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-

diazaspiro[3.4]octan-5-yl)phenyl)butanoic acid, RD141 (Formula 51) (60 mg, 0.12 mmol) in DMF (3 mL) was added thionyl chloride (0.01 mL, 0.15 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hour. Then ammonia was bubbled into the mixture. The mixture was partitioned with ethyl acetate (25 mL) and water (25 mL). The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 70:30) to yield 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)butanamide, **RD130** (Formula 52) (37 mg, 61%) as a white powder. ^{1}H NMR δ 7.97 (d, 1H, J = 1.8 Hz), 7.95 (d, 1H, J = 8.3 Hz), 7.85 (dd, 1H, J = 8.3 Hz), 7.39 (d, 2H, J = 8.3 Hz), 7.22 (d, 2H, J = 8.3 Hz), 5.59 (br s, 2H), 2.77 (t, 2H, J = 7.5 Hz), 2.62-2.68 (m, 2H), 2.51-2.59 (m, 2H), 2.31 (t, 2H, J = 7.5 Hz), 2.16-2.25 (m, 1H), 2.05 (p, 2H, J = 7.5 Hz), 1.57-1.70 (m, 1H).

Example 61

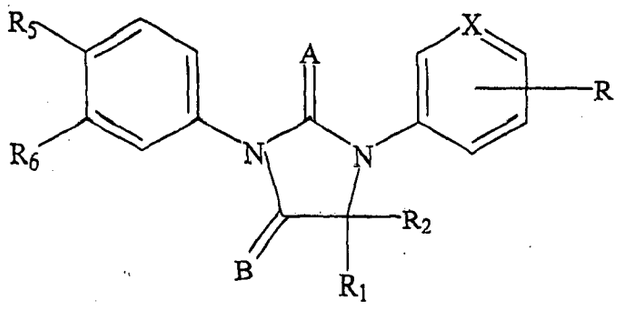


RD170 Formula 53

A solution of DMSO (0.01 mL, 0.12 mmol) in dry dichloromethane (1 mL) was added to a stirred solution of oxalyl chloride (0.01 mL, 0.09 mmol) in dry dichloromethane (2 mL) at -78 °C. After 15 min, a dichloromethane solution of 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)butanamide, RD130 (Formula 52) (35 mg, 0.07 mmol) was added to the reaction mixture. Stirring was continued for 20 min at -78 °C, and then triethylamine (0.03 mL, 0.22 mmol) was added. After 30 min at -78 °C, the reaction mixture was warmed to room temperature and then reaction was quenched with saturated *aq*. NH_4Cl solution. The reaction mixture was diluted with dichloromethane, and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield 4-(5-(4-(3-Cyanopropyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-7-yl)-2-(trifluoromethyl)benzonitrile, **RD170** (Formula 53) (29 mg, 87%) as a viscous oil. ^{1}H NMR δ 7.98 (d, 1H, J = 1.8 Hz), 7.98 (d, 1H, J = 8.3 Hz), 7.86 (dd, 1H, J = 8.3, 1.8 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.27 (d, 2H, J = 8.4 Hz), 2.90 (t, 2H, J = 7.3 Hz), 2.63-2.73 (m, 2H), 2.52-2.62 (m, 2H), 2.42 (t, 2H, J = 7.3 Hz), 2.18-2.30 (m, 1H), 2.07 (p, 2H, J = 7.3 Hz), 1.63-1.73 (m, 1H).

[00148] One skilled in the art could modify and/or combine the syntheses described herein to make other diarylhydantoin compounds.

[00149] Inventive compounds also include those with the following formulas.



Where R is selected from hydrogen, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated akynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, halogen, SO_2R_{11}, $NR_{11}R_{12}$, $NR_{12}(CO)OR_{11}$, $NH(CO)NR_{11}R_{12}$, $NR_{12}(CO)R_{11}$, $O(CO)R_{11}$, $O(CO)OR_{11}$, $O(CS)R_{11}$, $NR_{12}(CS)R_{11}$, $NH(CS)NR_{11}R_{12}$, $NR_{12}(CS)OR_{11}$.

R_1 and R_2 are independently selected from hydrogen, aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated akynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocylic aromaric or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl.

R_1 and R_2 can be connected to form a cycle which can be heterocyclic, substituted heterocyclic, cycloakyl, substituted cycloalkyl.

R_3 is selected from aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, SO_2R_{11}, $NR_{11}R_{12}$, $(CO)OR_{11}$, $(CO)NR_{11}R_{12}$, $(CO)R_{11}$, $(CS)R_{11}$, $(CS)R_{11}$, $(CS)NR_{11}R_{12}$, $(CS)OR_{11}$.

R_5 is CN or NO_2 or SO_2R_{11}

R_6 is CF_3, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated akynyl, halogen.

A is sulfur atom (S) or oxygen atom (O).

B is O or S or NR_3

X is carbon or nitrogen and can be at any position in the ring.

R_{11} and R_{12} are independently selected from hydrogen, aryl, aralkyl, substituted aralkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated akynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cyclolakyl, substituted cycloalkyl.

R_{11} and R_{12} can be connected to form a cycle which can be heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic, cycloakyl, substituted cycloalkyl.

[00150]

Pharmacological examination of the compounds

[00151] Compounds for which synthetic routes are described above were identified through screening on hormone refractory prostate cancer cells for antagonistic and agonistic activities against AR utilizing screening procedures similar to those in PCT applications US04/42221 and US05/05529, which are hereby incorporated by reference. A number of compounds exhibited potent antagonistic activities with minimal agonistic activities for over expressed AR in hormone refractory prostate cancer.

In vitro biological assay

Effect of compounds on AR by a reporter assay

[00152] The compounds were subjected to tests using an artificial AR response reporter system in a hormone refractory prostate cancer cell line. In this system, the prostate cancer LNCaP cells were engineered to stably express about 5-fold higher level of AR than endogenous level. The exogenous AR has similar properties to endogenous AR in that both are stabilized by a synthetic androgen R1881. The AR-over expressed cells were also engineered to stably incorporate an AR response reporter and the reporter activity of these cells shows features of hormone refractory prostate cancer. It responds to low concentration of a synthetic androgen R1881, is inhibited only by high concentrations of bicalutamide (see Table 1), and displays agonistic activity with bicalutamide (Figure 1 and Table 2). Consistent with published data, bicalutamide inhibited AR response reporter and did not have agonistic activity in hormone sensitive prostate cancer cells (Figure 2).

[00153] We examined the antagonistic activity of the compounds for which the synthesis is described above in the presence of 100 pM of R1881. Engineered LNCaP cells (LNCaP-AR, also abbreviated LN-AR) were maintained in Iscove's medium containing 10% fetal bovine serum (FBS). Two days prior to drug treatment, the cells were grown in Iscove's medium containing 10% charcoal-stripped FBS (CS-FBS) to deprive of androgens. The cells were split and grown in Iscove's medium containing 10% CS-FBS with 100 pM of R1881 and increasing concentrations of test compounds. After two days of incubation, reporter activities were assayed.

[00154] Table 1 lists the IC50 of these compounds to inhibit AR in hormone refractory prostate

cancer. The control substance bicalutamide has an IC50 of 889 nM. Most of the compounds identified (diarylthiohydantoins) have IC50s between 100 to 200 nM in inhibiting AR in hormone refractory prostate cancer. In contrast, antiandrogenic compounds listed as examples in US patent no. 5,705,654, such as examples 30-2, 30-3, 31-2, 31-3, and 24-3 (RD73-RD77) have no inhibitory activities on AR in this system.

Table 1

Antagonistic activities against AR in hormone refractory prostate cancer,

measured by an AR response reporter and by endogenous PSA expression.

		IC50 (nM)	IC50 (nM)
Example	**Name**	**Reporter**	**PSA**
Bicalutamide Comparative	N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide	889	>1000
29 Comparative	4-[3-(4-hydroxybutyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	No(*)	No
6-2 (6b) [RD10]	4-[3-phenyl-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	149	n/a (**)
5-3b (5c) [RD7]	4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile	125	132
3-3 (3c) [RD8]	4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	137	122
2-4 (2d) [RD9]	4-[3-(4-aminophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	273	n/a
4 (4a) [RD13]	Chloroacetic acid 4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]phenyl ester	131	n/a
8-2 (8b) [RD35]	4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	147	n/a
7-3b (7c) [RD37]	4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	124	128

9-3 (9c) [RD48]	4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile	194	n/a
10-3 (10c) [RD49]	4-(4-oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]undec-3-yl)-2-trifluoromethylbenzonitrile	232	n/a
28 Comparative (28a) [RD52]	4-(8-methyl-4-oxo-2-thioxo-1,3,8-triazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile	No	n/a
27-3 (27c) [RD53]	4-(8-methyl-4-oxo-2-thioxo-1-(4-methylphenyl)-1,3,8-triazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile	638	n/a
26 (26a) [RD54]	4-[1-(4-cyanophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl]-2-trifluoromethylbenzonitrile	469	n/a
25 (25a) [RD55]	4-[1-(4-nitrophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl]-2-trifluoromethylbenzonitrile	498	n/a
12-2 (12b) [RD57]	4-(8-oxo-6-thioxo-5-(4-biphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	283	n/a
11-2 (11b) [RD58]	4-(8-oxo-6-thioxo-5-(4-hydroxyphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	162	n/a
17 (17a) [RD59]	4-[3-(4-hydroxyphenyl)-4,4-dimethyl-2,5-dithioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	278	287
18 (18a) [RD60]	4-[3-(4-hydroxyphenyl)-4,4-dimethyl-2,5-dioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	369	511
22-2 (22b) [RD65]	2-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]benzoic acid	523	>500
20-2 (20b) [RD66]	4-(4,4-dimethyl-5-oxo-2-thioxo-3-(4-trifluoromethylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile	143	144
21-2 (21b) [RD67]	4-(4,4-bischloromethyl-5-oxo-2-thioxo-3-(4-methylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile	521	>500
19-2 (19b) [RD68]	4-(4-fluoromethyl-4-methyl-5-oxo-2-thioxo-3-(4-methylphenyl)imidazolidin-1-yl)-2-trifluoromethylbenzonitrile	126	129

23-2 (23b) [RD71]	4-(8-oxo-6-thioxo-5-(2-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	258	232
30-2 Comparative (30b) [RD73]	4-(5-methyl-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylenzonitrile	No	No
30-3 Comparative (30c) [RD74]	4-(5-methyl-6,8-dioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	No	No
31-2 Comparative (31b) [RD75]	4-(1-methyl-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	No	No
31-3 Comparative (31c) [RD76]	4-(1-methyl-2,4-dioxo-1,3-diaza-spiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	No	No
24-3 Comparative (24c) [RD77]	4-(4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	No	No
15-2 (15b) [RD82]	4-[4,4-dimethyl-3-(4-pyridin-2-yl)-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	723	n/a
14-2 (14b) [RD83]	4-[4,4-dimethyl-3-(4-methylpyridin-2-yl)-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	457	n/a
16-2 Comparative (16b) [RD84]	4-[5-(5-methyl-2H-pyrazol-3-yl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-7-yl]-2-trifluoromethyl-benzonitrile	>1000	n/a
13-2 (12b) [RD85]	4-(8-oxo-6-thioxo-5-(4-biphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	>1000	n/a
32 (32a) [RD90]	4-(8-methylimino-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-7-yl)-2-trifluoromethyl-benzonitrile	222	421
33 (33a) [RD91]	1-[3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene]-3-ethyl-thiourea	157	239
34 (34a) [RD92]	1-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-3-phenyl-thiourea	176	276

35 (35a) [RD93]	1-(4-Cyano-3-trifluoromethyl-phenyl)-3-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-thiourea	144	158
36-2 (36b) [RD110]	4-[8-(4-hydroxymethyl-phenyl)-5-oxo-7-thioxo-6-aza-spiro[3.4]oct-6-yl]-2-trifluoromethyl-benzonitrile	311	337
37 (37a) [RD114]	4-[5-(4-formylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethyl-benzonitrile	n/a	263
38 (38a) [RD116]	4-{5-[4-(1-hydroxyethyl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethyl-benzonitrile	n/a	187
39 (39a) [RD117]	3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-acrylic acid ethyl ester	n/a	197
40 (40a) [RD120]	4-{5-[4-(3-hydroxypropenyl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethylbenzonitrile	n/a	114
41-2 (41b) [RD128]	3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-propionic acid methyl ester	No	n/a
41-4 (41d) [RD133]	3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-propionamide	224	n/a
41-5 (41e) [RD134]	3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-N-methyl-propionamide	234	n/a
41-6 (41f) [RD135]	3-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-N-(2-hydroxyethyl)-propionamide	732	n/a
42-2 (42b) [RD129]	4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-phenyl}-butyric acid methyl ester	432	n/a
42-4	4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-	112	n/a

(42d) [RD130]	thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-butyramide		
42-5 (42e) [RD131]	4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-N-methyl-butyramide	92	n/a
43-4 (43e) [RD137]	4-[8-Oxo-5-(4-piperazin-1-yl-phenyl)-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile	718	n/a
43-5 (43f) [RD138]	4-{5-[4-(4-methanesulfonylpiperazin-1-yl)-phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethylbenzonitrile	138	n/a
44-2 (44b) [RD119]	44-2) 3-{4-[7-(4-Cyano-3-trifluoromethyl-phenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-phenyl}-acrylamide,		113

(*) No: the compound did not inhibit AR response reporter; (**) n/a: the compound was not examined in this assay.

[00155] One previously unrecognized property of AR overexpression in hormone refractory prostate cancer is its ability to switch antagonists to agonists. Therefore, only those compounds with minimal or no agonistic activities are qualified to be anti-androgens for this disease. To determine agonistic activities of different compounds, we examined their stimulating activities on AR using the AR response reporter as the measure in the LN-AR system in the absence of R1881. Table 2 lists the agonistic activities of different compounds. Consistent with previous results, bicalutamide activated AR in hormone refractory prostate cancer. The diarylthiohydantoin derivatives such as examples 7-3b (RD37), 33 (RD91), 34 (RD92), and 35 (RD93) have no agonistic activity. In contrast, RU59063, and other anti-androgenic compounds listed as examples in US Patent Number 5,705,654, such as examples 30-2, 30-3, 31-2, 31-3, and 24-3 (RD73-RD77) strongly activated AR in hormone refractory prostate cancer.

Table 2

Agonistic activities of selective test substances on
AR response reporter in hormone refractory prostate cancer

Fold induction by increasing

		concentrations of compounds		
Example	**Name**	**0.1 μM**	**1 μM**	**10 μM**
DMSO	Dimethyl sulfoxide	1.00 (*)	1.00	1.00
R1881	*methyltrienolone*	44.33	n/a(**)	n/a
Bicalutamide	N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide	1.66	3.04	10.40
29 Comp.	4-[3-(4-hydroxybutyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	10.99	20.84	34.62
7-3b (7c) [RD37]	4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	0.87	1.19	0.89
33 (33a) [RD91]	1-[3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene]-3-ethyl-thiourea	1.30	1.18	1.28
34 (34a) [RD92]	1-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-3-phenyl-thiourea	1.19	1.41	1.17
35 (35a) [RD93]	1-(4-Cyano-3-trifluoromethyl-phenyl)-3-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-thiourea	1.26	1.10	1.30
30-2 Comp. (30b) [RD73]	4-(5-methyl-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylenzonitrile	14.88	19.41	35.22
30-3 Comp. (30c) [RD74]	4-(5-methyl-6,8-dioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	11.39	14.26	30.63
31-2 Comp. (31b) [RD76]	4-(1-methyl-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	17.03	16.63	33.77
31-3	4-(1-methyl-2,4-dioxo-1,3-diaza-spiro[4.4]non-	11.99	19.77	38.95

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Comp. (31c) [RD76]	3-yl)-2-trifluoromethylbenzonitrile			
24-3 Comp. (24c) [RD77]	4-(4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	14.88	22.48	37.09

(*) Fold induction: activities induced by a specific test substance over activities in DMSO vehicle; (**) n/a: the compound was not examined in this assay.

[00156] To examine the specificity of AR inhibitors, selective compounds were tested in LNCaP cells with an over expression of glucocorticoid receptor (GR), the closest member of AR in the nuclear receptor family. These cells also carry a GR response reporter and the reporter activity was induced by dexamethasone, a GR agonist and the induction was blocked by RU486, a GR inhibitor. Example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethyl benzonitrile) had no effect on GR in this system.

Effect of compounds on AR by measuring secreted levels of prostate specific antigen (PSA)

[00157] It is well established that PSA levels are indicators of AR activities in prostate cancer. To examine if the compounds affect AR function in a physiological environment, we determined secreted levels of endogenous PSA induced by R1881 in the AR-overexpressed LNCaP cells (LNCaP-AR, also abbreviated LN-AR). The LNCaP-AR cells are a line of lymph node carcinoma of prostate cells transduced with a plasmid that makes express androgen receptors. LNCaP-AR cells were maintained in Iscove's medium containing 10% FBS. Two days prior to drug treatment, the cells were grown in Iscove's medium containing 10% CS-FBS to deprive of androgens. The cells were split and grown in Iscove's medium containing 10% CS-FBS with appropriate concentrations of R1881 and the test compounds. After four days incubation, secreted PSA levels were assayed using PSA ELISA kits (American Qualex, San Clemente, CA)

[00158] The secreted PSA level of LNCaP-AR cells was strongly induced by 25 pM of R1881. In contrast, PSA was not induced in the parental LNCaP cells until concentration of R1881 reached 100 pM. This is consistent with our previous report that the AR in hormone refractory prostate cancer is hyper-

sensitive to androgens. A dose-dependent inhibition on AR activity was carried out to determine the IC50s of different compounds in inhibiting PSA expression, and the results were listed in Table 1. IC50s of the selective compounds on PSA expression closely resemble those measured by the reporter assay, confirming that the diarylhydantoin derivatives are strong inhibitors of AR in hormone refractory prostate cancer.

[00159] We also examined agonistic activities of selective compounds on AR in hormone refractory prostate cancer using secreted PSA as the surrogate marker. To do this, androgen-starved AR over expressed LNCaP cells were incubated with increasing concentrations of the compounds for which a synthesis is described above in the absence of R1881 and secreted PSA in the culture medium was measured 4 days later.

[00160] Table 3 lists the agonistic activities of the selective compounds. Consistent with the results obtained from the reporter assay, the diarylthiohydantoin derivatives such as examples 7-3b (RD37), 33 (RD91), 34 (RD92), and 35 (RD93) have no agonistic activities. In contrast, RU59063, and other antiandrogenic compounds listed as examples in US patent no. 5,705,654, such as examples 30-2 (RD73), 30-3 (RD74), and 31-2 (RD75) stimulated PSA expression in hormone refractory prostate cancer.

Table 3

Agonistic activities of selective test substances on endogenous PSA in hormone refractory prostate cancer

Fold induction by increasing concentrations of compounds

Example	Name	0.1 µM	1 µM	10 µM
DMSO	Dimethyl sulfoxide	1.00 (*)	1.00	1.00
R1881	methyltrienolone	20.69	n/a(**)	n/a
Bicalutamide	N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide	2.00	2.55	5.55
29 Comp.	4-[3-(4-hydroxybutyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile	6.88	11.50	21.50
7-3b (7c) [RD37]	4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	1.25	1.20	1.15
33	1-[3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-	1.06	1.30	0.85

(33a) [RD91]	dimethyl-2-thioxo-1-p-tolyl-imidazolidin-4-ylidene]-3-ethyl-thiourea			
34 (34a) [RD92]	1-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-3-phenyl-thiourea	1.31	1.05	0.90
35 (35a) [RD93]	1-(4-Cyano-3-trifluoromethyl-phenyl)-3-[7-(4-cyano-3-trifluoromethyl-phenyl)-6-thioxo-5-p-tolyl-5,7-diaza-spiro[3.4]oct-8-ylidene]-thiourea	1.44	1.30	1.05
30-2 Comp. (30b) [RD73]	4-(5-methyl-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylenzonitrile	6.25	17.95	25.65
30-3 Comp. (30c) [RD74]	4-(5-methyl-6,8-dioxo-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile	7.50	15.20	23.75
31-2 Comp. (31b) [RD75]	4-(1-methyl-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile	8.13	18.20	17.50

(*) Fold induction: activities induced by a specific test substance over activities in DMSO vehicle; (**) n/a: the compound was not examined in this assay.

[00161]

Effect of compounds on AR mitochondrial activity by MTS assay

[00162] LNCaP-AR cells were maintained in Iscove's medium containing 10% FBS. The compounds were examined for their effect on growth of hormone refractory prostate cancer cells. Overexpressed LNCaP cells were used because these cells behave as hormone refractory prostate cancer cells in vitro and in vivo *(1)*. We measured mitochondria activity by MTS assay, a surrogate for growth. LNCaP cells with overexpressed AR (LN-AR) were maintained in Iscove's medium containing 10% FBS. Two days prior to drug treatment, the cells were grown in Iscove's medium containing 10% CS-FBS to deprive of androgens. The cells were then split and grown in Iscove's medium containing 10% CS-FBS with appropriate concentrations of R1881 and increasing concentrations of the test compounds. After four days incubation, cell growth was monitored by MTS (Promega, Madison, WI).

[00163] Consistent with the reporter assay and PSA assay, growth of the AR-overexpressed LNCaP was stimulated by 25 microM of R1881, but the parental cells were not stimulated until R1881 concentration reached 100 microM. Figure 2 shows the inhibitory effect of selected compounds on growth of hormone refractory prostate cancer in the presence of 100 pM of R1881. The current clinical drug bicalutamide did not inhibit hormone refractory prostate cancer. In contrast, example 5-3b (RD7) (4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile) and example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) inhibited hormone refractory prostate cancer with high potency.

[00164] We examined if growth inhibition in the MTS assay occurs by targeting AR, example 5-3b (RD7) (4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile) and example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) were tested in DU-145 cells, a prostate cancer cell line that lacks AR expression. These compounds had no growth inhibitory effect on DU-145 cells. The compounds did not inhibit cells other than AR-expressed prostate cancer cells, as they had no growth effect on MCF7 and SkBr3, two commonly used breast cancer cells, or 3T3, a normal mouse fibroblast cell line.

[00165] Examples of in vitro biological activity of diarylthiohydantoin derivatives are shown in the Figures 3, 4 and 5. For example, based on relative luciferase activity, Fig. 3 indicates that at a concentration of 500 nM the compounds ranked, in order of most active to least active as follows: RD152 > RD153 > RD145 > RD163 > RD161 = RD162 > bicalutamide. For example, based on relative PSA level, Fig 4 indicates that at a concentration of 500 nM the compounds ranked, in order of most active to least active as follows: RD138 > RD131 > RD37 > RD133 > RD134 > RD137 > RD138 > RD135 > bicalutamide. For example, based on relative MTS units, Fig. 5 indicates that at a concentration of 500 nM the compounds ranked, in order of most active to least active as follows: RD168 > RD37 > RD141 > RD162 > bicalutamide.

Inhibitory effect on hormone refractory prostate cancer xenograft tumors.

[00166] Example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) was used to examine if the diarylhydantoin derivatives have in vivo effects on hormone refractory prostate cancer. First we examined this compound on xenograft tumors established from AR-overexpressed LNCaP cells. The engineered cells in Matrigel (Collaborative Biomedical) were injected subcutaneously into the flanks of the castrated male SCID mice. Tumor size was measured weekly in three dimensions using calipers. After xenograft tumors established (tumor size reached at least 40 mm^3), mice with tumors were randomized and treated with different doses of

compounds orally once daily. Consistent with clinical observation, current clinical drug bicalutamide did not inhibit growth of hormone refractory prostate cancer (same as vehicle) (Figure 7a). In contrast, example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) strongly inhibited growth of these tumors (Figure 7a) and the inhibition is dose-dependent (Figure 7b). Furthermore, example 7-3b (RD37) inhibited PSA expression (Figure 8), the clinical marker for hormone refractory prostate cancer.

[00167] Example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) was also tested in another xenograft model of hormone refractory prostate cancer, hormone refractory LAPC4. This model was established from passaging of hormone sensitive prostate cancer in castrated mice, which mimics the clinical progression of prostate cancer *(2)*. Similar to the finding using AR-overexpressed LNCaP xenograft model, current clinical drug bicalutamide did not inhibit growth and PSA expression in hormone refractory LAPC4 xenograft model (same as vehicle) (Figure 9a and 9b). In contrast, example 7-3b (RD37) strongly inhibited growth and PSA expression of these tumors (Figure 9a and 9b).

Inhibitory effect on growth of hormone sensitive prostate cancer cells.

[00168] To determine if the diarylthiahydantoin derivatives also inhibit hormone sensitive prostate cancer cells, we tested some selective compounds on growth of LNCaP cells by measuring MTS of mitochondria activities. In contrast to have no effect on growth of hormone refractory prostate cancer, the current clinical drug bicalutamide mildly inhibited hormone sensitive LNCaP cells in a dose-dependent manner. Example 5-3b (RD7) (4-[3-(4-methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethyl-benzonitrile) and example 7-3b (RD37) (4-(8-oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile) inhibited hormone sensitive prostate cancer with a 10-fold higher potency than bicalutamide (Figure 10).

In vivo biological assay

[00169] All animal experiments were performed in compliance with the guidelines of the Animal Research Committee of the University of California at Los Angeles. Animals were bought from Taconic and maintained in a laminar flow tower in a defined flora colony. LNCaP-AR and LNCaP-vector cells were maintained in RPMI medium supplemented with 10% FBS. 10^6 cells in 100 µl of 1:1 Matrigel to RPMI medium were injected subcutaneously into the flanks of intact or castrated male SCID mice. Tumor size was measured weekly in three dimensions (length x width x depth) using calipers. Mice were randomized to treatment groups when tumor size reached approximately 100 mm^3. Drugs were given orally every day at 10 mg/kg and 50 mg/kg. To obtain pharmacodynamic readout, the animals were

imaged via an optical CCD camera, 3 hours after last dose of the treatment. A ROI is drawn over the tumor for luciferase activity measurement in photon/second. The right panels were a representation of the ROIs measurements. Data are shown in figures 11 and 12. Over 18 days RD162 was effective to prevent tumor growth and even to cause tumor shrinkage, and was distinctly more effective than bicalutamide.

[00170] The pharmacokinetics of bicalutamide, 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-toluene [RD37], *N*-methyl-4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}butanamide [RD131], and *N*-methyl-4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-2-fluorobenzamide (52d) [RD162] were evaluated in vivo using 8 week-old FVB mice which were purchased from Charles River Laboratories. Mice were divided into groups of three for each time points. Two mice were not treated with drug and two other mice were treated with vehicle solution. Each group was treated with 10 mg per kilogram of body weight.

[00171] The drug was dissolved in a mixture 1:5:14 of DMSO : PEG400 : H_20. (Vehicle solution) and was administered into mice through the tail vein. The animals are warmed under a heat lamp for approximately 20 minutes prior to treatment to dilate their tail vein. Each mouse was placed into a mouse restrainer (Fisher Sci. Cat# 01-288-32A) and was injected with 200 µl of drug in vehicle solution into the dilated tail vein. After drug administration, the animals were euthanized via CO_2 inhalation at different timepoints: 5 mn, 30 mn, 2 h, 6 h, 16 h. Animals were immediately bleed after exposure to CO_2 via cardiac puncture (1 ml BD syringe + 27G 5/8 needle). For oral dosage, the drug was dissolved in a mixture 50:10:1:989 of DMSO : Carboxymethylcellulose : Tween80:H20 before oral administration via a feeding syringe.

[00172] The serum samples were analyzed to determine the drug's concentration by the HPLC which (Waters 600 pump, Waters 600 controller and Waters 2487 detector) was equipped with an Alltima C18 column (3µ, 150 mm×4.6 mm). The RD37, RD131, and RD162 compounds were detected at 254 nm wave length and bicalutamide was detected at 270 nm wave length.

[00173] The samples for HPLC analysis were prepared according to the following procedure:

- Blood cells were separated from serum by centrifugation.

- To 400 µl of serum were added 80 µl of a 10 µM solution of an internal standard and 520 µl of acetonitrile. Precipitation occurred.

- The mixture was vortexed for 3 minutes and then placed under ultrasound for 30 minutes.

- The solid particles were filtered off or were separated by centrifugation.

- The filtrate was dried under an argon flow to dryness. The sample was reconstructed to 80 µl with acetonitrile before analyzing by HPLC to determine the drug concentration.

- Standard curve of drug was used to improve accuracy.

[00174] The concentration of RD162 in plasma as a function of time resulting from intravenous and from oral administration is shown in figure 13. The steady state concentration (Css) of bicalutamide, RD131, and RD162 is shown in Table 4. The concentration at steady state of RD162 is essentially as good as that of bicalutamide, and substantially better than RD131.

Name	IC50 [nM]	LogP	Css,10 mg/kg [µM]	Css,25 mg/kg [µM]	Css,50 mg/kg [µM]
Bic.	1000	2.91	10.0	11.4	11.9
RD131	92	3.44	0.39	0.43	0.40
RD162	122	3.20	9.9	10.7	10.2

Table 4. Steady-state concentration of bicalutamide, RD131, and RD162 in mice plasma.

Ranking of Compounds in Tiers

[00175] Tables 5 – 10 present diarylhydantoin compounds grouped into Tiers 1-6. Table 11 presents diarylhydantoin compounds which have not been placed into a tier. The placement of compounds into tiers was based on available data coupled with analytical judgment. Data considered included in vitro assays (AR response reporter system in LNCaP cell line, PSA level measurement, MTS mitochondrial assay) and in vivo experiments (tumor size measured directly or by emission induced by luciferase reporter gene, pharmacokinetic assays based on blood plasma levels). Not every compound was subjected to each assay. Not all data that was generated is shown. Judgment was applied in ranking compounds relative to each other for their utility in treating prostate cancer, in particular when ranking two compounds for which the same experiments were not performed. Characteristics considered in establishing the ranking include AR antagonism activity, lack of AR agonism in hormone refractory cells, prevention of tumor growth, tumor shrinkage, and pharmacokinetic behavior, with a longer residence time in blood being advantageous.

Tier 1

[00176] Generally, Tier 1 compounds are diarylthiohydantoins with a disubstituted left hand aryl ring that are disubstituted on the right hydantoin carbon, and have either an oxygen or N substituent on the left hydantoin carbon. It is expected that the amido substituent hydrolyzes to an oxygen in aqueous solutions such as encountered in biological systems, in vitro and in vivo. RD100 has good activity with an iodine instead of a CF_3 substituent on the left hand aryl ring.

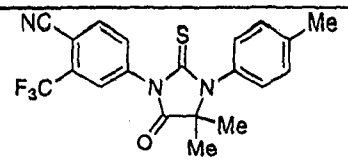
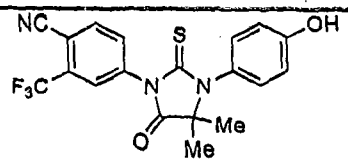
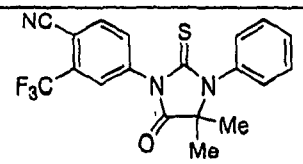
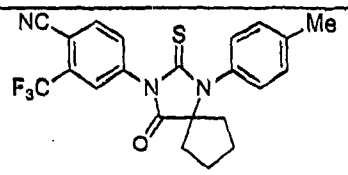
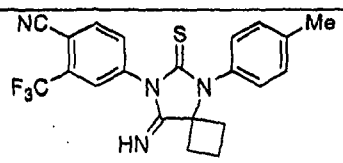
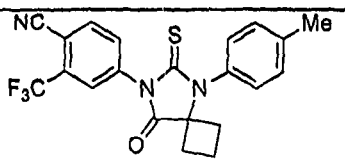
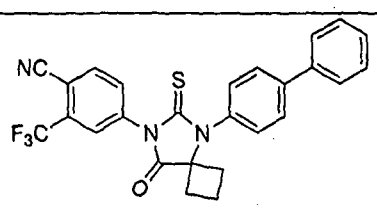
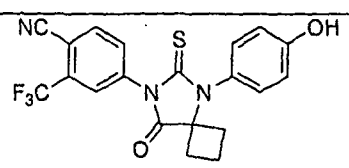
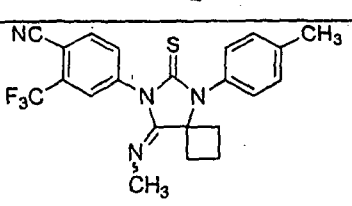
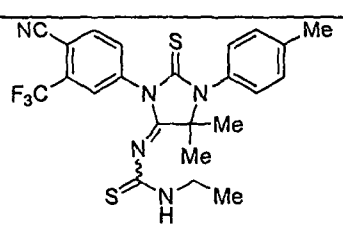
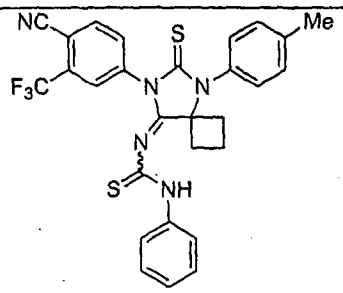
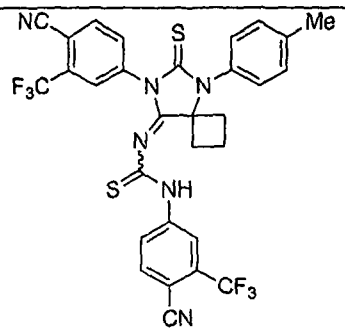
[00177] Tier 1 compounds (see Table 5) were judged to be much better than bicalutamide for treating prostate cancer. However, RD37 and RD131 were found to metabolize fast, that is, have a short residence time in blood. RD162 had desirable pharmacokinetics.

[00178] Figure 17 shows that under treatment with bicalutamide, PSA levels for LNCaP cells stayed the same or increased relative to treatment with vehicle solution, whereas under treatment with RD162, PSA levels decreased. Figure 18 illustrates that under treatment with vehicle solution, tumors continued to increase in size. By contrast, under treatment with RD162 at a dose of 1 mg per kg body weight per day, the rate of tumor increase decreased, and the size of the tumor appeared to be stabilizing after about 17 days. Under treatment with RD162 at a dose of 10 mg per kg body weight per day, tumor size decreased with time. Figure 19 illustrates that under treatment with RD162 at a dose of 10 mg per kg body weight per day, photon emission associated with luciferase activity decreased. Figure 20 shows that treatment with RD162 at this dose resulted in a decrease or stabilization of tumor size and a decrease in photon emission associated with luciferase activity.

[00179] Figure 21 shows that under treatment with RD162, RD162', RD162", RD169, and RD170 at doses of 100, 200, 500, and 1000 nM, PSA levels of LN-AR cells decreased. Moreover, the higher the dose, the lower the PSA level. Figure 23 presents urogenital tract weight and rate of photon emission associated with luciferase activity initially and after 14 days of treatment with bicalutamide or with RD162 for intact and castrated mice. The weight and rate of photon emission increased for both intact and castrated mice. Treatment of castrated mice with RD162 resulted in a decrease in weight and photon emission with respect to the untreated castrated mice, as did treatment with bicalutamide.

[00180] Thus, Tier 1 compounds are particularly advantageous for use as AR antagonists, and as therapeutic agents for hormone refractory prostate cancer. They may be useful to treat other AR related diseases or conditions such as benign prostate hyperplasia, hair loss, and acne. These and related compounds may also be useful as modulators of other nuclear receptors, such as glucocorticoid receptor, estrogen receptor, and peroxisome proliferator-activated receptor, and as therapeutic agents for diseases in which nuclear receptors play a role, such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases. They may be useful in assays e.g. as standards, or as intermediates or prodrugs.

TABLE 5

TIER 1 COMPOUNDS	
RD7 	RD8 
RD10 	RD35 
RD36 	RD37 
RD57 	RD58 
RD90 	RD91 
RD92 	RD93 

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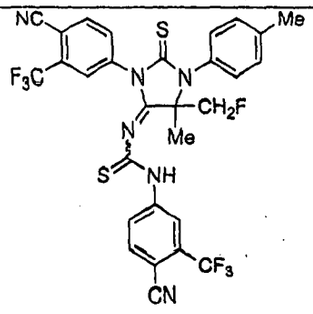
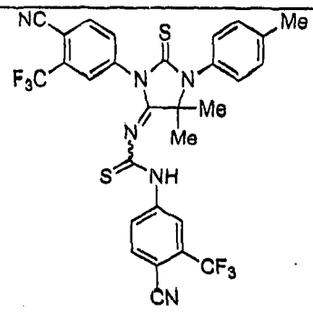
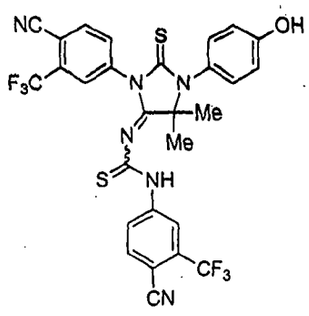
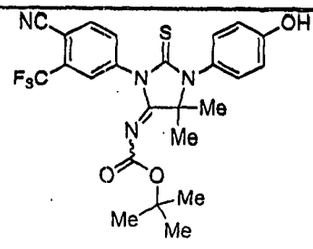
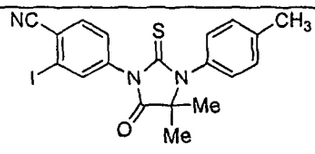
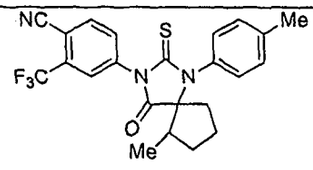
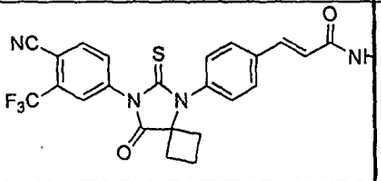
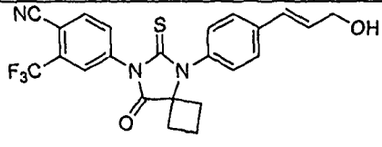
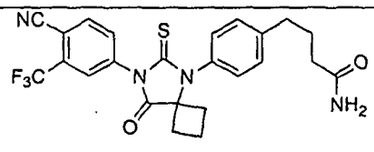
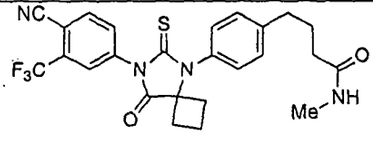
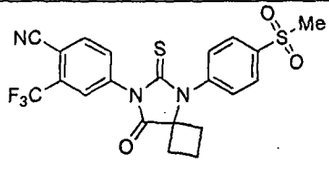
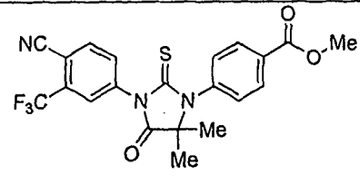
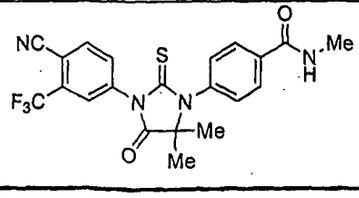
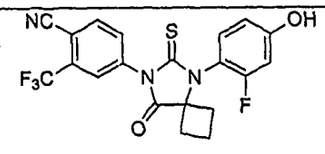
RD94 	RD95 
RD96 	RD97 
RD100 	RD102 
RD119 	RD120 
RD130 	RD131 
RD145 	RD152 
RD153 	RD163 

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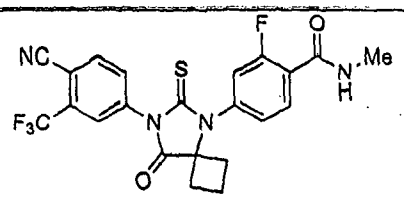
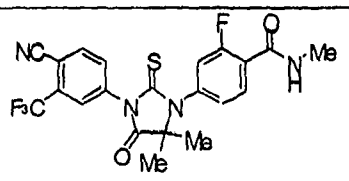
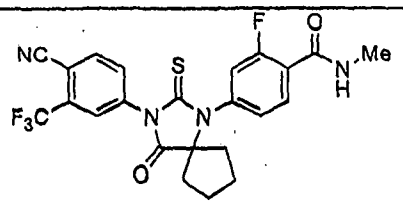
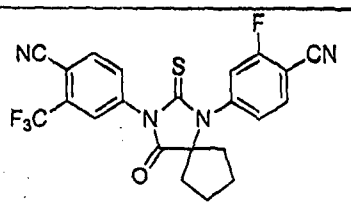
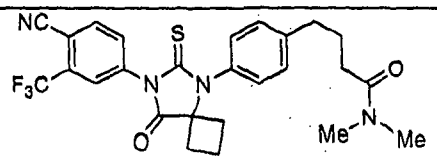
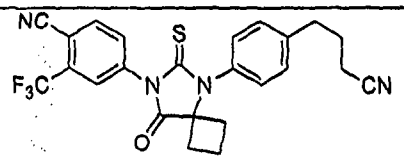
RD162 	RD162' 
RD162" 	RD168 
RD169 	RD170 

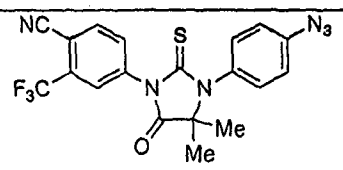
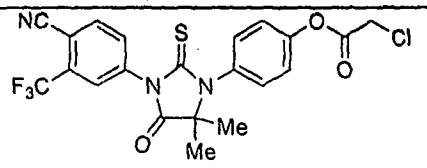
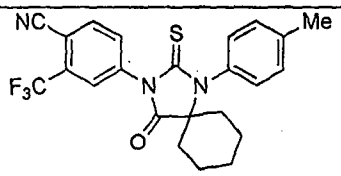
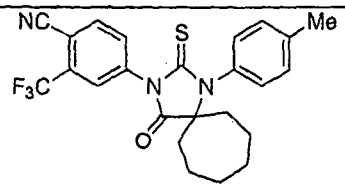
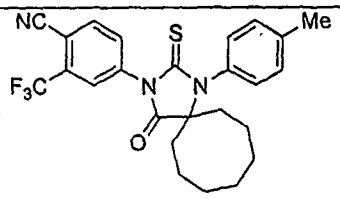
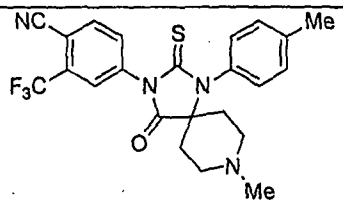
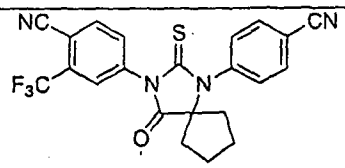
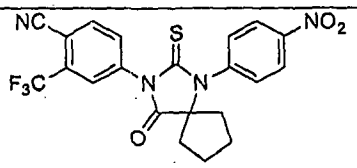
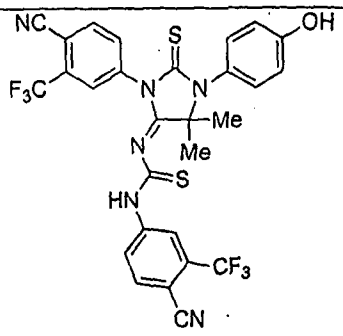
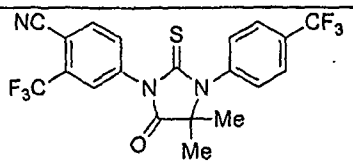
Tier 2

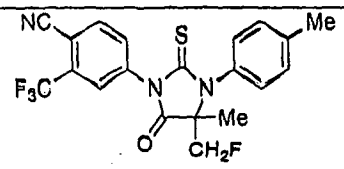
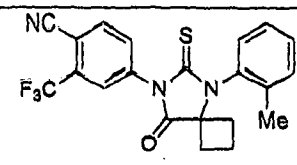
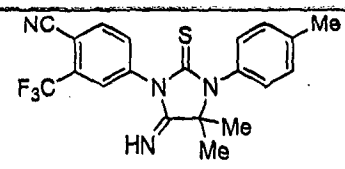
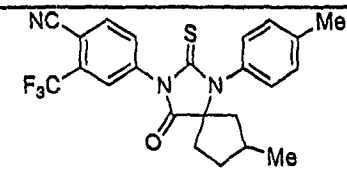
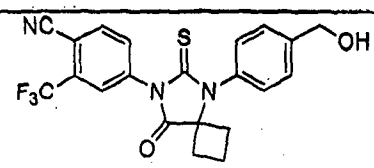
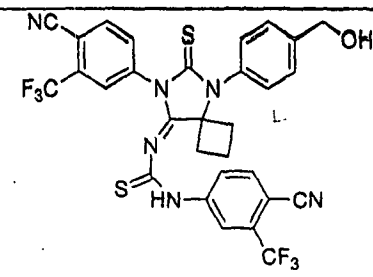
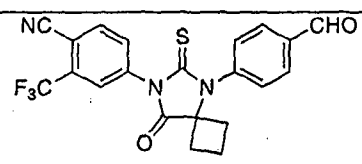
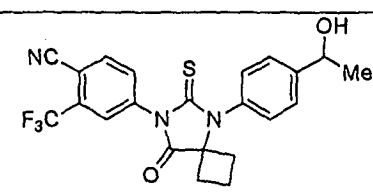
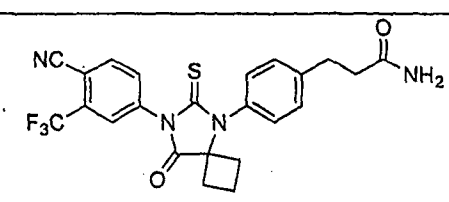
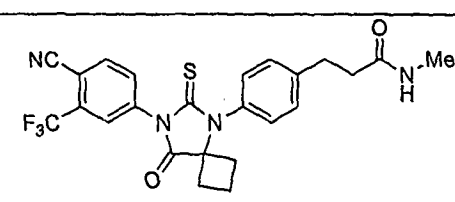
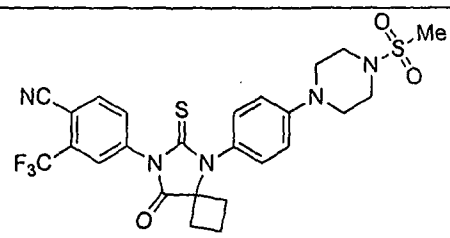
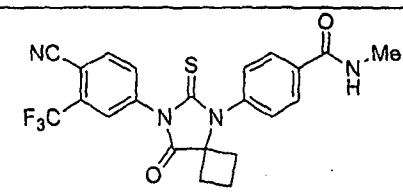
[00181] Tier 2 compounds (see Table 6) were significantly better than bicalutamide for treating prostate cancer, although there were indications that RD54 could act as an agonist. Figure 3 illustrates that compounds RD145, RD152, RD153, RD162, and RD163 in Tier 1 and RD161 in Tier 2 dosed at concentrations ranging from 125 nM to 1000 nM acted to reduce luciferase activity in LNCaP-AR cells whereas control solutions of DMSO and of bicalutamide had little or no effect. Figure 4 illustrates, for example, that at concentrations of 1000 nM, compounds RD37 and RD131, in Tier 1, caused a greater decrease in PSA level of LNCaP-AR cells than RD133, RD134, and RD138 in Tier 2. Figure 11 presents tumor volume over time, and illustrates that under treatment with bicalutamide or vehicle solution, tumors continued to grow, whereas under treatment with RD162, in Tier 1, tumors decreased in size. Figure 12 illustrates that photon emission associated with luciferase activity remained about the same or increased under treatment with bicalutamide relative to treatment with vehicle solution, whereas photon emission decreased under treatment with RD162. Figure 14 illustrates that under treatment with bicalutamide, there was little or no decrease in PSA levels, whereas under treatment with RD131 and RD162, PSA levels decreased. Figure 15 illustrates that the IC_{50} for RD37, RD 131, and RD162, in Tier 1, was much lower than the IC_{50} for bicalutamide.

[00182] Generally, Tier 2 compounds are structurally similar to Tier 1 compounds, but with different substituents on the right hand aryl ring. Tier 2 compounds are advantageous for use as AR antagonists, and as therapeutic agents for hormone refractory prostate cancer. They may be useful to treat other AR related diseases or conditions such as benign prostate hyperplasia, hair loss, and acne.

These and related compounds may also be useful as modulators of other nuclear receptors, such as estrogen receptor and peroxisome proliferator-activated receptor, and as therapeutic agents for diseases in which nuclear receptors play a role, such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases. They may be useful in assays e.g. as standards, or as intermediates or prodrugs.

TABLE 6

TIER 2 COMPOUNDS	
RD6  (comparative)	RD13 
RD48 	RD49 
RD51 	RD53 
RD54 	RD55 
RD63 	RD66 

TIER 2 COMPOUNDS	
RD68 	RD71 
RD87 	RD103 
RD110 	RD111 
RD114 	RD116 
RD133 	RD134 
RD138 	RD161 

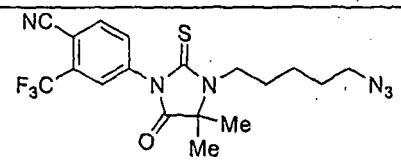
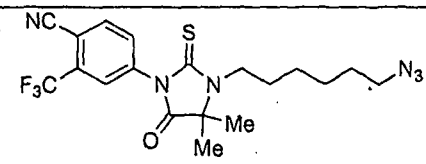
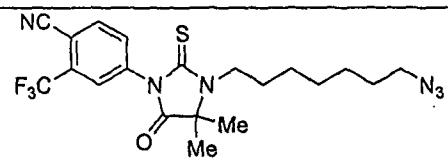
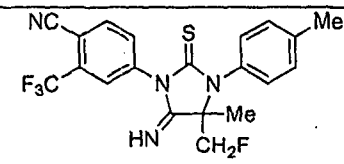
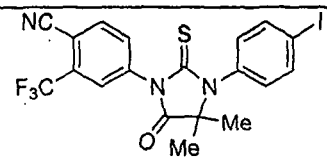
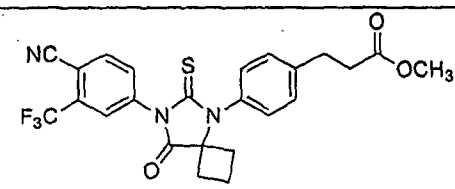
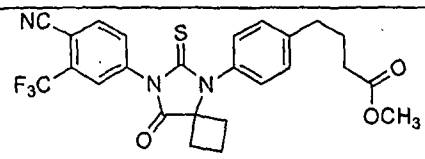
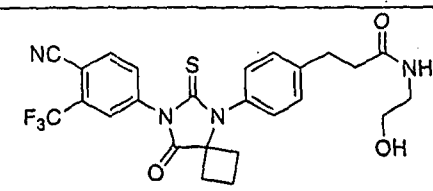
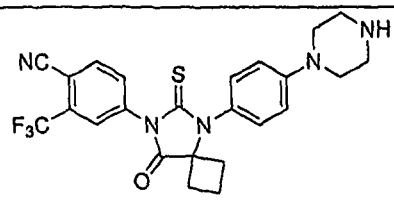
Tier 3

[00183] Tier 3 compounds (see Table 7) were judged to be slightly better than bicalutamide for treating prostate cancer. RD133, RD134, and RD138 (in Tier 2) caused a greater decrease in PSA level of LNCaP-AR cells than RD135 and RD137, in Tier 3. All of these compounds caused a greater decrease in PSA level than bicalutamide.

[00184] Other Tier 3 compounds (not shown) were not diarylthiohydantoins, and were comparable in activity to prior art monoarylhydantoin compounds RD2, RD4, and RD5.

[00185] Thus, Tier 3 compounds are useful as AR antagonists, and as therapeutic agents for hormone refractory prostate cancer. They may be useful to treat other AR related diseases or conditions such as benign prostate hyperplasia, hair loss, and acne. These and related compounds may also be useful as modulators of other nuclear receptors, such as estrogen receptor and peroxisome proliferator-activated receptor, and as therapeutic agents for diseases in which nuclear receptors play a role, such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases. They may be useful in assays e.g. as standards, or as intermediates or prodrugs.

TABLE 7

TIER 3 COMPOUNDS	
RD3  (comparative)	RD4  (comparative)
RD5  (comparative)	RD69 
RD127 	RD128 
RD129 	RD135 
RD137 	

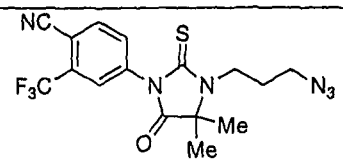
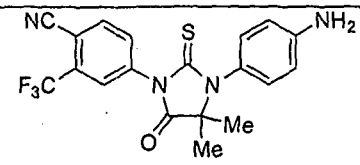
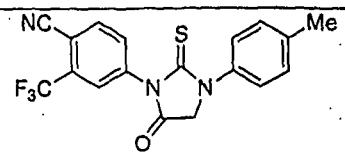
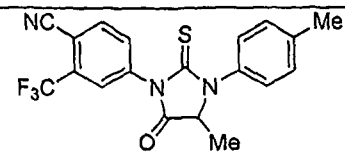
Tier 4

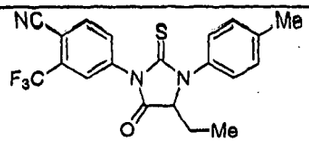
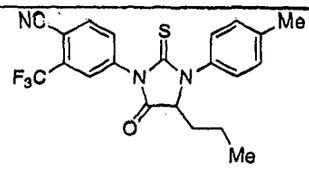
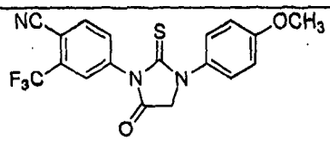
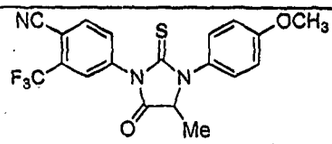
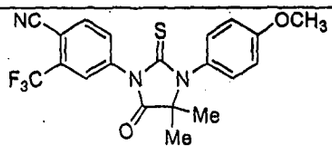
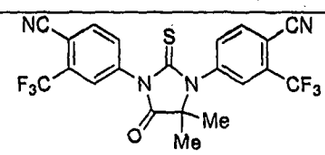
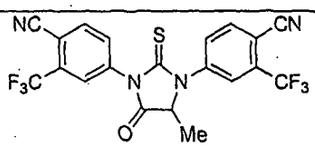
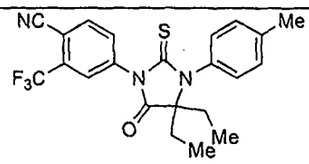
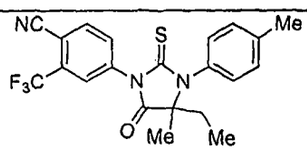
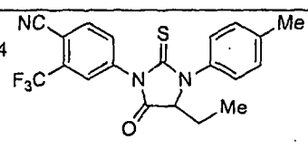
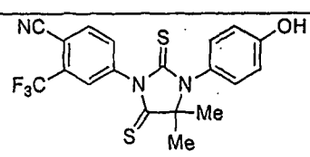
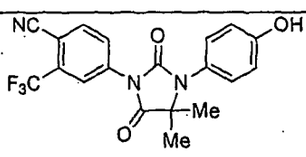
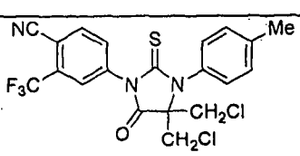
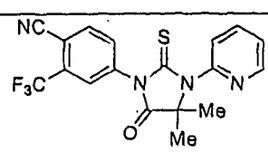
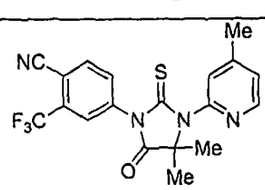
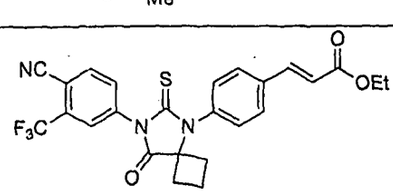
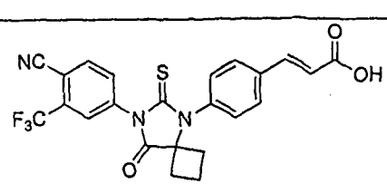
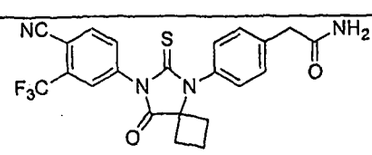
[00186] Tier 4 compounds (see Table 8) were judged to be no better than bicalutamide for treating prostate cancer. Tier 4 RD 39 and RD40 and Tier 1 RD37, for example, differ only in the substituent on the lower right carbon of the hydantoin ring. The substituents on the right hand aryl ring may also affect activity.

[00187] Some Tier 4 compounds (including those shown and others that are not shown) were not diaryl compounds (lacking the right hand aryl ring), were not thiohydantoins, were not disubstituted on the carbon on the lower right hand of the hydantoin ring, and/or had substituents other than oxygen or amido on the lower left hand carbon of the hydantoin ring. This provides evidence of the surprising advantages of diarylthiohydantoins that are disubstituted on the lower right hand carbon of the hydantoin ring and have oxygen or amido on the lower left hand carbon of the hydantoin ring.

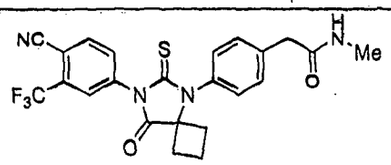
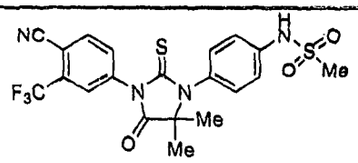
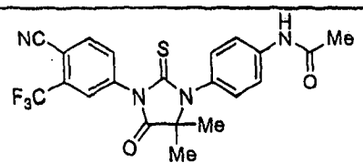
Thus, Tier 4 compounds may be useful as AR antagonists, and as therapeutic agents for hormone refractory prostate cancer, at least to the extent that they are comparable to bicalutamide. They may be useful to treat other AR related diseases or conditions such as benign prostate hyperplasia, hair loss, and acne. These and related compounds may also be useful as modulators of other nuclear receptors, such as estrogen receptor and peroxisome proliferator-activated receptor, and as therapeutic agents for diseases in which nuclear receptors play a role, such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases. They may be useful in assays e.g. as standards, or as intermediates or prodrugs.

TABLE 8

TIER 4 COMPOUNDS	
RD2  (comparative)	RD9 
RD21 	RD22 

TIER 4 COMPOUNDS	
RD23 	RD24 
RD25 	RD26 
RD27 	RD30 
RD31 	RD39 
RD40 	RD44 
RD59 	RD60 
RD67 	RD82 
RD83 	RD117 
RD118 	RD148 

Q69

TIER 4 COMPOUNDS			
RD149		RD150	
RD151			

Tier 5

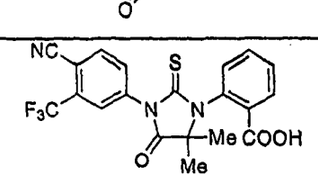
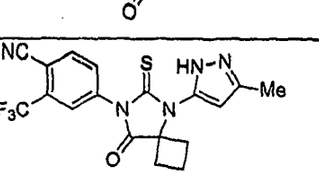
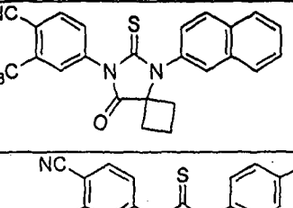
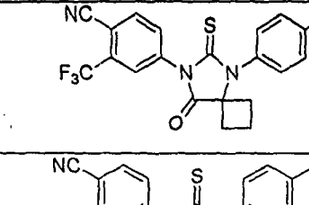
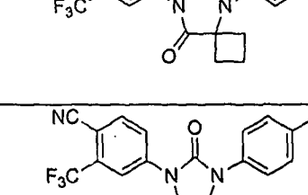
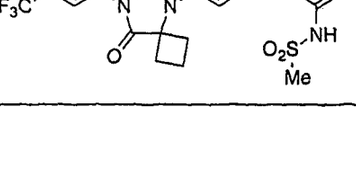
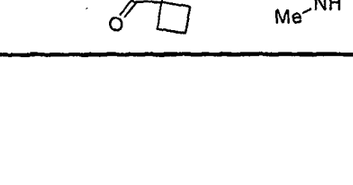
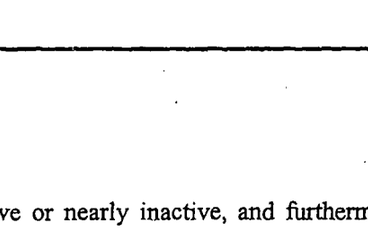
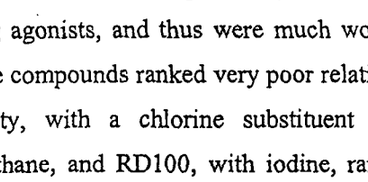
[00188] Tier 5 compounds (see Table 9) were inactive or nearly inactive, and thus, were worse than bicalutamide for treating prostate cancer. The substituents on the right hand aryl ring are important to determining activity.

[00189] Some Tier 5 compounds (some of which are shown and some that are not shown) were not diaryl compounds (lacking the right hand aryl ring), were not thiohydantoins, were not disubstituted on the carbon on the lower right hand of the hydantoin ring, and/or had substituents other than oxygen or amido on the lower left hand carbon of the hydantoin ring. This provides evidence of the surprising advantages of diarylthiohydantoins that are disubstituted on the lower right hand carbon of the hydantoin ring and have oxygen or amido on the lower left hand carbon of the hydantoin ring. In particular, the terminal substituent in RD155, RD 156, and 158 ($CH_2NR_xR_y$, where $R_{x,y}$ = H or methyl) is not seen as contributing to activity in these compounds.

[00190] Tier 5 compounds would not be desirable for treatment of prostate cancer or as AR antagonists, although these and related compounds may be useful as modulators of other nuclear receptors, such as estrogen receptor and peroxisome proliferator-activated receptor, and as therapeutic agents for diseases in which nuclear receptors play a role, such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases. They may be useful in assays e.g. as standards, or as intermediates or prodrugs.

TABLE 9

TIER 5 COMPOUNDS

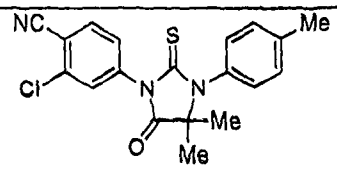
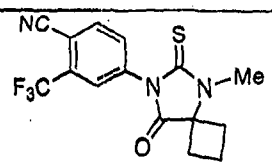
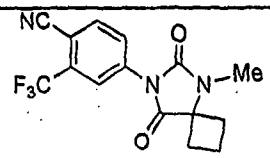
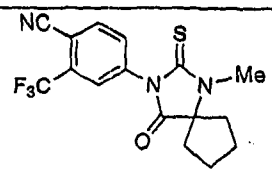
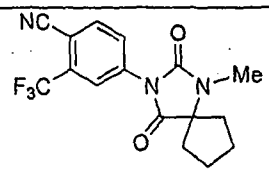
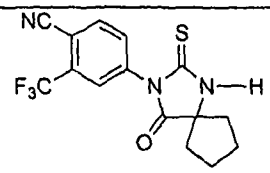
TIER 5 COMPOUNDS			
RD32		RD33	
RD65		RD84	
RD85		RD155	
RD156		RD157	
RD158			

Tier 6

[00191] Tier 6 compounds (see Table 10) were inactive or nearly inactive, and furthermore were strong agonists, and thus were much worse than bicalutamide for treating prostate cancer. The comparative compounds ranked very poor relative to the inventive compounds. Notably, RD72 had very poor activity, with a chlorine substituent on the left hand aryl ring, whereas RD7, with a trifluoromethane, and RD100, with iodine, ranked in Tier 1. The results for the Tier 6 compounds provide evidence of the surprising advantages of diarylthiohydantoins that are disubstituted on the lower right hand carbon of the hydantoin ring and have oxygen or amido on the lower left hand carbon of the hydantoin ring, and have certain substituents on the left hand aryl ring.

[00192] Tier 6 compounds would not be desirable for treatment of prostate cancer or as AR antagonists.

TABLE 10

TIER 6 COMPOUNDS	
RD72 	RD73  (comparative)
RD74  (comparative)	RD75 
RD76  (comparative)	RD77 

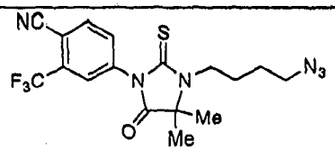
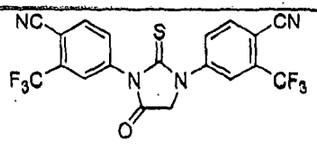
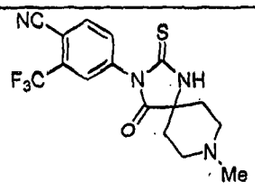
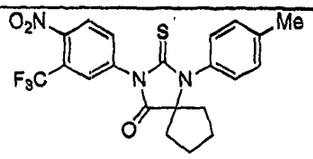
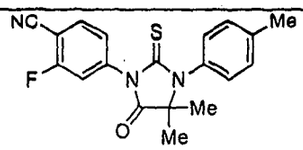
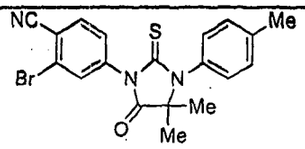
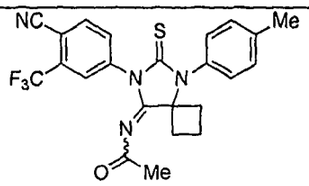
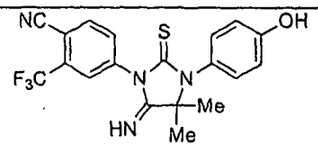
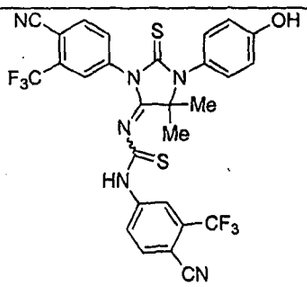
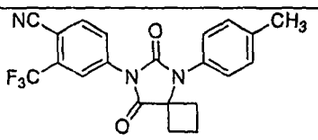
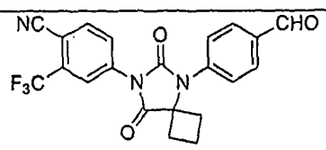
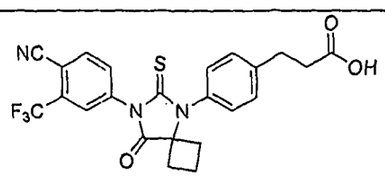
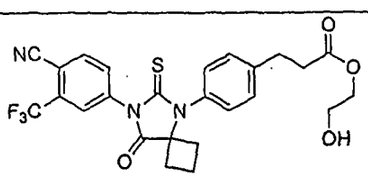
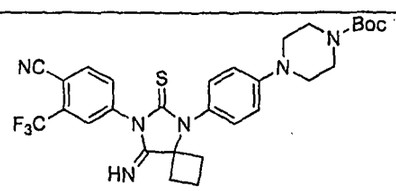
Untiered compounds

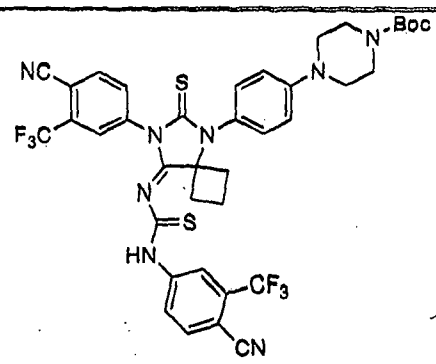
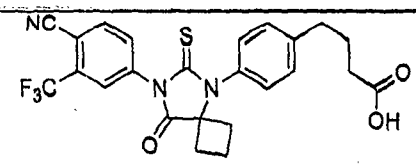
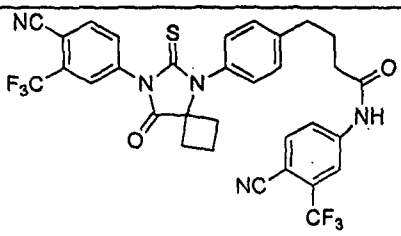
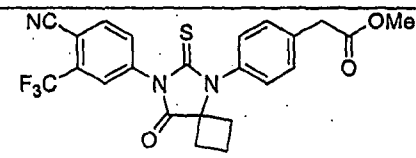
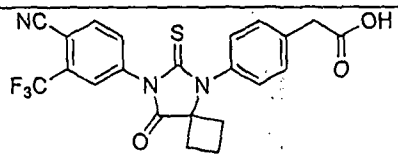
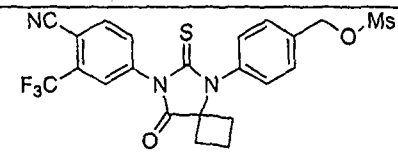
[00193] For several compounds, there was insufficient experimental data to rank them. These untiered compounds are presented in Table 11.

[00194] Based on the data and methods of the invention, and applying judgment based on review of many compounds, including some not shown here, one can make some observations about the untiered compounds. Comparative example RD1 is expected to be in Tier 3 with comparative examples RD3-RD5. RD89 is expected to hydrolyze to RD37 (Tier 1), and should therefore have comparable activity. RD104 is expected to hydrolyze to RD58 (Tier 1), and should therefore have comparable activity. RD105 is expected to hydrolyze to RD8 (Tier 1), and RD 139 and RD140 are expected to hydrolyze to RD138 (Tier 2), and they should therefore have comparable activity.

TABLE 11

UNTIERED COMPOUNDS

UNTIERED COMPOUNDS	
RD1  (comparative)	RD19 
RD52 	RD79 
RD80 	RD81 
RD89 	RD104 
RD105 	RD106 
RD115 	RD132 
RD136 	RD139 

UNTIERED COMPOUNDS	
RD140 	RD141 
RD142 	RD146 
RD147 	RD154 

[00195] In short, novel compounds which show evidence of being far superior to bicalutamide in treating prostate cancer were identified and produced.

Sensitivity of Anti-Cancer Activity of Compounds to Structural Differences

[00196] The inventors have determined that what might appear to be a small change in the structure of hydantoin compounds may result in a large change in that compound's performance in treating prostate cancer. For example, RD161 and RD162 differ only by a single fluorine substituent on an aryl ring, and RD162 is in Tier 1, while RD161 is in Tier 2, both being better than bicalutamide for the treatment of prostate cancer, but RD162 being superior. However, RD149, which differs from RD 161 only in having an additional carbon atom between the methylcarbamoyl group and the aryl ring, is no better than bicalutamide for the treatment of prostate cancer and is ranked in Tier 4. The effect of RD161, RD162, and RD149 on luciferase activity can be seen in Figure 24. At a given concentration of compound, the luciferase activity upon exposure to RD161 and RD162 is less than the luciferase activity upon exposure to RD149.

[00197] RD9 differs from RD8 only in that an amino group is substituted for a hydroxyl group. However, whereas RD8 is in Tier 1, much better than bicalutamide for the treatment of prostate cancer, RD9 is in Tier 4, no better than bicalutamide. The effect of RD8 and RD9 on luciferase activity in the 1AR cell line can be seen in Figure 27. For a given dose, the luciferase activity upon exposure to RD8 is less than the luciferase activity upon exposure to RD9. The effect of RD8 and RD9 on luciferase activity in the 4AR cell line can be seen in Figure 26. For a given dose, the luciferase activity upon exposure to RD8 is less than the luciferase activity upon exposure to RD9. The effect of RD8 and RD9 on PSA levels in the LN/AR cell line can be seen in Figure 25. For a given dose, the PSA level upon exposure to RD8 is less than the PSA level upon exposure to RD9.

[00198] RD130 and RD131 differ from each other only by a methyl substituent on the end of a carbamoyl group and both compounds are ranked in Tier 1, although RD131 has been found to be particularly advantageous. RD129 is the same as RD130, with the exception of a methoxy group being substituted for an amino group. However, RD129 is ranked in Tier 3. RD128 is similar to RD129, but has one less carbon in the chain linking the ester group to the aryl ring; RD128 is ranked in Tier 3. The effect of RD130, RD131, RD128, and RD129 on PSA levels in the LN/AR cell line can be seen in Figure 28. For a given concentration, the PSA level upon exposure to RD130 and RD131 is less than the PSA level upon exposure to RD128 and RD129.

[00199] RD153 and RD155 differ from each other in that the former has a methylcarbamoyl group attached to an aryl ring and a dimethyl substituent attached to the thiohydantoin group, whereas the latter has a methylamino group attached to the right hand aryl ring and a cyclobutyl substituent attached to the thiohydantoin group. Whereas RD153 is in Tier 1, much better than bicalutamide for the treatment of prostate cancer, RD155 is in Tier 5, inactive or nearly inactive in the treatment of prostate cancer. The effect of RD153 and RD155 on luciferase activity in the LN/AR cell line can be seen in Figure 29. For a given concentration, the luciferase activity upon exposure to RD153 is less than the luciferase activity upon exposure to RD155.

[00200] RD58 and RD60 differ from each other in the substitution of a thio for an oxo group and a dimethyl substituent for a cyclobutyl substituent. Whereas RD58 is in Tier 1, RD60 is in Tier 4.

Pharmaceutical Compositions and Administration

[00201] The compounds of the invention are useful as pharmaceutical compositions prepared with a therapeutically effective amount of a compound of the invention, as defined herein, and a pharmaceutically acceptable carrier or diluent.

[00202] The diarylhydantoin compounds of the invention can be formulated as pharmaceutical

compositions and administered to a subject in need of treatment, for example a mammal, such as a human patient, in a variety of forms adapted to the chosen route of administration, for example, orally, nasally, intraperitoneally, or parenterally, by intravenous, intramuscular, topical or subcutaneous routes, or by injection into tissue.

[00203] Thus, diarylhydantoin compounds of the invention may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier, or by inhalation or insufflation. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the diarylhydantoin compounds may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The diarylhydantoin compounds may be combined with a fine inert powdered carrier and inhaled by the subject or insufflated. Such compositions and preparations should contain at least 0.1% diarylhydantoin compounds. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of a given unit dosage form. The amount of diarylhydantoin compounds in such therapeutically useful compositions is such that an effective dosage level will be obtained.

[00204] The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the diarylhydantoin compounds may be incorporated into sustained-release preparations and devices. For example, the diarylhydantoin compounds may be incorporated into time release capsules, time release tablets, and time release pills.

[00205] The diarylhydantoin compounds may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the diarylhydantoin compounds can be prepared

in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

[00206] The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the diarylhydantoin compounds which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00207] Sterile injectable solutions are prepared by incorporating the diarylhydantoin compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

[00208] For topical administration, the diarylhydantoin compounds may be applied in pure form. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

[00209] Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Other solid carriers include nontoxic polymeric nanoparticles or microparticles. Useful liquid carriers include water, alcohols or glycols or water/alcohol/glycol blends, in which the diarylhydantoin compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using

pump-type or aerosol sprayers.

[00210] Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

[00211] Examples of useful dermatological compositions which can be used to deliver the diarylhydantoin compounds to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508), all of which are hereby incorporated by reference.

[00212] Useful dosages of the compounds of formula I can be determined by comparing their in vitro activity, and in vivo activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949, which is hereby incorporated by reference.

[00213] For example, the concentration of the diarylhydantoin compounds in a liquid composition, such as a lotion, can be from about 0.1-25% by weight, or from about 0.5-10% by weight. The concentration in a semi-solid or solid composition such as a gel or a powder can be about 0.1-5% by weight, or about 0.5-2.5% by weight.

[00214] The amount of the diarylhydantoin compounds required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

[00215] Effective dosages and routes of administration of agents of the invention are conventional. The exact amount (effective dose) of the agent will vary from subject to subject, depending on, for example, the species, age, weight and general or clinical condition of the subject, the severity or mechanism of any disorder being treated, the particular agent or vehicle used, the method and scheduling of administration, and the like. A therapeutically effective dose can be determined empirically, by conventional procedures known to those of skill in the art. See, *e.g.*, *The Pharmacological Basis of Therapeutics*, Goodman and Gilman, eds., Macmillan Publishing Co., New York. For example, an effective dose can be estimated initially either in cell culture assays or in suitable animal models. The animal model may also be used to determine the appropriate concentration ranges and routes of administration. Such information can then be used to determine useful doses and routes for administration in humans. A therapeutic dose can also be selected by analogy to dosages for comparable

therapeutic agents.

[00216] The particular mode of administration and the dosage regimen will be selected by the attending clinician, taking into account the particulars of the case *(e.g.,* the subject, the disease, the disease state involved, and whether the treatment is prophylactic). Treatment may involve daily or multi-daily doses of compound(s) over a period of a few days to months, or even years.

[00217] In general, however, a suitable dose will be in the range of from about 0.001 to about 100 mg/kg, e.g., from about 0.01 to about 100 mg/kg of body weight per day, such as above about 0.1 mg per kilogram, or in a range of from about 1 to about 10 mg per kilogram body weight of the recipient per day. For example, a suitable dose may be about 1 mg/kg, 10 mg/kg, or 50 mg/kg of body weight per day.

[00218] The diarylhydantoin compounds are conveniently administered in unit dosage form; for example, containing 0.05 to 10000 mg, 0.5 to 10000 mg, 5 to 1000 mg, or about 100 mg of active ingredient per unit dosage form.

[00219] The diarylhydantoin compounds can be administered to achieve peak plasma concentrations of, for example, from about 0.5 to about 75 μM, about 1 to 50 μM, about 2 to about 30 μM, or about 5 to about 25 μM. Exemplary desirable plasma concentrations include at least or no more than 0.25, 0.5, 1, 5, 10, 25, 50, 75, 100 or 200 μM. For example, plasma levels may be from about 1 to 100 micromolar or from about 10 to about 25 micromolar. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the diarylhydantoin compounds, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the diarylhydantoin compounds. Desirable blood levels may be maintained by continuous infusion to provide about 0.00005 - 5 mg per kg body weight per hour, for example at least or no more than 0.00005, 0.0005, 0.005, 0.05, 0.5, or 5 mg/kg/hr. Alternatively, such levels can be obtained by intermittent infusions containing about 0.0002 - 20 mg per kg body weight, for example, at least or no more than 0.0002, 0.002, 0.02, 0.2, 2, 20, or 50 mg of the diarylhydantoin compounds per kg of body weight.

[00220] The diarylhydantoin compounds may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator.

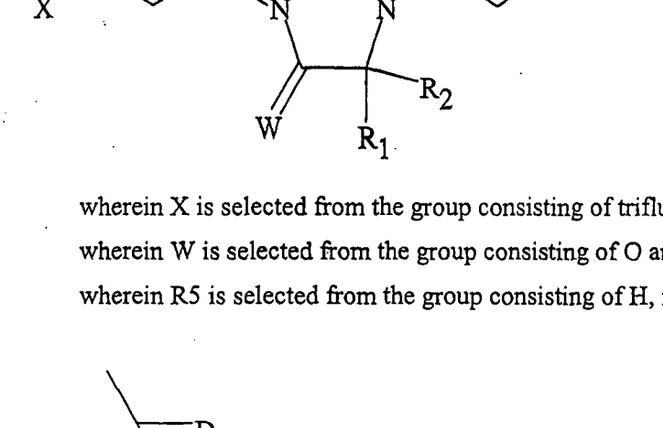
[00221] A number of the above-identified compounds exhibit little or no agonistic activities with respect to hormone refractory prostate cancer cells. Because these compounds are strong AR inhibitors, they can be used not only in treating prostate cancer, but also in treating other AR related diseases or conditions such as benign prostate hyperplasia, hair loss, and acne. Because AR belongs to

the family of nuclear receptors, these compounds may serve as scaffolds for drug synthesis targeting other nuclear receptors, such as estrogen receptor and peroxisome proliferator-activated receptor. Therefore, they may be further developed for other diseases such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases, in which nuclear receptors play a role.

[00222] The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present invention. All examples presented are representative and non-limiting. The above-described embodiments of the invention may be modified or varied, without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.

CLAIMS

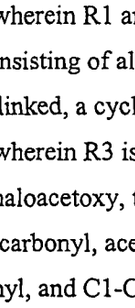
Claim 1. A compound having the formula



wherein X is selected from the group consisting of trifluoromethyl and iodo,

wherein W is selected from the group consisting of O and NR5,

wherein R5 is selected from the group consisting of H, methyl, and



wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or D is S or O and E-G together are C1-C4 lower alkyl,

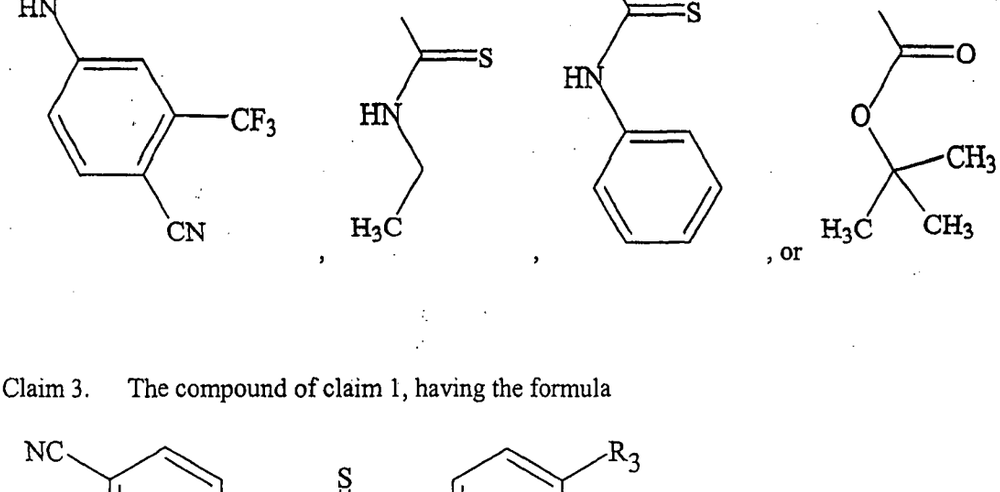
wherein R1 and R2 together comprise eight or fewer carbon atoms and are selected from the group consisting of alkyl, substituted alkyl including haloalkyl, and, together with the carbon to which they are linked, a cycloalkyl or substituted cycloalkyl group,

wherein R3 is selected from the group consisting of hydrogen, halogen, methyl, C1-C4 alkoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methoxycarbonyl, acetamido, methanesulfonamino, methanesulfonyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, and C1-C6 alkyl or alkenyl optionally substituted with hydroxyl, methoxycarbonyl, cyano, amino, amido, nitro, carbamoyl, or substituted carbamoyl including methylcarbamoyl, dimethylcarbamoyl, and hydroxyethylcarbamoyl,

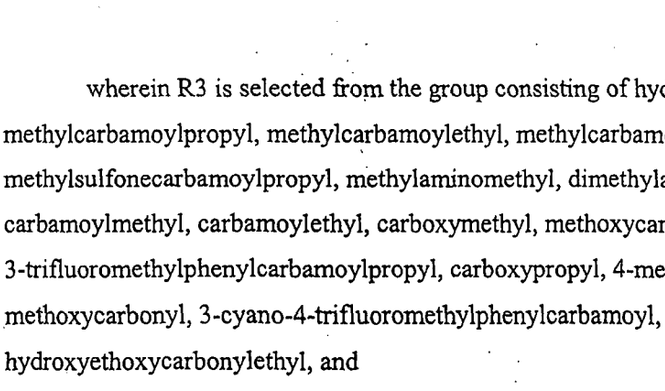
wherein R4 is selected from the group consisting of hydrogen, halogen, alkyl, and haloalkyl,

wherein R3 is not methylaminomethyl or dimethylaminomethyl.

Claim 2. The compound of claim 1, wherein R5 is



Claim 3. The compound of claim 1, having the formula



wherein R3 is selected from the group consisting of hydroxy, methylcarbamoyl, methylcarbamoylpropyl, methylcarbamoylethyl, methylcarbamoylmethyl, methylsulfonecarbamoylpropyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, carbamoylmethyl, carbamoylethyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoylpropyl, carboxypropyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, methoxycarbonyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, hydroxyethylcarbamoylethyl, and hydroxyethoxycarbonylethyl, and

wherein R10 and R11 are both H or, respectively, F and H, or H and F.

Claim 4. The compound of claim 3, wherein R10 and R11 are both H.

Claim 5. The compound of claim 3, wherein R10 and R11 are, respectively, F and H.

Claim 6. The compound of claim 3, wherein R3 is methylcarbamoyl.

Claim 7. The compound of claim 3, wherein R3 is methylcarbamoyl and R10 and R11 are, respectively, F and H.

Claim 8. The compound of claim 1,

wherein R1 and R2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms, and

R3 is selected from the group consisting of carbamoyl, alkylcarbamoyl, carbamoylalkyl, and alkylcarbamoylalkyl, and R4 is H or F.

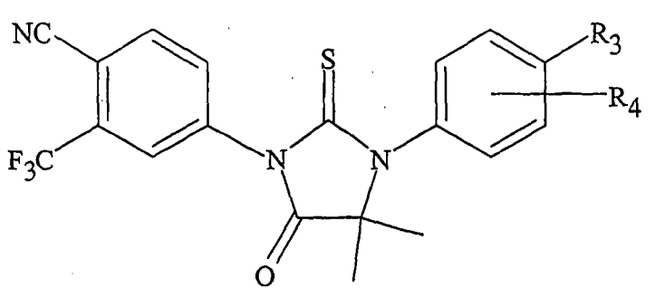
Claim 9. The compound of claim 8, wherein R4 is 3-fluoro.

Claim 10. The compound of claim 1,

wherein R1 and R2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms,

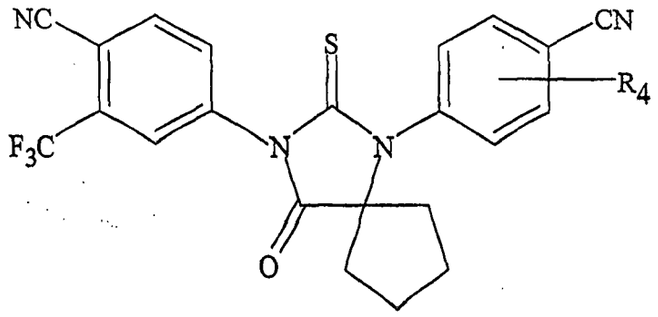
R3 is selected from the group consisting of cyano, hydroxy, methylcarbamoyl, methylcarbamoyl-substituted alkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, acetamido, methanesulfonamido, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-(1,1-dimethylethoxy)carbonyl)-1-piperazinyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyethoxycarbonyl-substituted alkyl, and 3-cyano-4-trifluoromethylphenylcarbamoyl, and R4 is F.

Claim 11. The compound of claim 1, having the formula



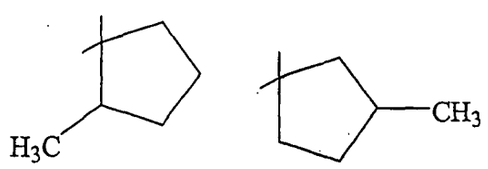
wherein R3 is selected from the group consisting of methylcarbonyl, methoxycarbonyl, acetamido, and methanesulfonamido, and R4 is selected from the group consisting of F and H.

Claim 12. The compound of claim 1, having the formula

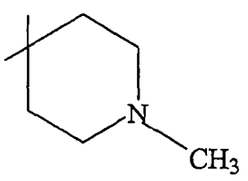


wherein R4 is selected from the group consisting of F and H.

Claim 13. A compound according to claim 1, wherein R1 and R2 together with the carbon to which they are linked are

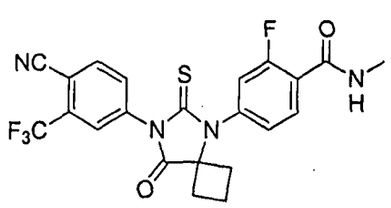


, or



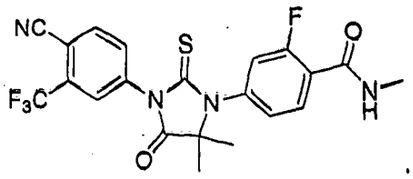
Claim 14. A compound selected from the compounds of Tier 1 and Tier 2.

Claim 15. The compound of claim 1, having the formula



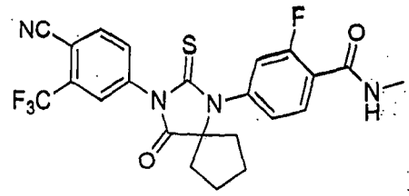
[RD162]

Claim 16. The compound of claim 1, having the formula



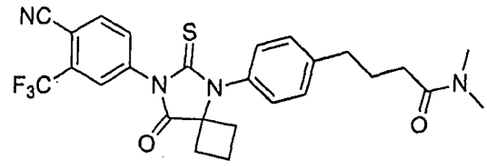
[RD162']

Claim 17. The compound of claim 1, having the formula



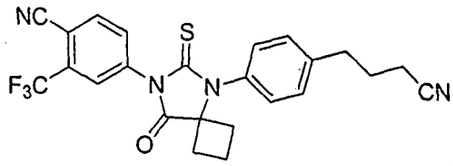
[RD162"]

Claim 18. The compound of claim 1, having the formula



[RD169]

Claim 19. The compound of claim 1, having the formula



[RD170]

Claim 20. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-19 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

Claim 21. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

Claim 22. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

Claim 23. A method for treating a hyperproliferative disorder comprising administering a pharmaceutical composition of claim 20 to a subject in need of such treatment, thereby treating the hyperproliferative disorder.

Claim 24. The method of claim 23, wherein the composition is administered at a dosage of the compound in the range of from about 0.001 mg per kg body weight per day to about 100 mg per kg body weight per day.

Claim 25. The method of claim 23, wherein the composition is administered at a dosage of the compound in the range of from about 0.01 mg per kg body weight per day to about 100 mg per kg body weight per day.

Claim 26. The method of claim 23, wherein the composition is administered at a dosage of the compound in the range of from about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day.

Claim 27. The method of claim 23, wherein the composition is administered at a dosage of the compound of about 1 mg per kg body weight per day.

Claim 28. A method for treating a hyperproliferative disorder comprising administering a composition according to claim 21 to a subject in need of such treatment, thereby treating the hyperproliferative disorder.

Claim 29. The method of claim 28, wherein the composition is administered at a dosage of the compound in the range of from about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day.

Claim 30. The method of claim 28, wherein the composition is administered at a dosage of the compound of about 1 mg per kg body weight per day.

Claim 31. The method of claim 23, wherein the hyperproliferative disorder is hormone refractory

prostate cancer.

Claim 32. The method of claim 23, wherein the compound is administered by intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally.

Claim 33. The method of claim 28, wherein the composition is administered orally.

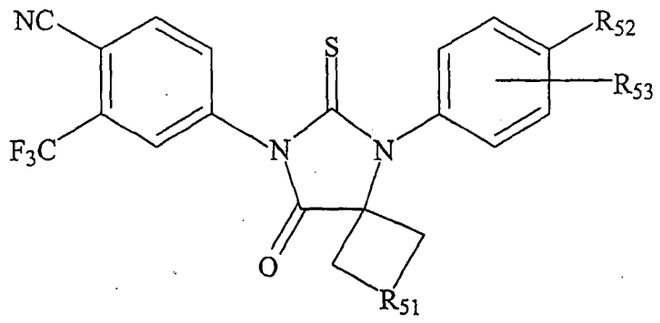
Claim 34. The method of claim 23, wherein the composition has a form selected from the group consisting of a solution, dispersion, suspension, powder, capsule, tablet, pill, time release capsule, time release tablet, and time release pill.

Claim 35. The method of claim 28, wherein the composition has a form selected from the group consisting of a capsule, tablet, and pill.

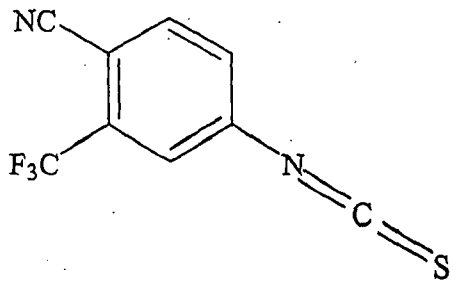
Claim 36. The method of claim 28, wherein the compound is selected from the group consisting of RD162', RD162", RD 169, or RD170, or a pharmaceutically acceptable salt thereof.

Claim 37. The method of claim 28, wherein the compound is *N*-methyl-4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]-2-fluorobenzamide [RD162] or a pharmaceutically acceptable salt thereof.

Claim 38. A method of synthesizing a diaryl compound of formula:

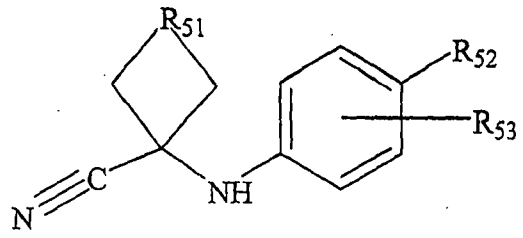


comprising mixing Compound I



Compound I

with Compound II



Compound II

in a first polar solvent to form a mixture,

heating the mixture,

adding a second polar solvent, the same as or different from the first polar solvent, and an aqueous acid to the mixture,

refluxing the mixture,

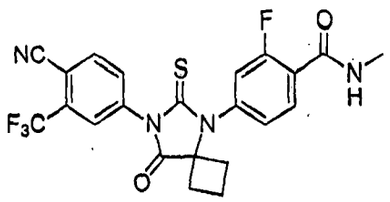
cooling the mixture and combining with water, and

separating the diaryl compound from the mixture,

wherein R51 comprises an alkyl chain of from 1 to 4 carbon atoms, R52 is selected from the group consisting of cyano, hydroxy, methylcarbamoyl, methylcarbamoyl-substituted alkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, and hydroxyethoxycarbonyl-substituted alkyl, and R53 is selected from the group consisting of F and H.

Claim 39. The method of claim 38, wherein R51 comprises an alkyl chain of from 1 to 2 carbon atoms, R52 is selected from the group consisting of carbamoyl and methylcarbamoyl, and R53 is F.

Claim 40. A method of synthesizing a compound of formula:



[RD162]

comprising

mixing 4-isothiocyanato-2-trifluoromethylbenzonitrile and *N*-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide in dimethylformamide to form a first mixture,

heating the first mixture to form a second mixture,

adding alcohol and acid to the second mixture to form a third mixture,

refluxing the third mixture to form a fourth mixture,

cooling the fourth mixture,

combining the fourth mixture with water and extracting an organic layer;

isolating the compound from the organic layer.

Claim 41. A method of synthesizing the compound of claim 16 [RD162'], comprising

mixing *N*-Methyl-2-fluoro-4-(1,1-dimethyl-cyanomethyl)-aminobenzamide and 4-Isothiocyanato-2-trifluoromethylbenzonitrile in DMF and heating to form a first mixture;

adding an alcohol and an acid to the first mixture to form a second mixture;

refluxing the second mixture;

cooling the second mixture,

combining the second mixture with water and extracting an organic layer;

isolating the compound from the organic layer.

Claim 42. A method of synthesizing the compound of claim 17 [RD162"], comprising

mixing *N*-Methyl-2-fluoro-4-(1-cyanocyclopentyl)aminobenzamide, 4-isothiocyanato-2-trifluoromethyl benzonitrile, and DMF and heating under reflux to form a first mixture;

adding an alcohol and an acid to the first mixture to form a second mixture;

refluxing the second mixture;

cooling the second mixture;

combining the second mixture with water and extracting an organic layer;

isolating the compound from the organic layer.

Claim 43. A method of synthesizing the compound of claim 18 [RD169], comprising

mixing *N*,*N*-Dimethyl 4-[4-(1-cyanocyclobutylamino)phenyl]butanamide, 4-isothiocyanato-2-trifluoromethyl benzonitrile, and DMF and heating under reflux to form a first mixture;

adding an alcohol and an acid to the first mixture to form a second mixture;

refluxing the second mixture;

cooling the second mixture;

combining the second mixture with water and extracting an organic layer;

isolating the compound from the organic layer.

Claim 44. A method of synthesizing the compound of claim 19[RD170], comprising

mixing DMSO, dichloromethane, and oxalyl chloride to form a first mixture,

adding 4-(4-(7-(4-Cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)butanamide to the first mixture to form a second mixture;

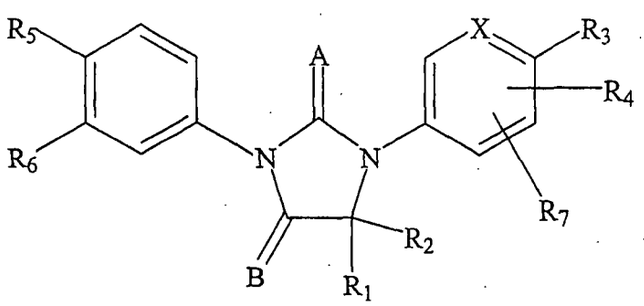
adding triethylamine to the second mixture to form a third mixture;

warming the third mixture and quenching with aqueous NH_4Cl to form a fourth mixture;

extracting an organic layer from the fourth mixture;

isolating the compound from the organic layer.

Claim 45. A compound having the formula



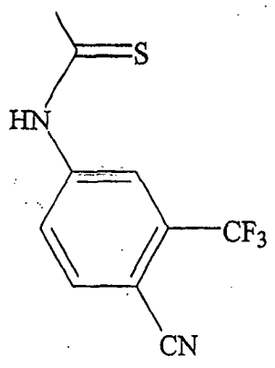
wherein R_5 is CN or NO_2 or SO_2R_{11},

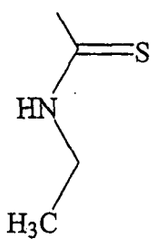
wherein R_6 is CF_3, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated akynyl, halogen,

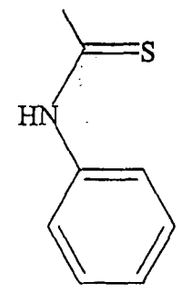
wherein A is sulfur (S) or oxygen (O),

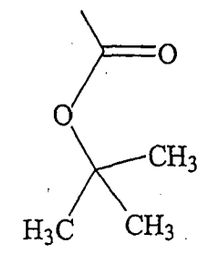
wherein B is O or S or NR_8,

wherein R_8 is selected from the group consisting of H, methyl, aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, SO_2R_{11}, $NR_{11}R_{12}$, $(CO)OR_{11}$, $(CO)NR_{11}R_{12}$, $(CO)R_{11}$, $(CS)R_{11}$, $(CS)NR_{11}R_{12}$, $(CS)OR_{11}$,

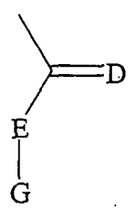


,


,


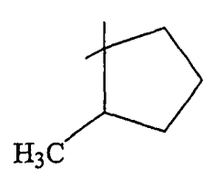
, and


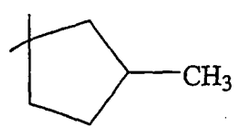
, and

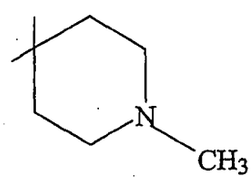


wherein D is S or O and E is N or O and G is alkyl, aryl, substituted alkyl or substituted aryl; or D is S or O and E-G together are C1-C4 lower alkyl,

wherein R1 and R2 are independently alkyl, haloalkyl, hydrogen, aryl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkenyl, halogenated akynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocylic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, or R_1 and R_2 are connected to form a cycle which can be heterocyclic, substituted heterocyclic, cycloalkyl, substituted cycloalkyl,



,


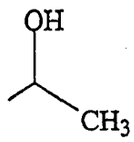
, or


,

wherein X is carbon or nitrogen and can be at any position in the ring, and

wherein R3, R4, and R7 are independently selected from the group consisting of hydrogen, halogen, methyl, methoxy, formyl, haloacetoxy, trifluoromethyl, cyano, nitro, hydroxyl, phenyl, amino, methylcarbamoyl, methylcarbamoyl-substituted alkyl, dimethylcarbamoyl-substituted alkyl,

methoxycarbonyl, acetamido, methanesulfonamino, carbamoyl-substituted alkyl, methanesulfonyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyl-substituted alkyl, hydroxyl-substituted alkenyl, carbamoyl-substituted alkenyl, methoxycarbonyl-



substituted alkyl, cyano-substituted alkyl, , aryl, substituted aryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkenyl, halogenated alkynyl, SO_2R_{11}, $NR_{11}R_{12}$, $NR_{12}(CO)OR_{11}$, $NH(CO)NR_{11}R_{12}$, $NR_{12}(CO)R_{11}$, $O(CO)R_{11}$, $O(CO)OR_{11}$, $O(CS)R_{11}$, $NR_{12}(CS)R_{11}$, $NH(CS)NR_{11}R_{12}$, $NR_{12}(CS)OR_{11}$, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, substituted cycloalkyl, haloalkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, acetamido, methanesulfonamido, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-(1,1-dimethylethoxy)carbonyl)-1-piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, hydroxyethoxycarbonyl-substituted alkyl, 3-cyano-4-trifluoromethylphenylcarbamoyl,

wherein R_{11} and R_{12} are independently hydrogen, aryl, aralkyl, substituted aralkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogenated alkyl, halogenated alkenyl, halogenated alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic or non-aromatic, cycloalkyl, or substituted cycloalkyl, or R_{11} and R_{12} can be connected to form a cycle which can be heterocyclic aromatic or non-aromatic, substituted heterocyclic aromatic, cycloalkyl, or substituted cycloalkyl.

Claim 46. The compound of claim 45, wherein the compound has substantial androgen receptor antagonist activity and no substantial agonist activity on hormone refractory prostate cancer cells.

Claim 47. A method comprising:

providing at least one compound according to claim 45;

measuring inhibition of androgen receptor activity for the compound and determining if the inhibition is above a first predetermined level,

measuring stimulation of androgen receptor activity in hormone refractory cancer cells for the compound and determining if the stimulation is below a second predetermined level,

selecting the compound if the inhibition is above the first predetermined level and the stimulation is below the second predetermined level.

Claim 48. The method of claim 47, wherein the predetermined levels are those of bicalutamide.

Claim 49. The method of claim 47, wherein the step of measuring inhibition comprises measuring inhibitory concentration (IC50) in an AR response reporter system or a prostate specific antigen secreting system.

Claim 50. The method of claim 47, wherein the step of measuring stimulation comprises measuring fold induction by increasing concentrations in an AR response reporter system or a prostate specific antigen secreting system.

Claim 51. The method of claim 47, wherein the steps of measuring inhibition and/or stimulation comprise measuring an effect of the compound on tumor growth in an animal.

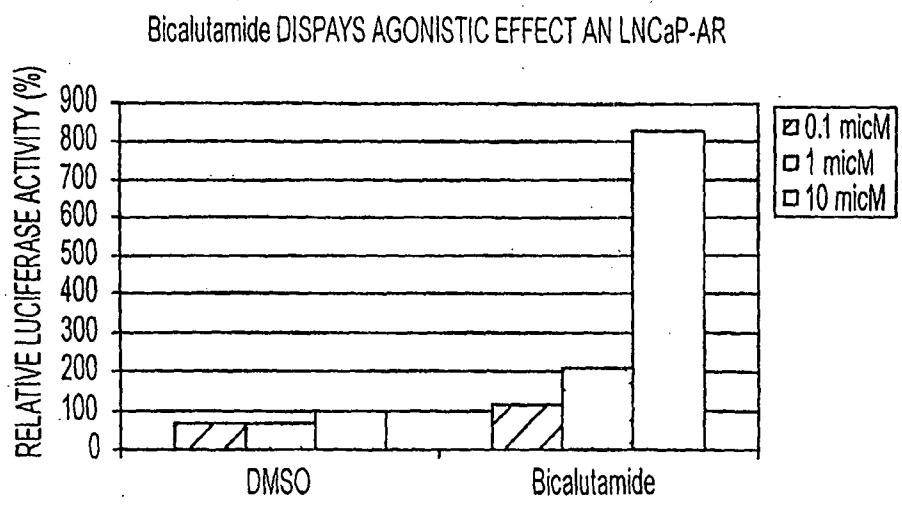

Bicalutamide DISPAYS AGONISTIC EFFECT AN LNCaP-AR
RELATIVE LUCIFERASE ACTIVITY (%)
900
800
700
600
500
400
300
200
100
0
DMSO
Bicalutamide
0.1 micM
1 micM
10 micM

FIG. 1

294

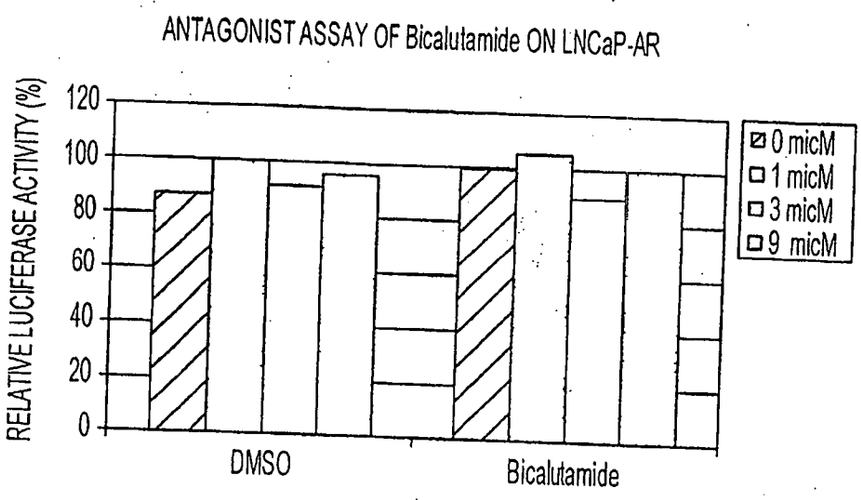

ANTAGONIST ASSAY OF Bicalutamide ON LNCaP-AR
RELATIVE LUCIFERASE ACTIVITY (%)
120
100
80
60
40
20
0
DMSO
Bicalutamide
0 micM
1 micM
3 micM
9 micM

FIG. 2

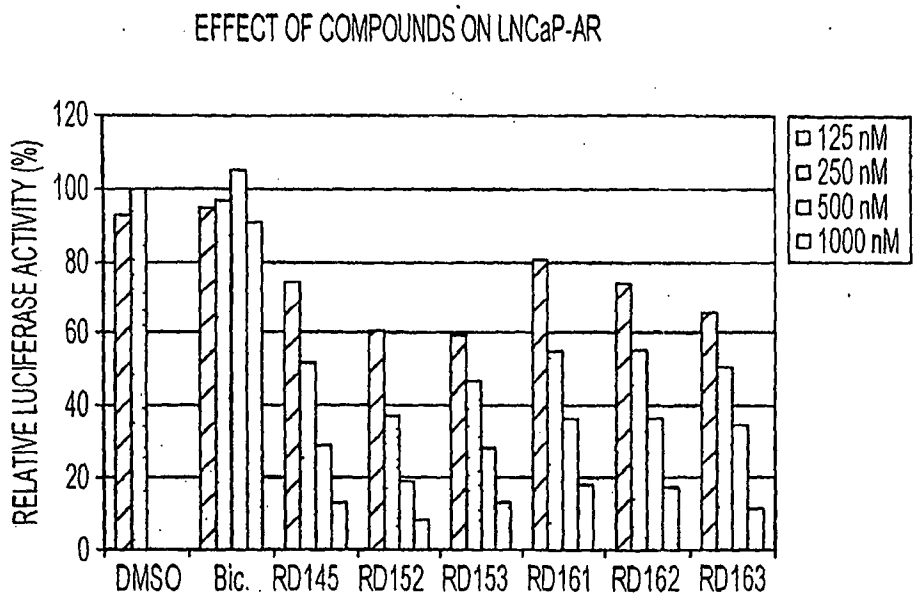

EFFECT OF COMPOUNDS ON LNCaP-AR
RELATIVE LUCIFERASE ACTIVITY (%)
120
100
80
60
40
20
0
DMSO
Bic.
RD145
RD152
RD153
RD161
RD162
RD163
125 nM
250 nM
500 nM
1000 nM

FIG. 3

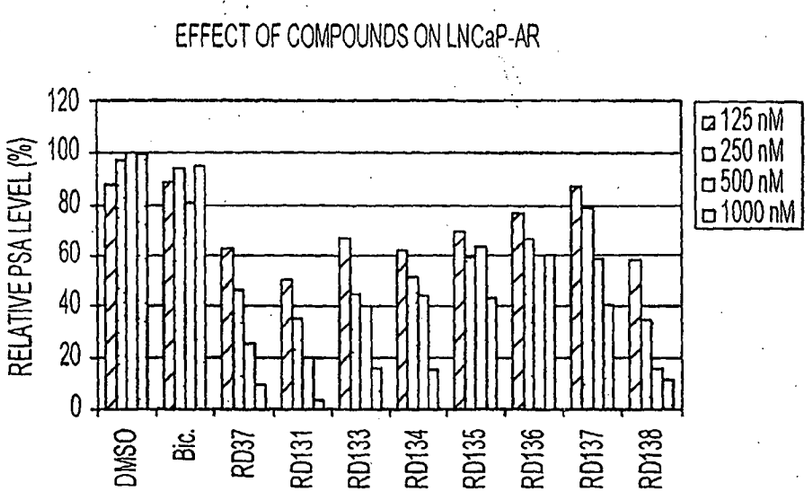

EFFECT OF COMPOUNDS ON LNCaP-AR
RELATIVE PSA LEVEL (%)
120
100
80
60
40
20
0
DMSO
Bic.
RD37
RD131
RD133
RD134
RD135
RD136
RD137
RD138
125 nM
250 nM
500 nM
1000 nM

FIG. 4

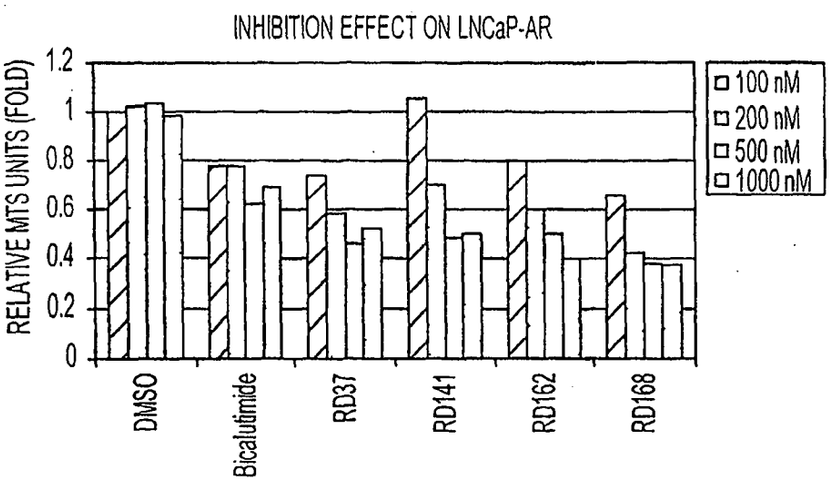

INHIBITION EFFECT ON LNCaP-AR
RELATIVE MTS UNITS (FOLD)
1.2
1
0.8
0.6
0.4
0.2
0
100 nM
200 nM
500 nM
1000 nM
DMSO
Bicalutimide
RD37
RD141
RD162
RD168

FIG. 5

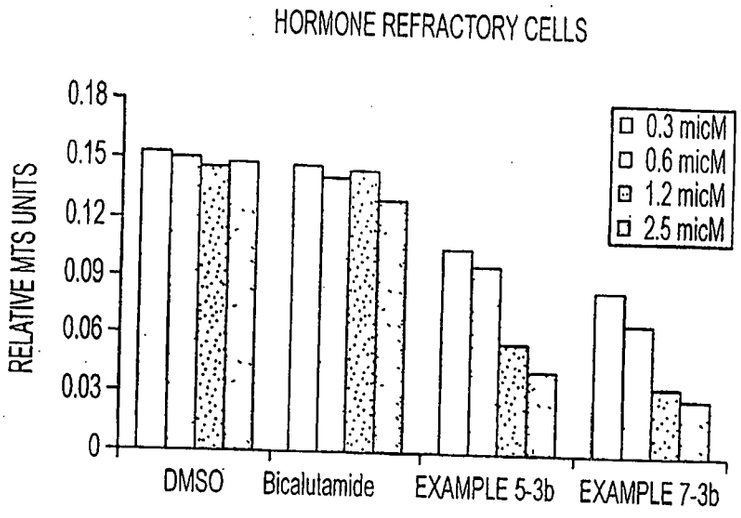

HORMONE REFRACTORY CELLS
RELATIVE MTS UNITS
0.18
0.15
0.12
0.09
0.06
0.03
0
0.3 micM
0.6 micM
1.2 micM
2.5 micM
DMSO
Bicalutamide
EXAMPLE 5-3b
EXAMPLE 7-3b

FIG. 6

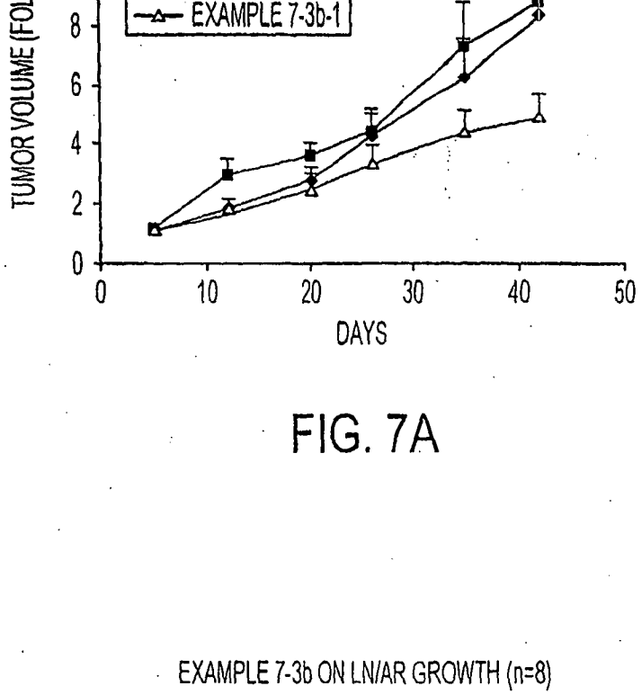


FIG. 7A

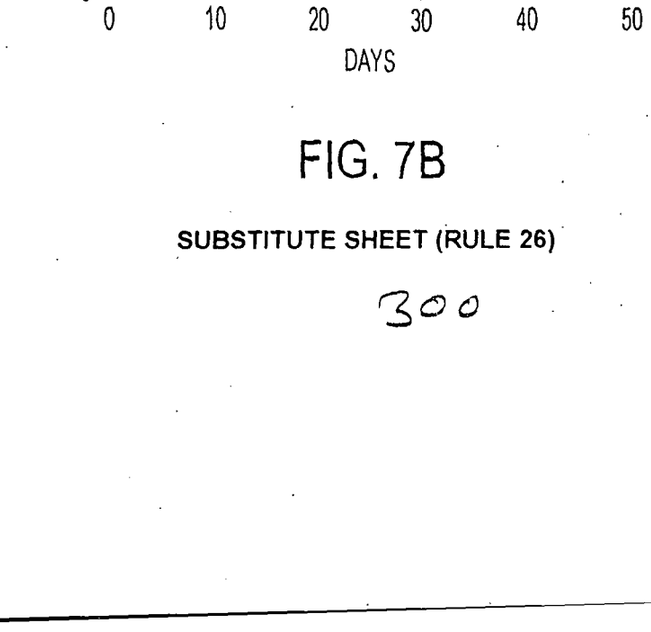


FIG. 7B

300

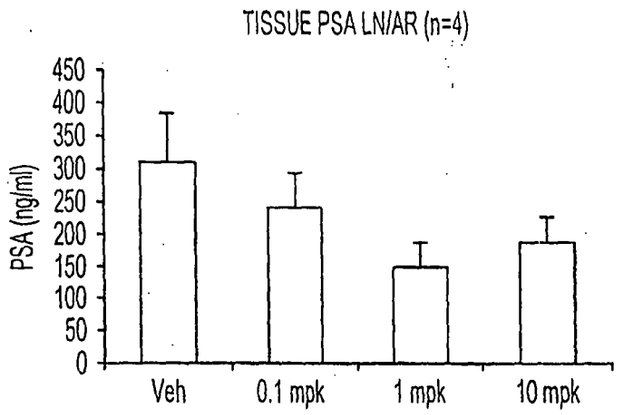

TISSUE PSA LN/AR (n=4)
PSA (ng/ml)
450
400
350
300
250
200
150
100
50
0
Veh
0.1 mpk
1 mpk
10 mpk

FIG. 8

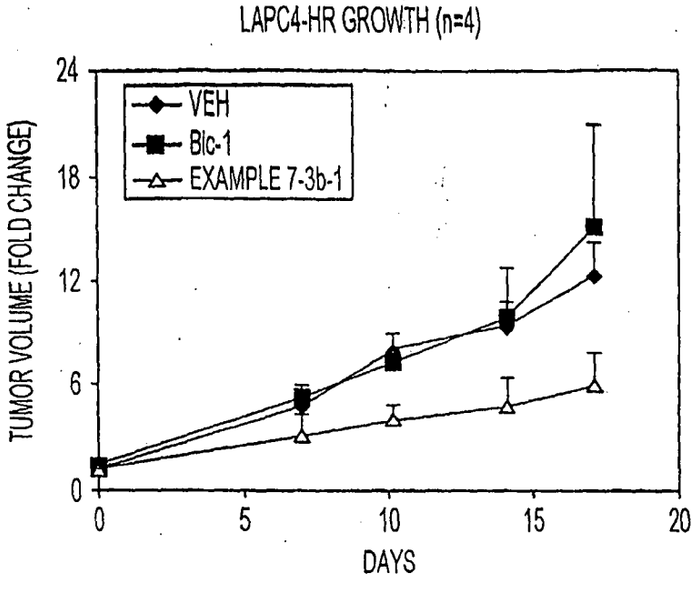


FIG. 9A

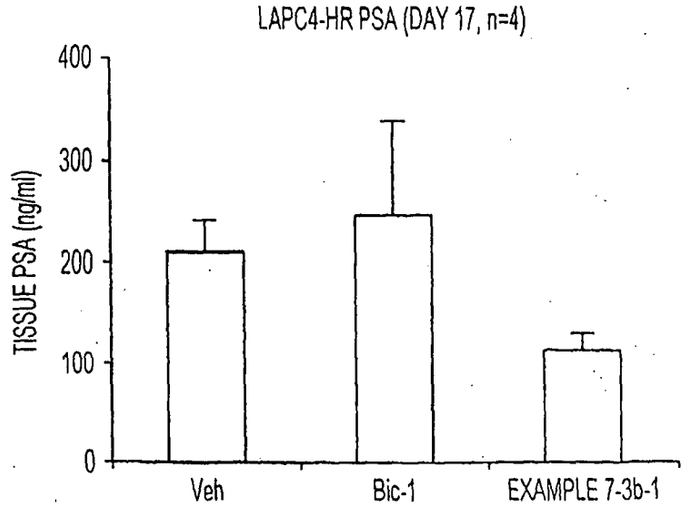


FIG. 9B

302

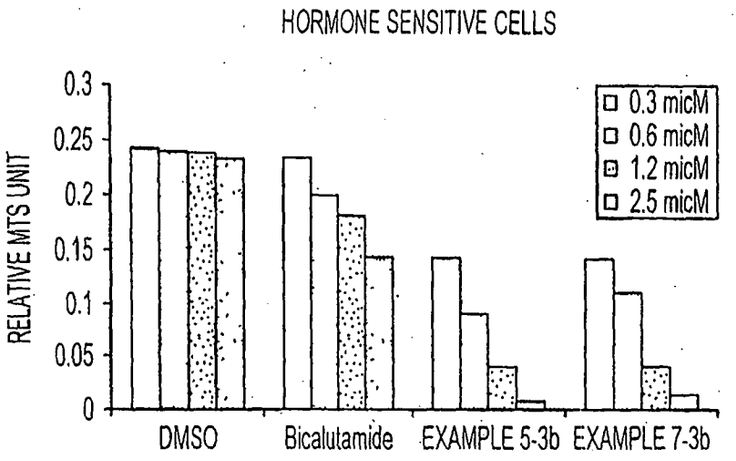

HORMONE SENSITIVE CELLS
RELATIVE MTS UNIT
0.3
0.25
0.2
0.15
0.1
0.05
0
0.3 micM
0.6 micM
1.2 micM
2.5 micM
DMSO
Bicalutamide
EXAMPLE 5-3b
EXAMPLE 7-3b

FIG. 10

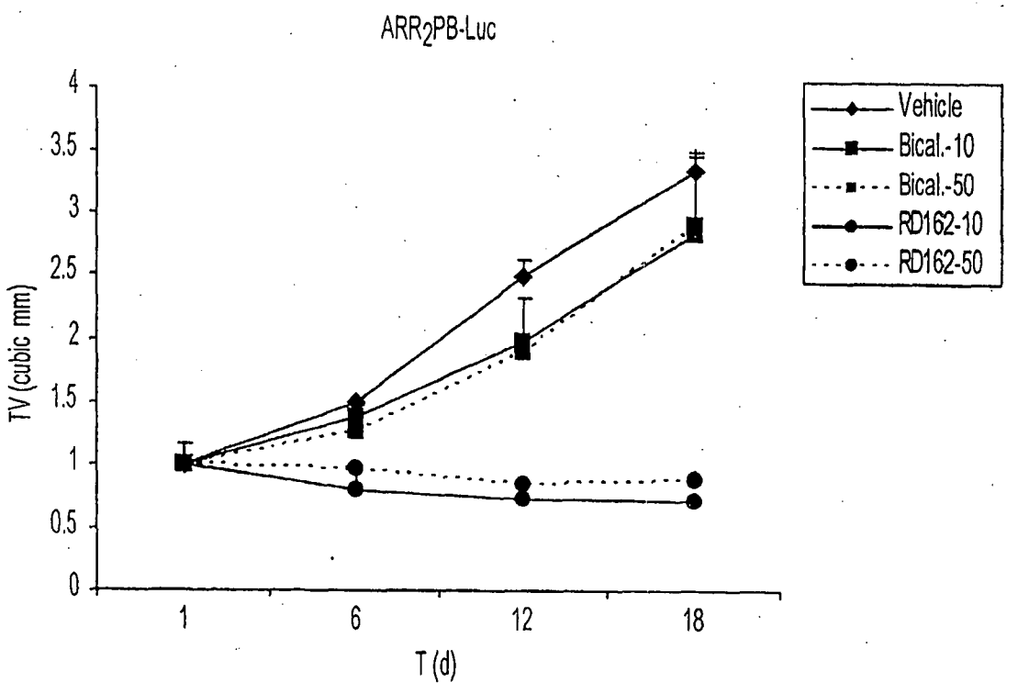

ARR2PB-Luc
TV (cubic mm)
4
3.5
3
2.5
2
1.5
1
0.5
0
1
6
12
18
T (d)
Vehicle
Bical.-10
Bical.-50
RD162-10
RD162-50

FIG. 11

305

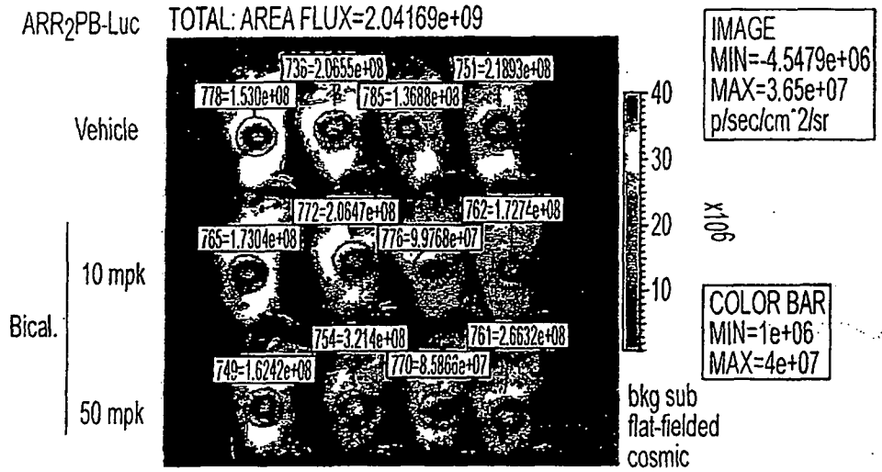


FIG. 12A

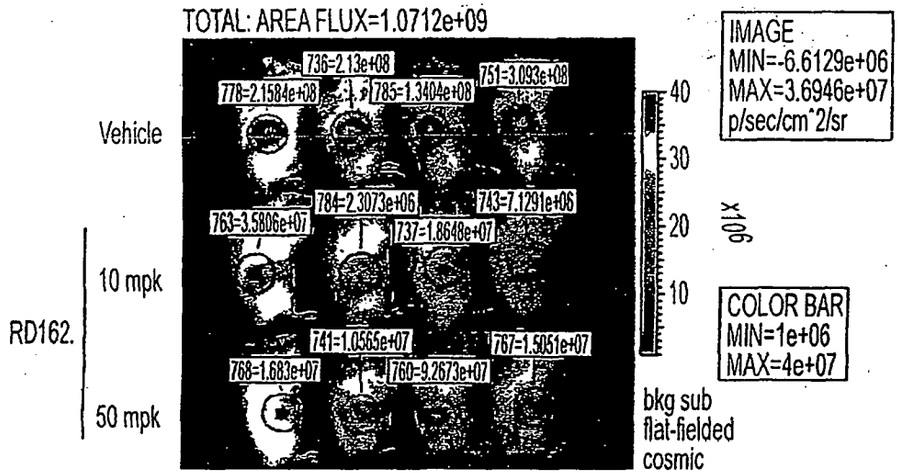


FIG. 12B

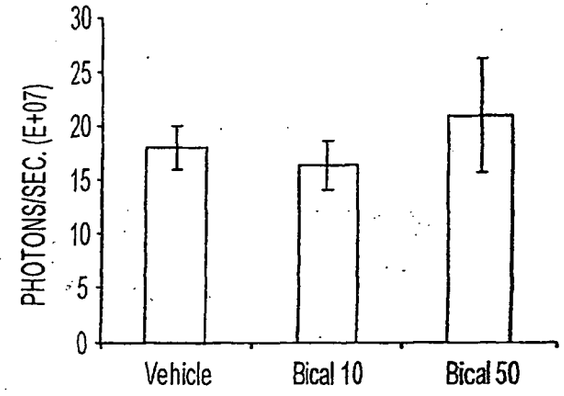


FIG. 12C

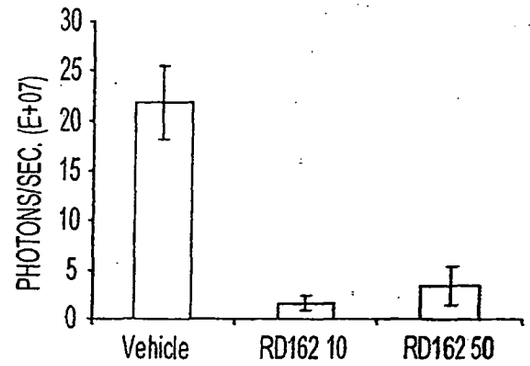


FIG. 12D

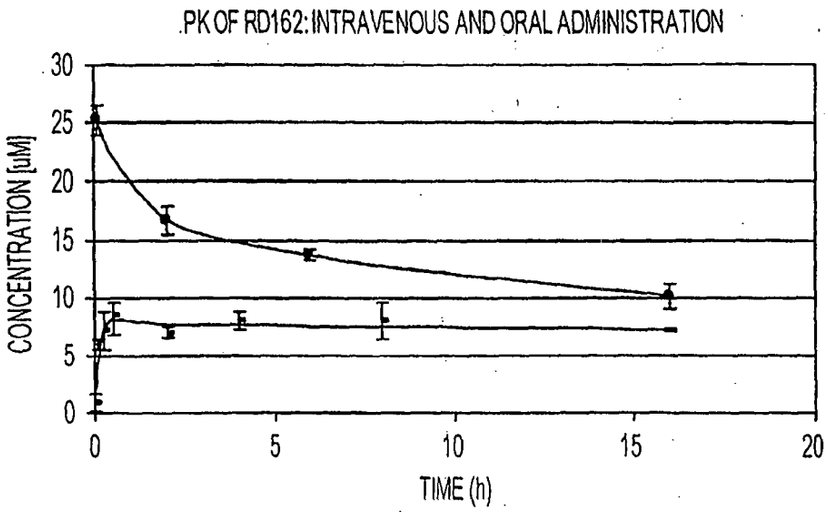

PK OF RD162: INTRAVENOUS AND ORAL ADMINISTRATION
CONCENTRATION [uM]
30
25
20
15
10
5
0
0
5
10
15
20
TIME (h)

FIG. 13

306

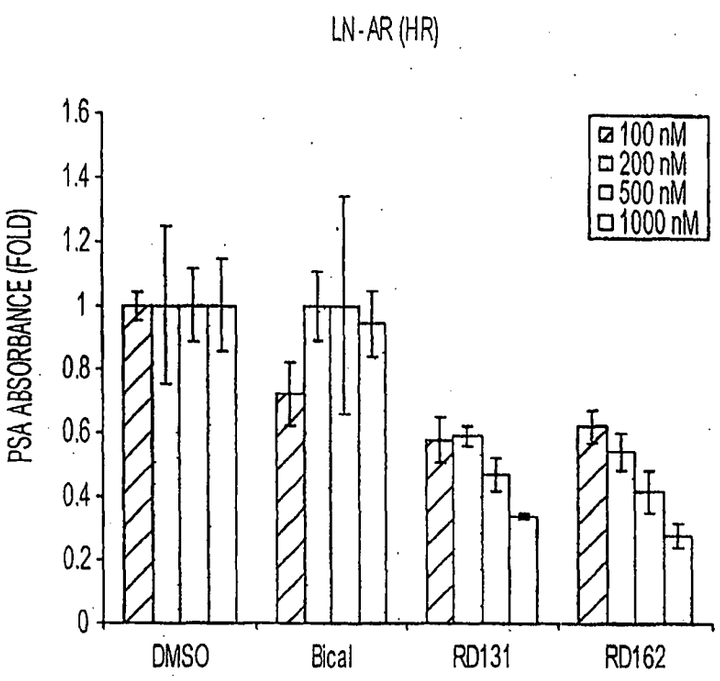

LN-AR (HR)
PSA ABSORBANCE (FOLD)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
100 nM
200 nM
500 nM
1000 nM
DMSO
Bical
RD131
RD162

FIG. 14

CHARACTERISTICS OF Bicalutimide, RD37, RD131 AND RD162

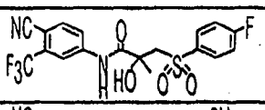
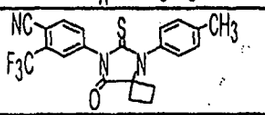
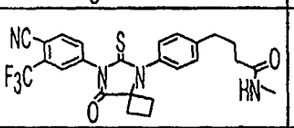
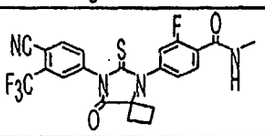
NAME	STRUCTURE	IC_{50} [nM]	LogP	C_{SS},10mpk [μM]	C_{SS},25mpk [μM]	C_{SS},50mpk [μM]
Bic.		1000	2.91	10.0	11.4	11.9
RD37		124	4.20	NA	NA	NA
RD131		92	3.44	0.39	0.43	0.40
RD162		122	3.20	9.9	10.7	10.2

FIG. 15A

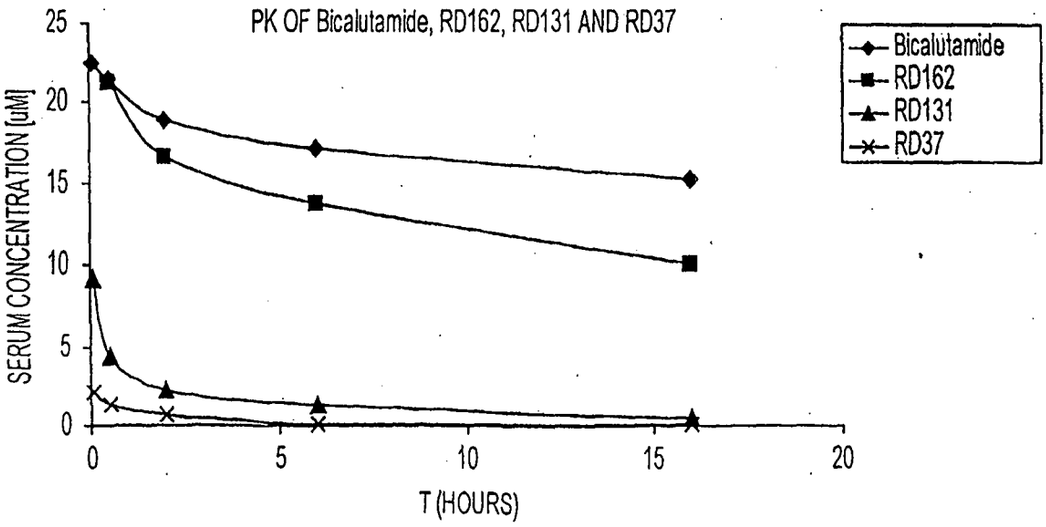


FIG. 15B

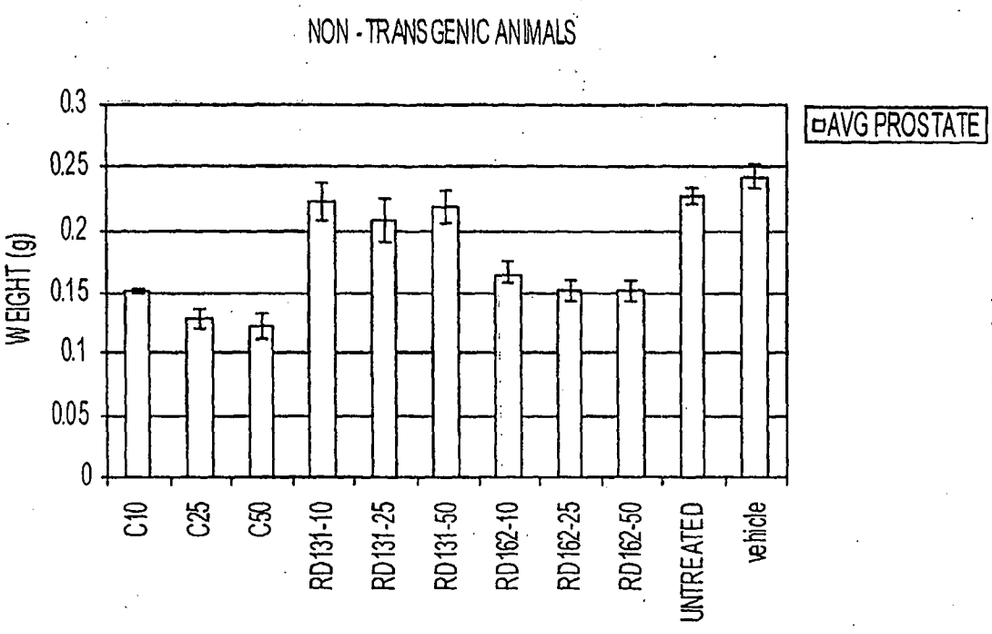

NON - TRANSGENIC ANIMALS
WEIGHT (g)
0.3
0.25
0.2
0.15
0.1
0.05
0
AVG PROSTATE
C10
C25
C50
RD131-10
RD131-25
RD131-50
RD162-10
RD162-25
RD162-50
UNTREATED
vehicle

FIG. 16

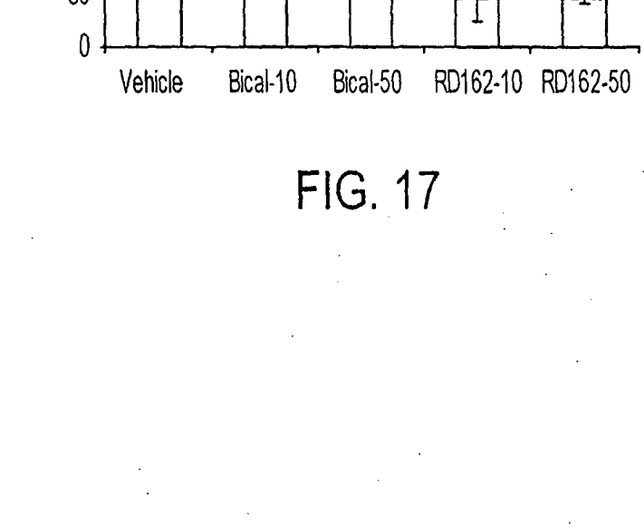

LN-AR (HR)
TISSUE PSA/OD
250
200
150
100
50
0
Vehicle
Bical-10
Bical-50
RD162-10
RD162-50

FIG. 17

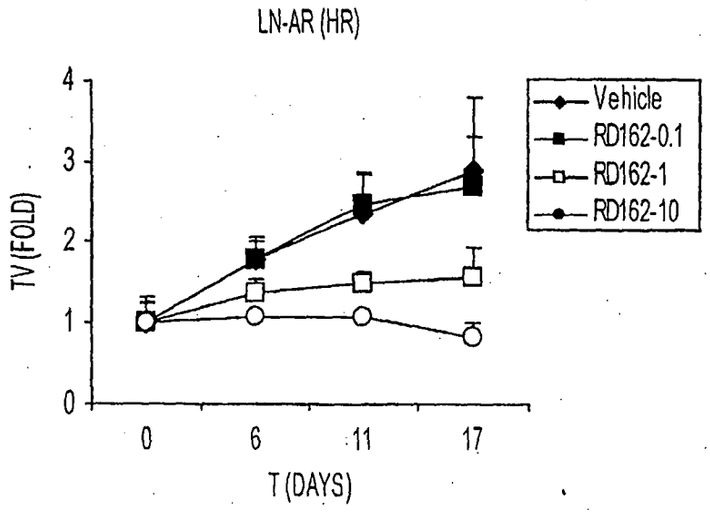

LN-AR (HR)
TV (FOLD)
4
3
2
1
0
0
6
11
17
T (DAYS)
Vehicle
RD162-0.1
RD162-1
RD162-10

FIG. 18

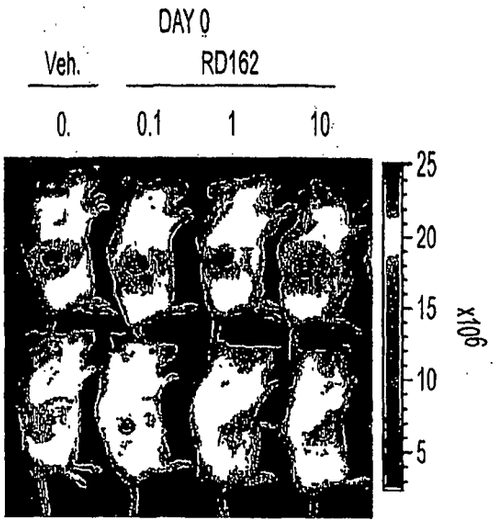


FIG. 19A

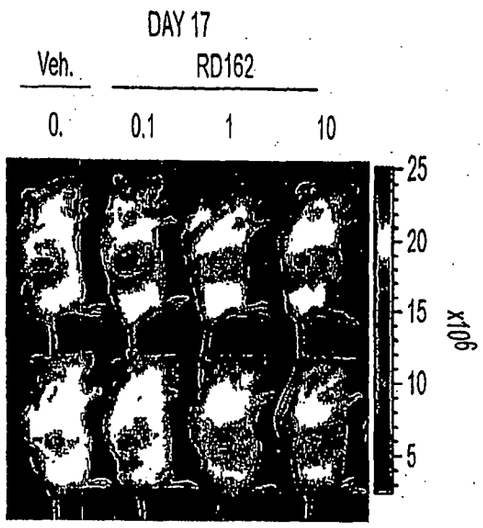


FIG. 19B

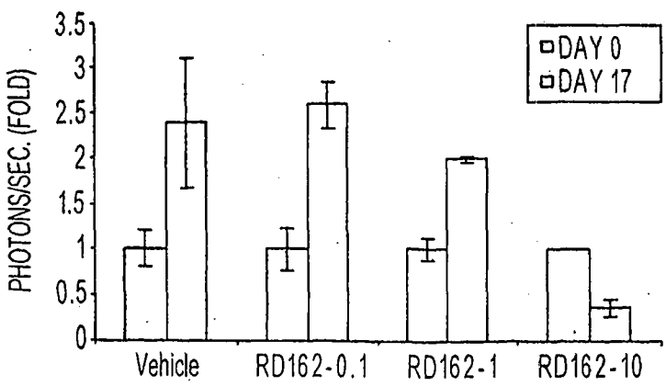


FIG. 19C

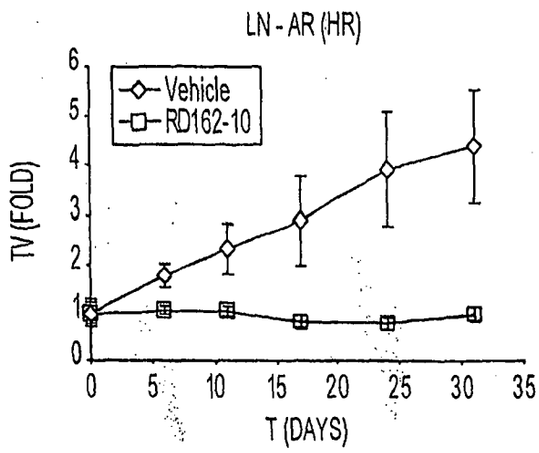


FIG. 20A

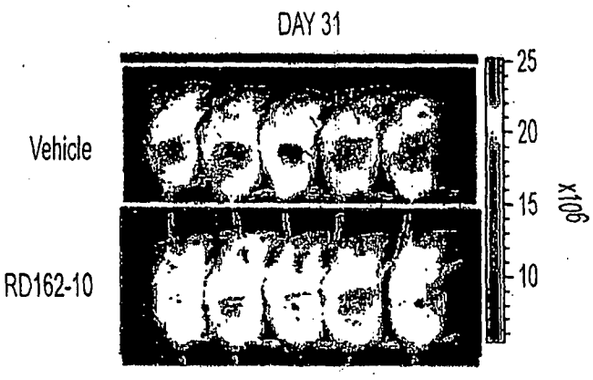


FIG. 20B

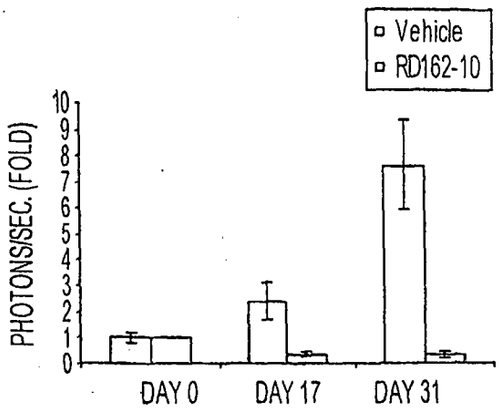


FIG. 20C

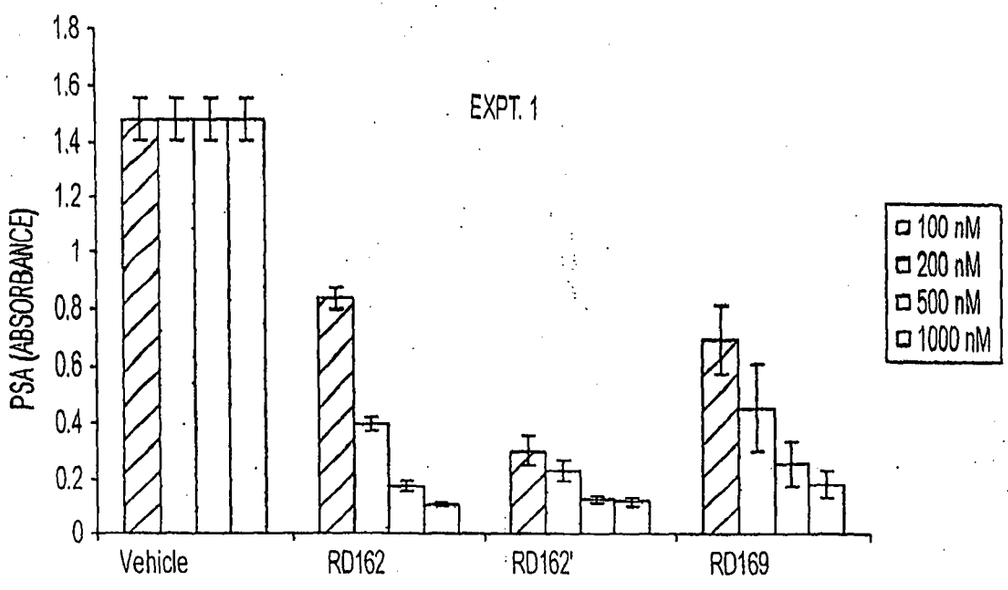


FIG. 21A

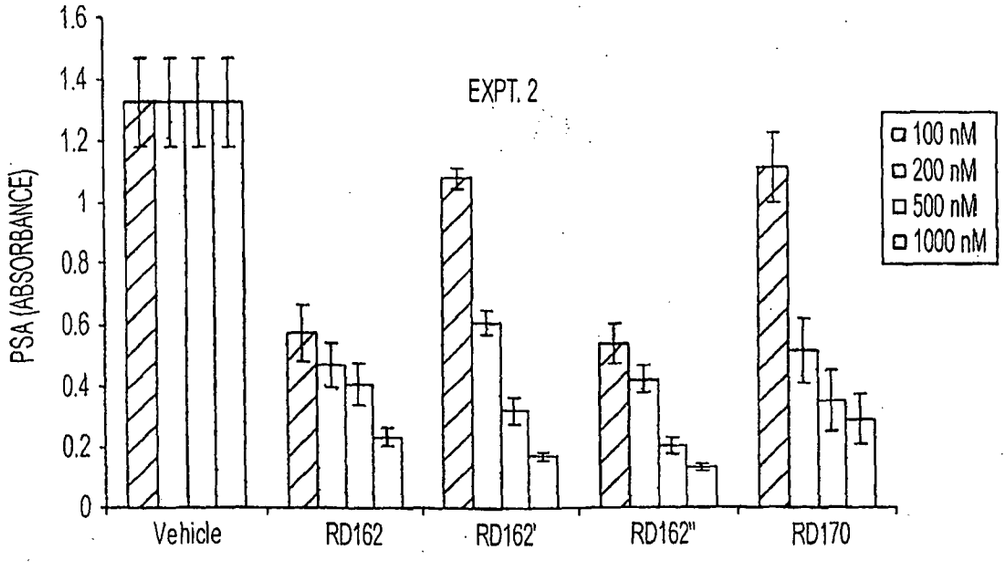


FIG. 21B

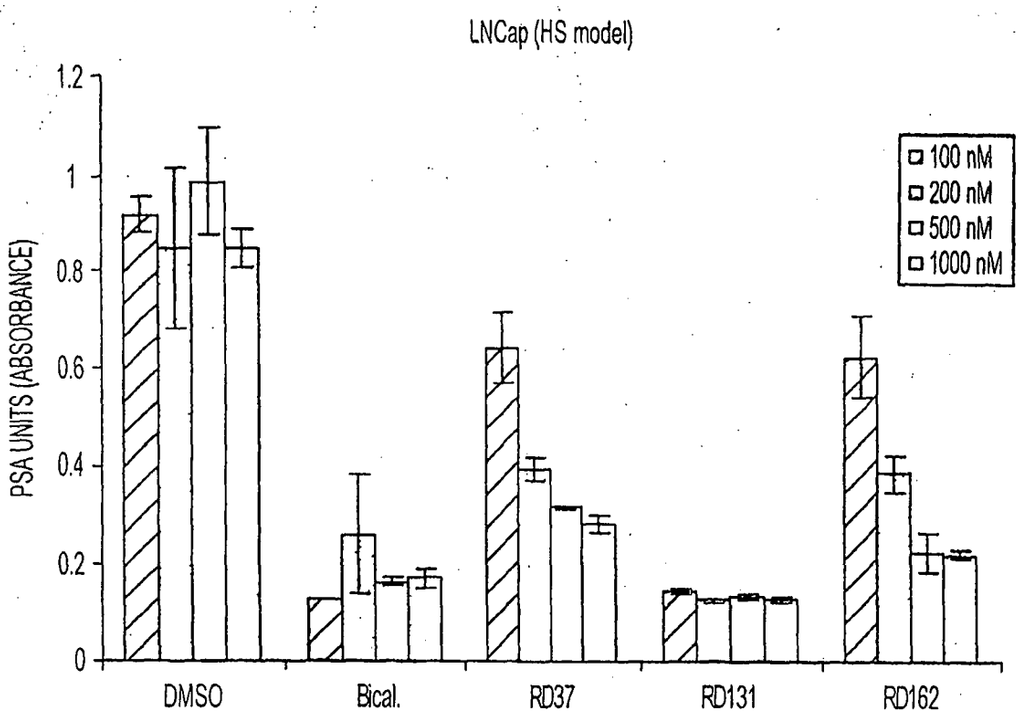

LNCap (HS model)
PSA UNITS (ABSORBANCE)
1.2
1
0.8
0.6
0.4
0.2
0
100 nM
200 nM
500 nM
1000 nM
DMSO
Bical.
RD37
RD131
RD162

FIG. 22

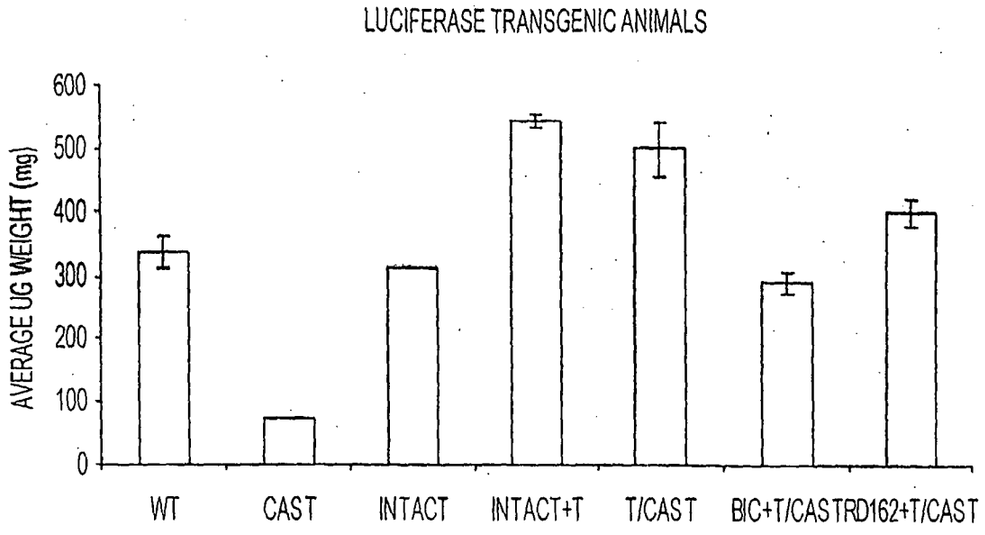


FIG. 23A

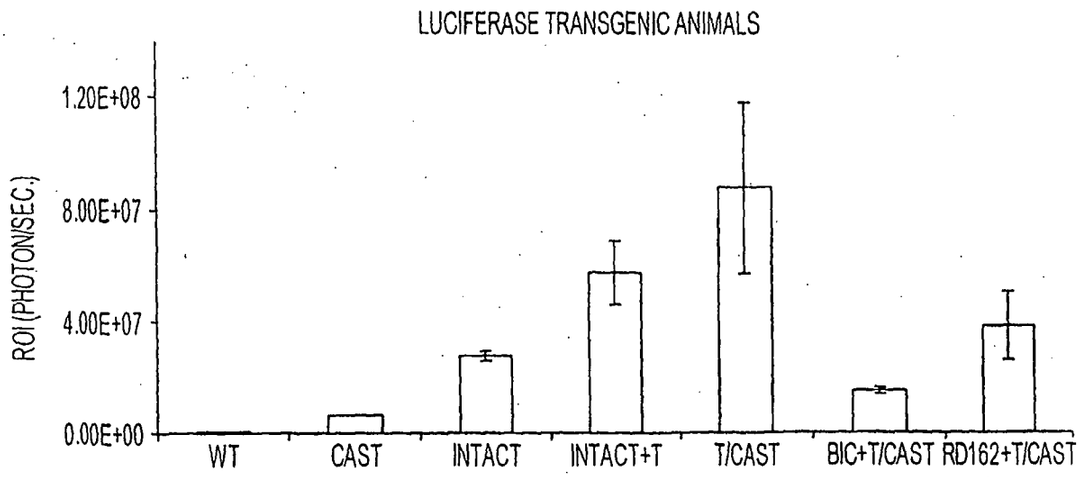


FIG. 23B

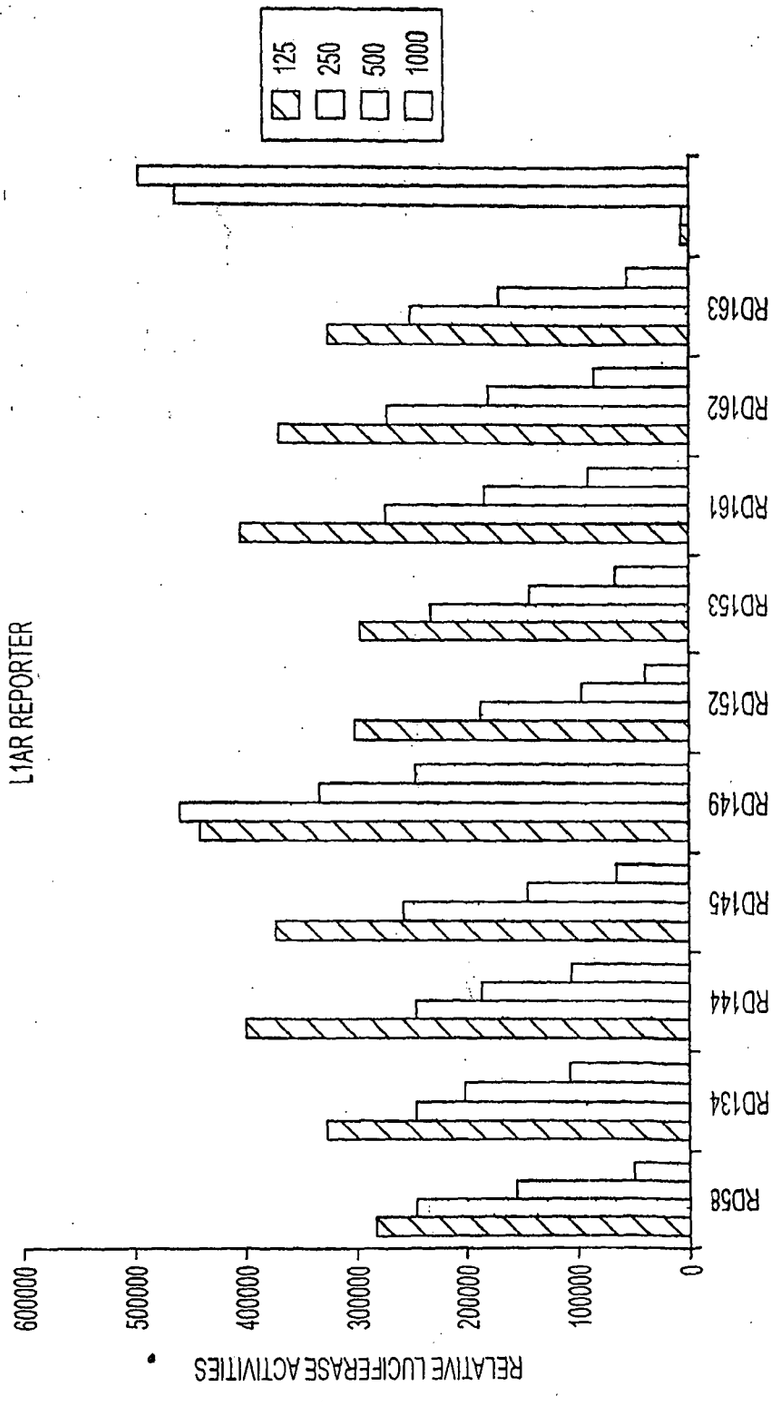

125
250
500
1000
RD163
RD162
RD161
RD153
RD152
RD149
RD145
RD144
RD134
RD58
L1AR REPORTER
600000
500000
400000
300000
200000
100000
0
RELATIVE LUCIFERASE ACTIVITIES

FIG. 24

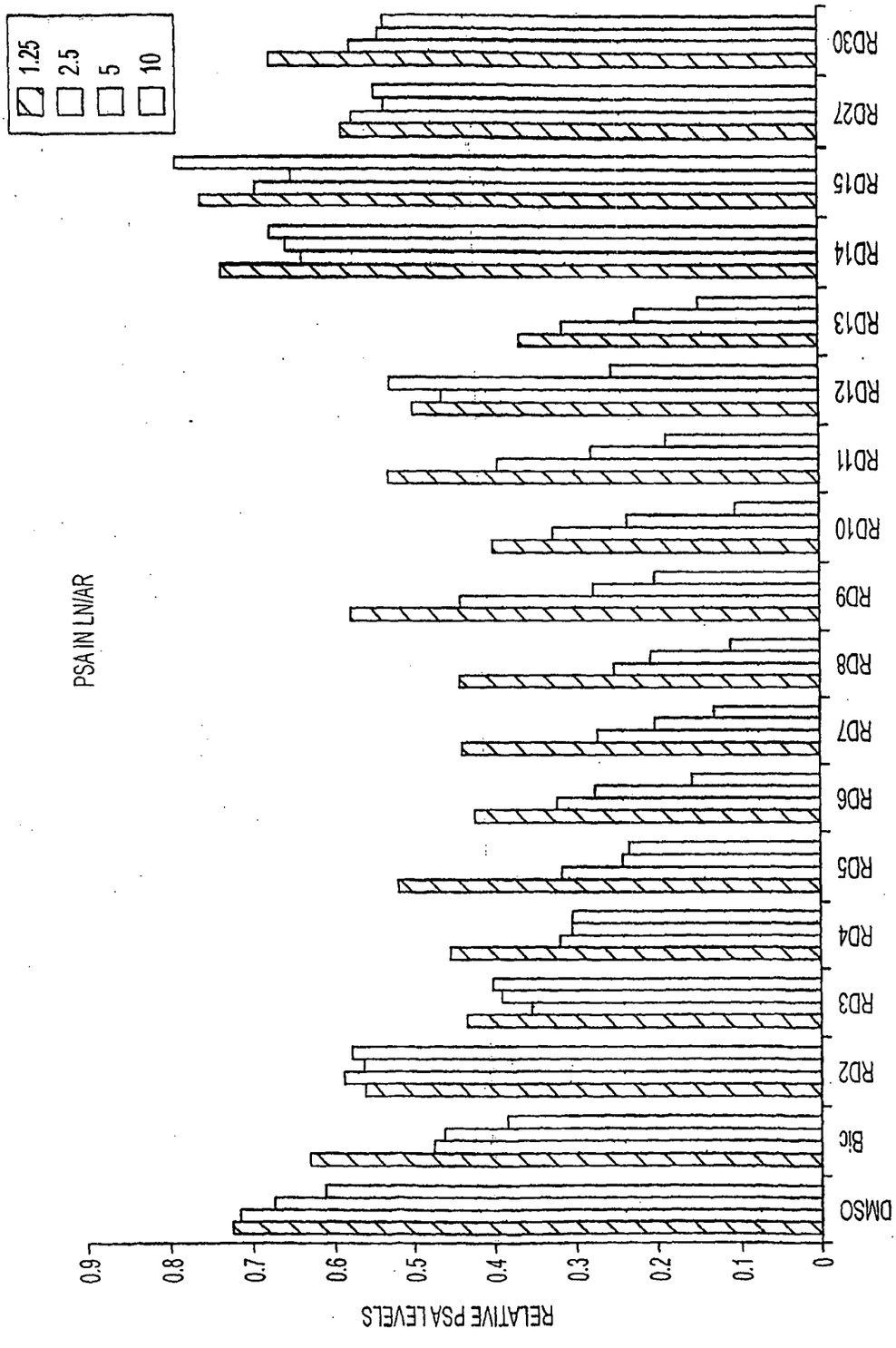

1.25
2.5
5
10
PSA IN LN/AR
RELATIVE PSA LEVELS
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
DMSO
Bic
RD2
RD3
RD4
RD5
RD6
RD7
RD8
RD9
RD10
RD11
RD12
RD13
RD14
RD15
RD27
RD30

FIG. 25

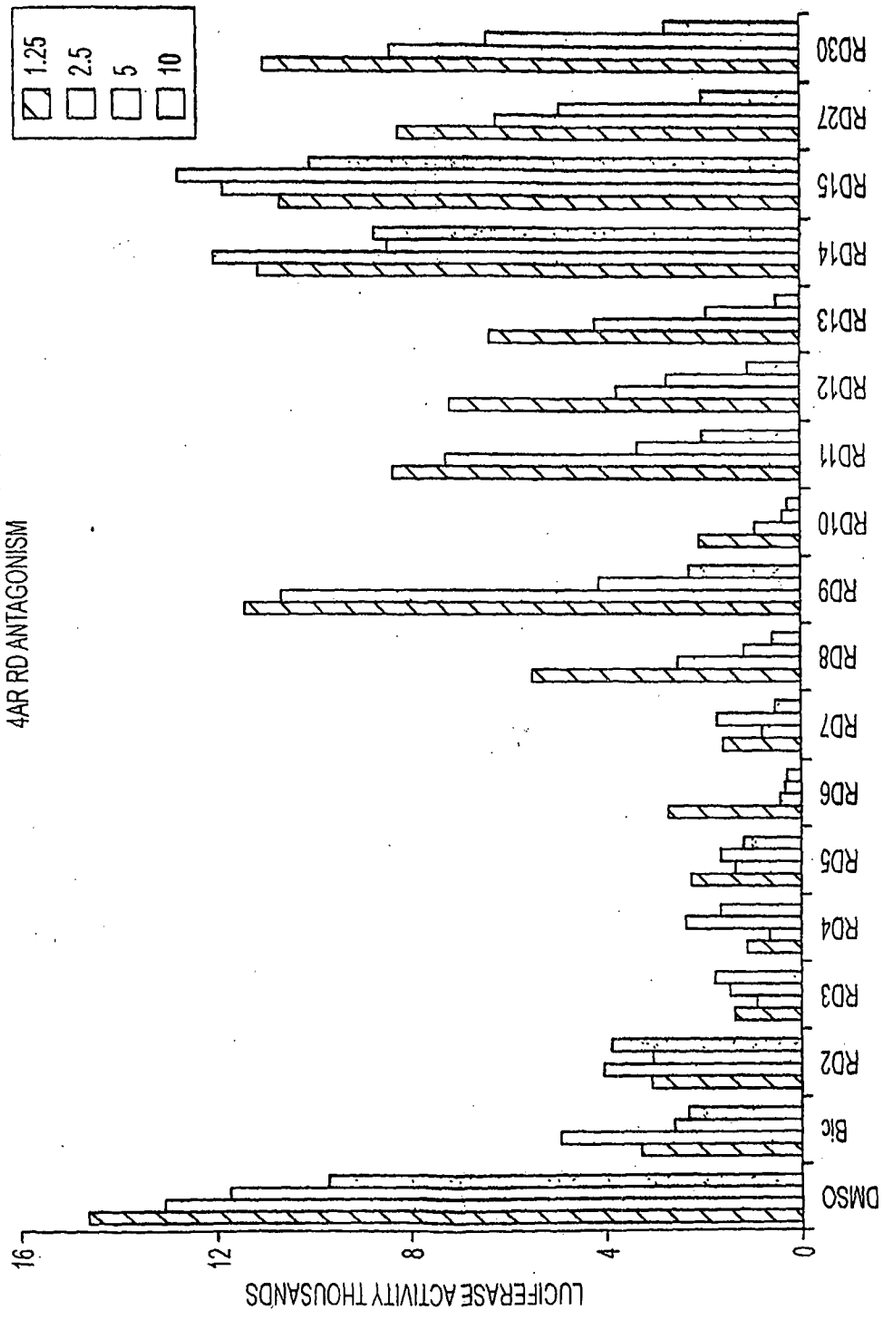

4AR RD ANTAGONISM
LUCIFERASE ACTIVITY THOUSANDS
16
12
8
4
0
1.25
2.5
5
10
DMSO
Bic
RD2
RD3
RD4
RD5
RD6
RD7
RD8
RD9
RD10
RD11
RD12
RD13
RD14
RD15
RD27
RD30

FIG. 26

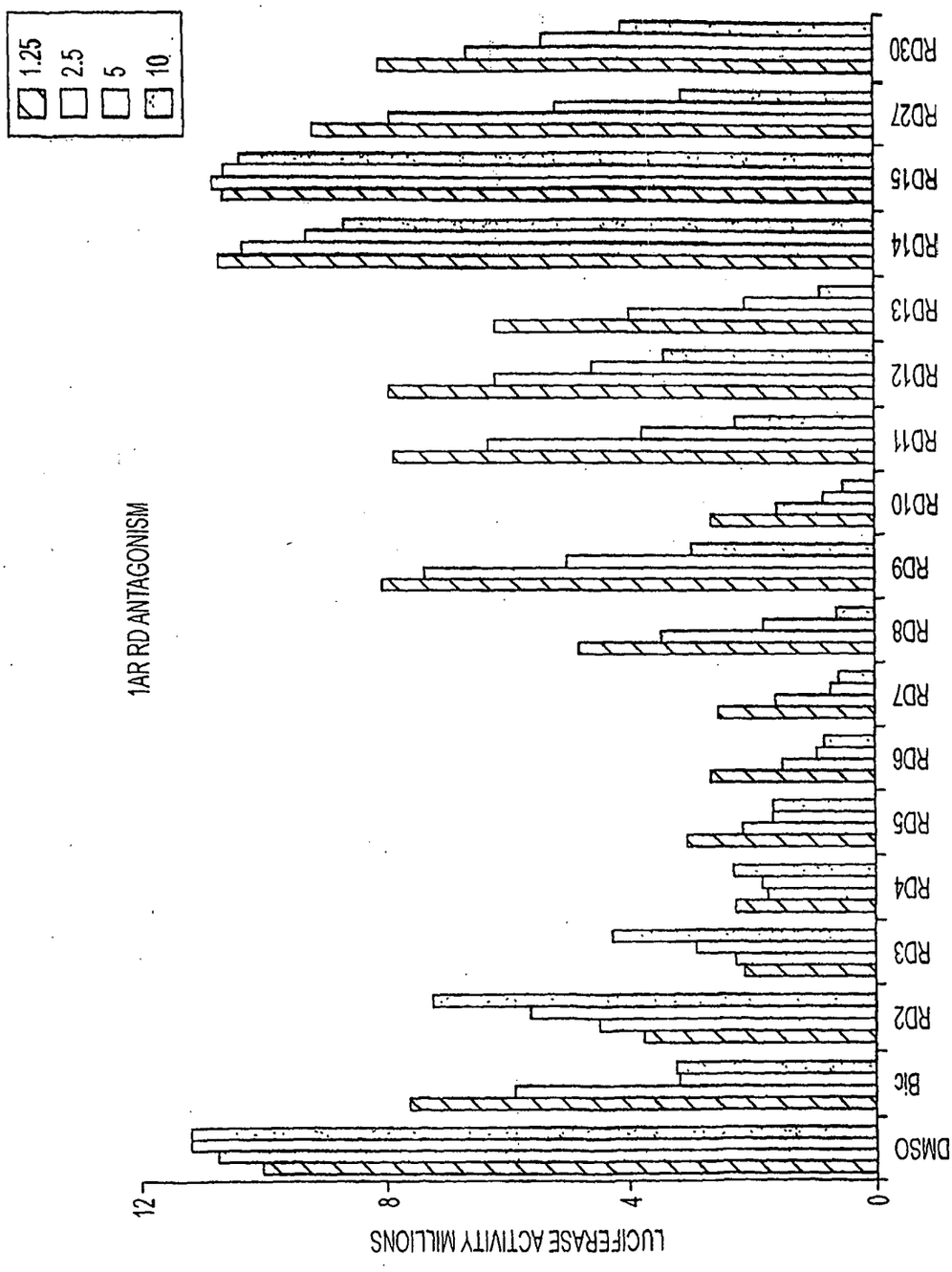

1.25
2.5
5
10
1AR RD ANTAGONISM
LUCIFERASE ACTIVITY MILLIONS
0
4
8
12
DMSO
Bic
RD2
RD3
RD4
RD5
RD6
RD7
RD8
RD9
RD10
RD11
RD12
RD13
RD14
RD15
RD27
RD30

FIG. 27

320

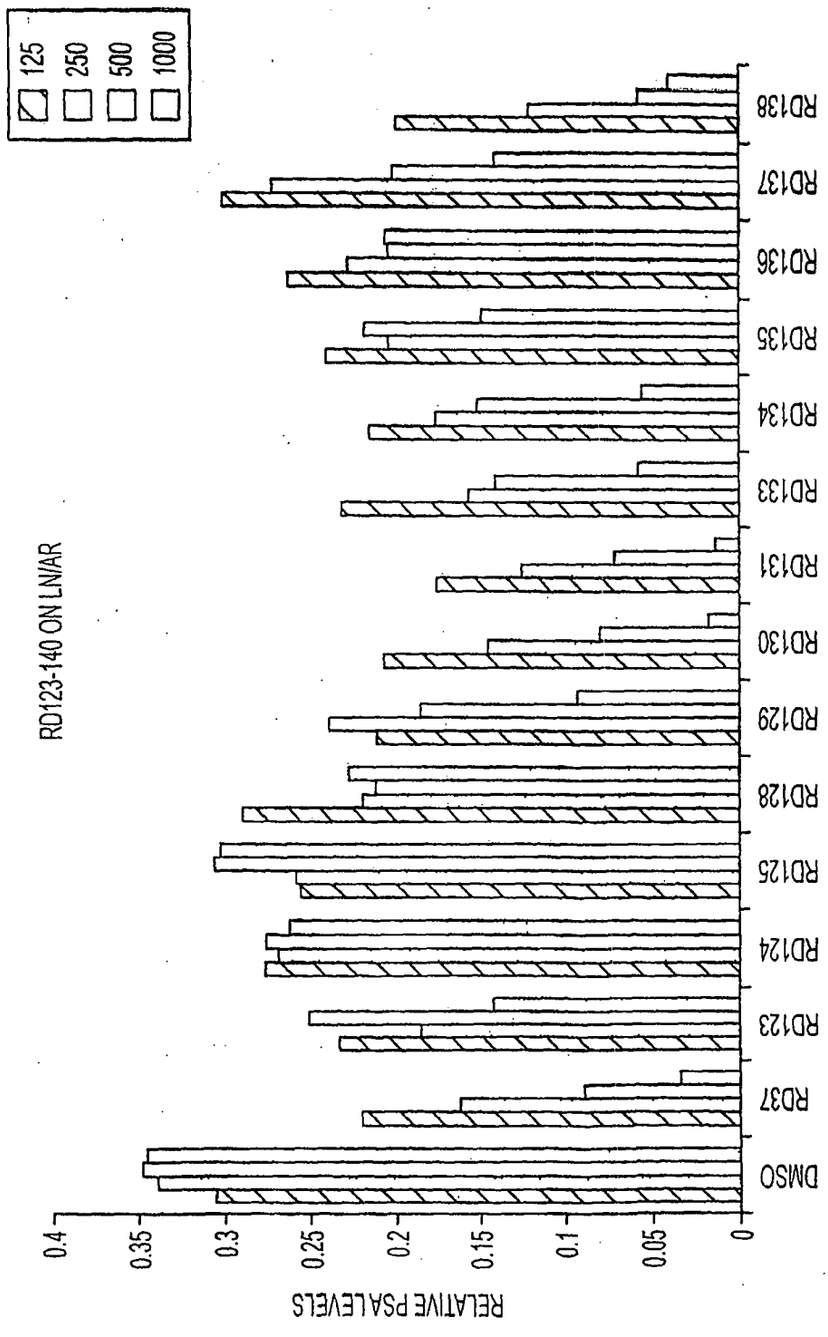

125
250
500
1000
RD123-140 ON LNAR
RELATIVE PSALEVELS
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
DMSO
RD37
RD123
RD124
RD125
RD128
RD129
RD130
RD131
RD133
RD134
RD135
RD136
RD137
RD138

FIG. 28

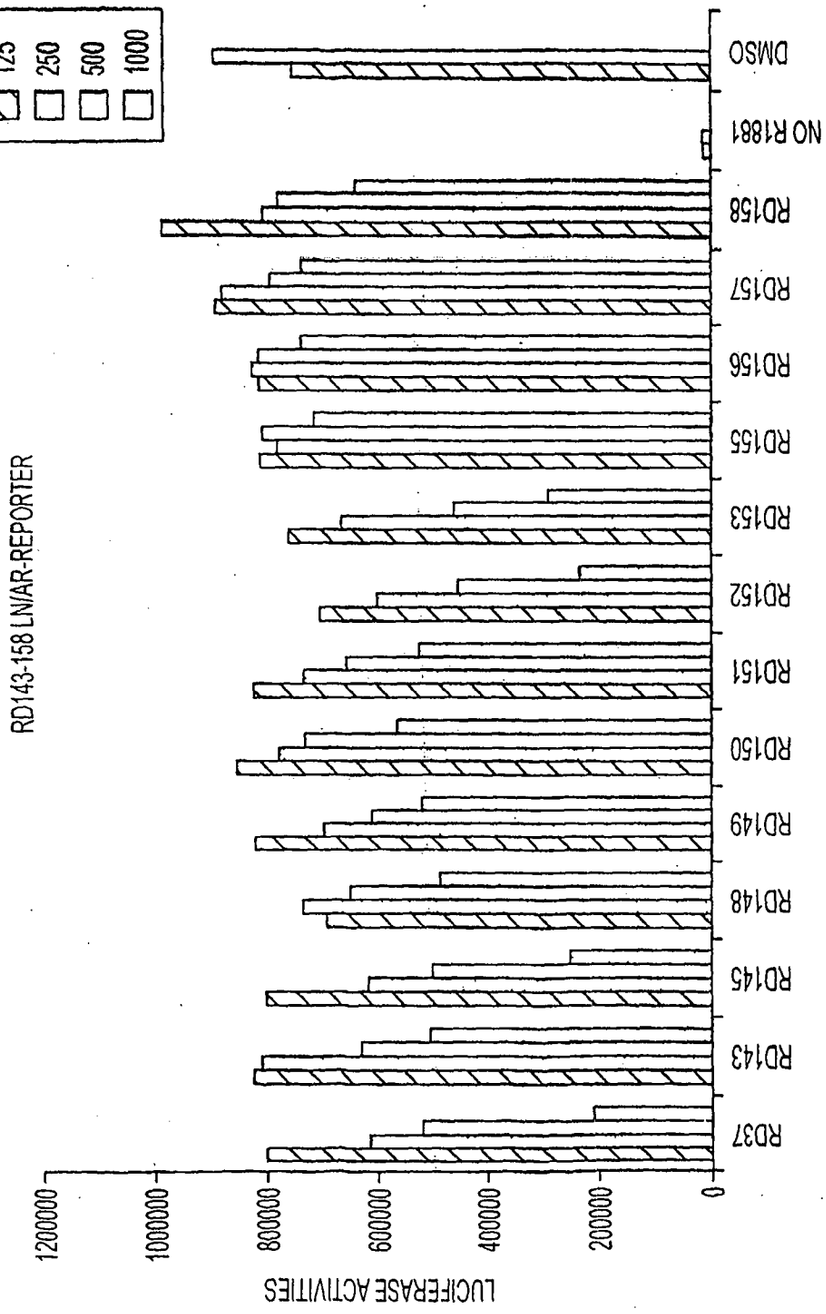

125
250
500
1000
DMSO
NO R1881
RD158
RD157
RD156
RD155
RD153
RD152
RD151
RD150
RD149
RD148
RD145
RD143
RD37
0
200000
400000
600000
800000
1000000
1200000
LUCIFERASE ACTIVITIES
RD143-158 LN/AR-REPORTER

FIG. 29

322

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/11417

A. CLASSIFICATION OF SUBJECT MATTER
IPC: A61K 31/4184(2006.01),31/4166(2006.01);C07D 235/02(2006.01),233/86(2006.01)

USPC: 514/387,391;548/301.4,321.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/387, 391; 548/301.4, 321.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,087,509 A (CLAUSSNER et al..) 11 July 2000 (11.07.2000), see entire document, especially column 1.	1-13, 15-17, 20-35, 37-42, 45 and 46

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
14 June 2006 (14.06.2006)

Date of mailing of the international search report
03 JUL 2006

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Laura L. Stockton, Ph.D.

Telephone No. 571/272-1600

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/11417

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 14,36 and 47-51
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/11417

Continuation of Box II Reason 2:

The compounds of Tier 1 and Tier 2, as found in claim 14, are not claimed by structure or nomenclature. In claim 36, the compounds of RD162', RD162", RD 169 and RD 170 are not claimed by structure or nomenclature. In claim 47, it is not clear what the method is to accomplish. A method for what or to do what? Therefore, claims 14, 36 and 47-51 are unsearchable.

Annexure III

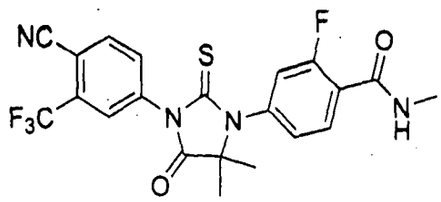
9668/DELNP/07 CLEAN COPY

ORIGINAL

11 FEB 2014

We Claim:

1. A compound having the formula



or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, for treatment of a hyperproliferative disorder.

3. A pharmaceutical composition comprising a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

4. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.001 mg per kg body weight per day to about 100 mg per kg body weight per day for treatment of a hyperproliferative disorder.

5. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.01 mg per kg body weight per day to about 100 mg per kg body weight per day for treatment of a hyperproliferative disorder.

6. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day for treatment of a hyperproliferative disorder.

7. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of about 1 mg per kg body weight per day for treatment of a hyperproliferative disorder.

8. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is prostate cancer.

9. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is hormone refractory prostate cancer.

10. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is hormone sensitive prostate cancer.

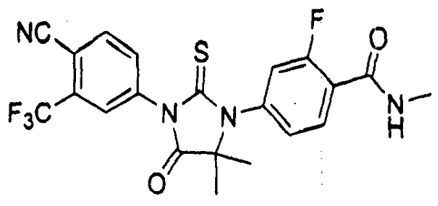
11. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is breast cancer.

12. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is ovarian cancer.

13. The pharmaceutical composition as claimed in claim 3, wherein the compound is in a form that can be administered as an intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally.

14. The pharmaceutical composition as claimed in claim 3, wherein the composition has a form selected from the group consisting of a solution, dispersion, suspension, powder, capsule, tablet, pill, time release capsule, time release tablet, and time release pill.

15. A method of synthesizing the compound comprising:



mixing N-Methyl-2-fluoro-4-(l,l-dimethyl-cyanomethyl)-aminobenzamide and 4-Isothiocyanato-2-trifluoromethylbenzonitrile in DMF and heating to form a first mixture;

adding an alcohol and an acid to the first mixture to form a second mixture;

refluxing the second mixture; and

cooling the second mixture, combining the second mixture with water and extracting an organic layer;

isolating the compound from the organic layer.

Dated this 13th day of December, 2007

Archana Shanker
Of Anand and Anand Advocates
Agent for the Applicant

Annexure IV

US005411981A

United States Patent [19]

Gaillard-Kelly et al.

[11] Patent Number: 5,411,981

[45] Date of Patent: May 2, 1995

[54] **PHENYLIMIDAZOLIDINES HAVING ANTIANDROGENIC ACTIVITY**

[75] Inventors: **Martine Gaillard-Kelly; Francois Goubet**, both of Paris; **Daniel Philibert**, La Verenne Saint Hilaire; **Jean-Georges Teutsch**, Pantin, all of France

[73] Assignee: **Roussel Uclaf**, France

[21] Appl. No.: **64,257**

[22] Filed: **May 18, 1993**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 819,910, Jan. 9, 1992, abandoned.

[30] **Foreign Application Priority Data**

Jan. 9, 1991 [FR] France 91 00185
Jul. 8, 1992 [FR] France 92 08431

[51] **Int. Cl.**[6] **C07D 233/72**; A61K 31/415

[52] **U.S. Cl.** **514/386**; 514/391; 514/342; 548/311.1; 548/317.1; 548/318.5; 548/320.1; 548/320.5

[58] **Field of Search** 514/391, 386, 342; 548/317.1, 318.5, 320.1, 320.5, 311.1

[56] **References Cited**

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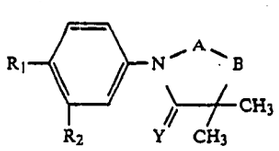
Primary Examiner—Floyd D. Higel
Attorney, Agent, or Firm—Bierman and Muserlian

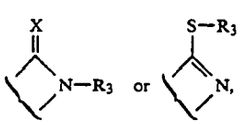
[57] **ABSTRACT**

A compound of the formula

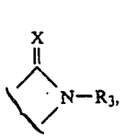


I

wherein R_1 is —CN, —NO_2 or halogen, R_2 is —CF_3 or halogen, —A–B— is of



X is —O— or —S—, R_3 is hydrogen, alkyl, alkenyl or alkynyl of up to 12 carbon atoms, aryl and aralkyl of up to 12 carbon atoms, all optionally substituted by —OH, halogen, —SH, —CN, acyl and acyloxy of up to 7 carbon atoms, —aryl, —O—aryl, —O—aralkyl —S— aryl of up to 12 carbon atoms the aryl and aralkyl being optionally substituted by halogen, —CF_3, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl or alkynyloxy with the sulfur being optionally oxidized to sulfone or sulfoxide, free, esterified, amidified or salified carboxy, —NH_2, mono and dialkylamino and heterocyclic of 3 to 6 ring members and containing at least one heteroatom selected from the group consisting of oxygen, sulfur and nitrogen, the alkyl, alkenyl and alkynyl being optionally interrupted by at least one oxygen, nitrogen or sulfur optionally oxidized to sulfoxide or sulfone, trialkylsilyl with the alkyl having 1 to 6 carbon atoms and acyl and acyloxy of an organic carboxylic acid of 1 to 7 carbon atoms and Y is —O—, —S— or —NH—, except the compounds wherein —A–B— is



X is oxygen, R_3 is hydrogen and Y is oxygen or —NH—, R_2 is —CF_3 or halogen and R_1 is —NO_2 or halogen and their non-toxic, pharmaceutically acceptable acid addition salts.

20 Claims, No Drawings

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PHENYLIMIDAZOLIDINES HAVING ANTIANDROGENIC ACTIVITY

PRIOR APPLICATION

This application is a continuation-in-part of U.S. Patent application Ser. No. 819,910, filed Jan. 9, 1992, now abandoned.

Japanese application No J 48087030 describes 3-phenyl-2-thiohydantoins useful for inhibiting the germination of certain plants. U.S. Pat. No. 4,097,578 describes imidazolidines different from formula I having antiandrogenic activity. Other pertinent art includes U.S. Pat. Nos. 3,823,240; No. 4,873,256; No. 4,407,814; No 4,482,739 and No. 4,234,736.

OBJECTS OF THE INVENTION

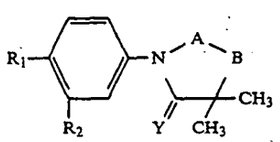
It is an object of the invention to provide the novel compounds of formula I and a novel process and novel intermediates for their preparation.

It is another object of the invention to provide novel anti-androgenic compositions and a novel method of inducing anti-androgenic activity in warm-blooded animals.

These and other objects and advantages of the invention will become obvious from the following detailed description.

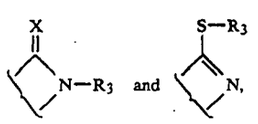
THE INVENTION

The novel phenylimidazolidines of the invention have the formula



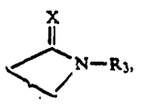
I

wherein R_1 is selected from the group consisting of —CN, —NO_2 and halogen, R_2 is —CF_3 or halogen, —A–B— is selected from the group consisting of



X is —O— or —S—, R_3 is selected from the group consisting of hydrogen, alkyl, alkenyl and alkynyl of up to 12 carbon atoms, aryl and aralkyl of up to 12 carbon atoms, all optionally substituted with at least one member of the group consisting of —OH, halogen, —SH, —CN, acyl and acyloxy of up to 7 carbon atoms, —aryl, —O—aryl, —O—aralkyl —S—aryl of up to 12carbon atoms, the aryl and aralkyl being optionally substituted with a member of the group consisting of halogen, —CF_3, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl and alkynyloxy with the sulfur being optionally oxidized to sulfone or sulfoxide, free, esterified, amidified or salified carboxy, —NH_2, mono and dialkylamino and heterocyclic of 3 to 6 ring members and containing at least one heteroatom selected from the group consisting of oxygen, sulfur and nitrogen, the alkyl, alkenyl and alkynyl being optionally interrupted with at least one member of the group consisting of oxygen, nitrogen and sulfur optionally oxidized to sulfoxide or sulfone, trialkylsilyl

with the alkyl having 1 to 6 carbon atoms and acyl and acyloxy of an organic carboxylic acid of 1 to 7 carbon atoms and Y is —O—, —S— or —NH—, except the compounds wherein —A–B— is



X is oxygen, R_3 is hydrogen and Y is oxygen or —NH—, R_2 is —CF_3 or halogen and R_1 is —NO_2 or halogen and their non-toxic, pharmaceutically acceptable acid addition salts.

The following examples are given for the values of R_3. Alkyl of up to 12 carbon atoms includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, sec.-pentyl, tert.-pentyl, neopentyl, hexyl, isohexyl, sec.-hexyl, tert.-hexyl, heptyl, octyl, decyl, undecyl and dodecyl, branched or linear. Preferred are alkyl of 1 to 6 carbon atoms, especially methyl, ethyl, propyl and isopropyl, n-butyl, isobutyl, tert-butyl and branched or linear pentyl and hexyl.

Examples of alkenyl of up to 12 carbon atoms are vinyl, allyl, 1-propenyl, butenyl, pentenyl and hexenyl and preferably alkenyl of 2 to 4 carbon atoms and especially vinyl, allyl or butenyl. Examples of alkynyl of up to 12 carbon atoms are ethynyl, propargyl, butynyl, pentynyl and hexynyl and preferably 2 to 4 carbon atoms such as ethynyl and propargyl.

Examples of aryl are carbocyclic aryl such asphenyl and naphthyl, heterocyclic aryl of 5 to 6 ring members containing at least one heteroatom selected from the group consisting of oxygen, sulfur and nitrogen. Examples of 5 ring heteroaryls are furyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, thiadiazolyl, pyrazolyl and isoxazolyl. Examples of 6 ring heteroaryl are pyridyl, pyrimidinyl, pyridazinyl and pyrazinyl. Examples of condensed aryls are indolyl, benzofurannyl, benzothienyl and quinoleinyl. The preferred aryl is phenyl.

Examples of aralkyl include the alkyl recited above substituted with the aryl cited above. The preferred aralkyl are triphenylmethyl, phenethyl and benzyl. Examples of halogen are fluorine, chlorine, bromine and iodine but preferred are fluorine, chlorine and bromine. Examples of alkyl substituted with at least one halogen are fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, dichloromethyl, dibromomethyl and trifluoromethyl.

Examples of substituents for aryl and aralkyl are phenyl substituted by fluorine, —OCH_3 or —CF_3 in the p-position.

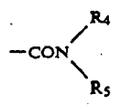
Examples of acyl are preferably those of up to 7 carbon atoms such as acetyl, propionyl, butyryl and benzoyl as well as valeryl, hexanoyl, acryloyl, crotonoyl, carbamoyl or formyl. The acyloxy may be derived for the same acids, especially acetyloxy and propionyloxy.

The esterified carboxy may be alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert.-butoxycarbonyl, cyclobutyloxy carbonyl, cyclopentyloxy carbonyl and cyclohexylocy carbonyl.

Examples of easily cleavable esters includes methoxymethyl, ethoxymethyl; acyloxyalkyl such as pivaloyloxymethyl, pivaloyloxyethyl, acetoxymethyl and acetoxyethel; alkoxycarbonyloxyalkyl such as methoxycar-

bonyloxymethyl, methoxycarbonyloxyethyl, isopropoxycarbonyloxymethyl and isopropoxycarbonyloxyethyl. Other esters are described in European Patent No. 0.034.536.

The amidified carboxy are of the type



wherein R_4 and R_5 are individually selected from the group consisting of hydrogen and alkyl of 1 to 4carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and tert.-butyl.

Examples of the mono and dialkylamino are methylamino, ethylamino, dimethylamino, diethylamino and methylethylamino. The hetero-cyclic of 5 to 6 ring members optionally containing another heteroatom may be pyrrolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidyl, indolyl, piperidino, morpholino and piperazinyl, preferably piperidino or morpholino.

Examples of salts of salified carboxy are sodium, potassium, lithium, calcium, magnesium, ammonium and organic bases such as methylamine, propylamine, trimethylamine, diethylamine and triethylamine. Sodium salt is preferred.

The alkylamino and dialkylamino are preferably alkyl of 1 to 4 carbon atoms such as methylamino, ethylamino, propylamino, isopropylamino, dimethylamino, diethylamino and ethylmethylamino.

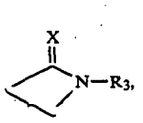
Examples of the heterocyclics containing at least one heteroatom are saturated monocyclics such as oxirannyl, oxolannyl, dioxolannyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl and morpholinyl.

The alkyl, alkenyl and alkynyl may be optionally interrupted by one or more sulfur, oxygen or nitrogen heteroatoms. Examples are alkoxyalkyl such as methoxymethyl, methoxyethyl, methoxypropyl or methoxybutyl or alkoxy alkoxyalkyl such as methoxyethoxymethyl.

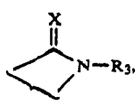
Examples of trialkylsilyl groups are trimethylsilyl, triethylsilyl and (1,1-dimethylethyl) dimethylsilyl.

When the products of formula I contain a salifiable amino group, the acid addition salts of non-toxic, pharmaceutically acceptable acids may be formed. Examples of said acids are inorganic acids such as nitric acid, hydrochloric acid, sulfuric acid and phosphoric acid and organic acids such as formic acid, acetic acid, propionic acid, benzoic acid and methane sulfonic acid.

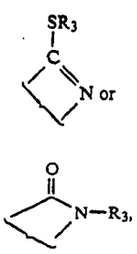
Among the preferred compounds of formula I are those wherein Y is oxygen except for the compounds wherein —A–B— is



X is oxygen, R_3 is hydrogen, R_2 is $—CF_3$ or halogen and R_1 is $—NO_2$ or halogen. Other preferred compounds of formula I are those wherein —A–B— is



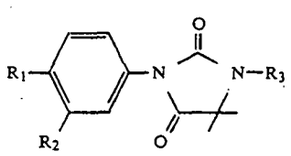
X is sulfur and R_3 has the above definition, those wherein R_3 is hydrogen or alkyl of 1 to 4 carbon atoms optionally substituted with —OH or methoxy, those wherein R_1 is cyano or halogen, preferably chlorine and those wherein —A–B— is



and R_3 is optionally substituted alkyl or alkenyl of up to 6 carbon atoms and optionally interrupted by oxygen or optionally oxidized sulfur or optionally substituted aralkyl, acyl or trialkylsilyl.

Other preferred examples of the invention are those in which R_3 is alkyl of up to 6 carbon atoms optionally substituted by at least one member of the group consisting of halogen, free or esterified hydroxy or carboxy, heterocyl, O-aralkyl or S-aryl in which the aryl radical is optionally substituted by at least one halogen or alkoxy and the sulfur atom is optionally oxidized in the form of the sulfoxide or sulfone and quite particularly those in which R_3 is alkyl of 2 to 4 carbon atoms substituted by a member of the group consisting of chlorine, ethoxycarbonyl, terbutoxycarbonyl, cyclopentyloxycarbonyl, 4-fluorophenylthio optionally oxidized in the form of the sulfoxide or sulfone, morpholino, phenylmethoxy, triphenylmethoxy and methylsulfonyloxy.

Other preferred compounds of formula I are those wherein R_3 is acetyl or benzoyl or (1,1-dimethylethyl) dimethylsilyl, those wherein R_1 is nitro and R_3 is alkyl or alkenyl of up to 4 carbon atoms optionally substituted with esterified or salified or free carboxy and those of the formula



I

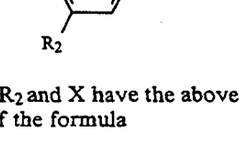
in which R_1, R_2 and R_3 have the above meaning with the exception of the products in which R_1 is nitro, R_2 is trifluoromethyl and R_3 is hydrogen.

Examples of specific preferred compounds of formula I are 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-(4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-[4,4-dimethyl 3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl]-2-(trifluoromethyl) benzonitrile, 3-(3,4-dichlorophenyl)-2-thioxo-1,5,5-trimethyl-4-imidazolidinone, 1-(4-nitro-3-(trifluoromethyl)-phenyl)-3,4,4-trimethyl-2,5-imidazoli-

dinedione, 4-[[4,5-dihydro-4,4-dimethyl-5-oxo-2-benzyl-thio]-1H-imidzao-1-yl]-2-(trifluoromethyl) benzonitrile, 4-[4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile and 3-(4-cyano 3-(trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoic acid.

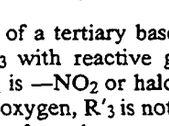
The process of the invention for the preparation of a compound of formula I comprises either reacting a compound of the formula

II



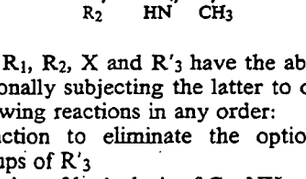
wherein R_1, R_2 and X have the above definitions with a compound of the formula

III



in the presence of a tertiary base wherein R'_3 has the definition of R_3 with reactive group optionally protected and if R_1 is $-NO_2$ or halogen, R_2 is halogen or $-CF_3$ and X is oxygen, R'_3 is not hydrogen to obtain a compound of the formula

IV



wherein R_1, R_2, X and R'_3 have the above definitions and optionally subjecting the latter to one or more of the following reactions in any order:

a) reaction to eliminate the optional protective groups of R'_3

b) reaction of hydrolysis of C=NH to a ketone function or transformation of C=S to C=O

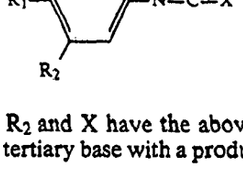
c) transformation reaction of C=O to C=S

d) and reacting the products of formula IV wherein R'_3 is hydrogen and after hydrolysis of C=NH to a ketone with a compound of the formula R''_3-Hal where Hal is a halogen and R''_3 is R'_3 except hydrogen to obtain a compound of formula I wherein —A–B— is

or

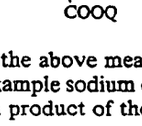
and optionally reacting the latter to eliminate the protective group of R''_3 or reacting the same with an esterification, salification or amidification agent or reacting a compound of the formula

II



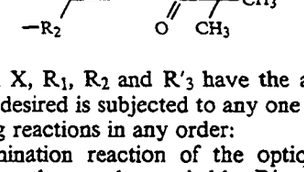
in which R_1, R_2 and X have the above meaning in the presence of a tertiary base with a product of the formula

III



in which R'_3 has the above meaning and Q is either an alkali metal for example sodium or alkyl of 1 to 6 carbon atoms to obtain a product of the formula

IVa

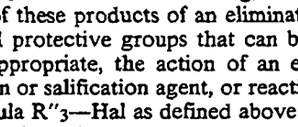


in which X, R_1, R_2 and R'_3 have the above meaning which if desired is subjected to any one or more of the following reactions in any order:

a) elimination reaction of the optional protective groups that can be carried by R'_3;

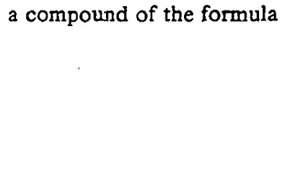
b) conversion reaction of the >C=O group or groups into the >C=S or if appropriate of >C=S into >C=O;

c) the action on the products of formula IV*a* in which R'_3 is hydrogen of a reagent of formula Hal—R''_3 in which R''_3 has the values of R'_3 with the exception of hydrogen and Hal is halogen to obtain the products of formula I in which —A–B— is

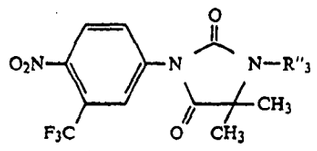


in which R''_3 has the above meaning, then, if desired, the action of these products of an elimination agent of the optional protective groups that can be carried by R''_3 or if appropriate, the action of an esterification, amidification or salification agent, or reacting a reagent of the formula R''_3—Hal as defined above with a compound of the formula

IV'



to obtain a compound of the formula



IV″

and optionally subjecting the latter to one or more of the following reactions:

a) elimination reaction of optional protective groups of R''_3 and then to reaction with an esterification, salification or amidification reagent

b) reaction of transformation of C═O to C═S.

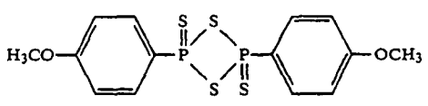
The reaction of the products of formula II with the products of formula III is preferably effected in an organic solvent such as tetrahydrofuran or dichloroethane or ethyl ether or isopropyl ether in the presence of a tertiary base such as pyridine or methylethyl pyridine.

The optional reactive functional groups of R_3 which are optionally protected in compounds of formula III, IV*a* or IV″ are —OH or amino which are protected by the usual protective groups. Examples of such protective groups for $—NH_2$ are tert.-butyl, tert.-amyl, trichloroacetyl, chloroacetyl, benzhydryl, trityl, formyl and benzyloxycarbonyl. Examples of hydroxy protective groups are formyl, chloroacetyl, tetrahydropyrannyl, trimethylsilyl and tert.-butyldimethylsilyl.

The above list of protective groups is not intended to be exhaustive and any protective group known, for example, in peptide chemistry may be used. Other known protective groups are described in French Patent No. 2,499,995 which is incorporated herein by reference. The optional reactions to eliminate groups are indicated in the said patent and the preferred method of elimination is acid hydrolysis with hydrochloric acid, benzene sulfonic acid, p-toluene sulfonic acid, formic acid or trifluoroacetic acid, preferably hydrochloric acid.

The optional reaction of hydrolysis of C═NH to C═O is preferably effected with an acid suchas refluxing aqueous hydrochloric acid. When the hydrolysis of C═NH into a C═O is effected with a molecule also containing C═S, the latter may be transformed in C═O group. The free hydroxy optionally contained in R_3 may also be transformed into —SH.

The transformation of the group C═O into C═S is effected with a Lawesson reagent of the formula



which is a commercial product sold by Fluka for example and is described in Bull. Soc. Chim. Belg., Vol 87 No. 3 (1987), p. 229. When two C═O groups are to be changed to C═S, the reaction is effected in an excess of the Lawesson reagent. The same is used also when the molecule contains both C═S and C═O and it is desired to change the C═O to C═S.

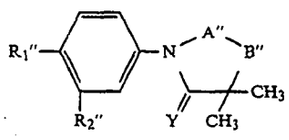
On the contrary, when part of the molecule contain two C═O and it is desired to obtain a product with only one C═S, a deficiency of the Lawesson reagent is used to obtain a mixture of 3 products, each of two products with a C═O and C═S and one containing two C═S. The said products can be separated by known methods such as chromatography.

The reaction of the compounds of formulae IV, IVA or IV′ with a compound of the formula R''_3—Hal is effected in the presence of a strong base such as sodium hydride or potassium hydride in a phase transfer reaction in the presence of quaternary ammonium salts such as tert.-butyl ammonium. The protective groups of R''_3 may be those discussed above for R_3. The reaction to eliminate the protective groups are as discussed above. For example, a tert-butyl dimethylsilyl group may be removed by hydrochloric acid as described in the examples infra.

The optional esterification of the compounds of formula I wherein R''_3 is free —OH is effected under the classical conditions using for example an acid or a functional derivative thereof such as its anhydride like acetic acid anhydride in the presence of a base such as pyridine. The optional esterification or salification of the compounds of formula I wherein R''_3 is —COOH may be effected by known methods.

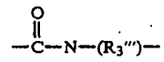
The optional amidification of the compounds of formula I wherein R''_3 is —COOH is effected also under classical conditions with primary or secondary amine with a functional derivative of —COOH such as a symetrical or mixed anhydride thereof.

The process of the invention to prepare compounds of the formula

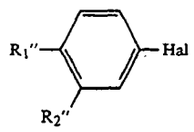


I″

wherein R''_1, R''_2 and —A″-B″— have the definitions of R_1, R_2 and —A–B— except when —A″-B″— is

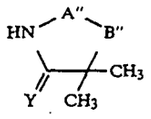


and R'''_3, is hydrogen or alkyl of 1 to 7 carbon atoms and Y is oxygen, R''_1 is —CN comprises reacting a compound of the formula



V

wherein R''_1 and R''_2 have the above definitions and Hal is halogen with a compound of the formula



VI

wherein —A″-B″— and Y have the above definitions in the presence of a catalyst and optionally a solvent. In the compounds of formula V, the halogen is preferably chlorine but may be iodine or bromine.

The role of the catalyst is obviously to trap the hydrogen halide as it forms and to facilitate the condensation reaction of the compounds of formulae V and VI to form the desired product. The catalyst is preferably a metal in its native form or its oxide or salt form or it may be a base. When the catalyst is a metal, it is preferably copper or nickel and the metallic salts are preferably the chloride or acetate. When the catalyst is a base, it is preferably sodium hydroxide or potassium hydroxide and dimethylsulfoxide may be added to the reaction medium.

The catalyst of the process may be selected from cuprous oxide, cupric oxide, metallic copper or a base such as sodium hydroxide or potassium hydroxide, preferably cuprous oxide in powdered form. The solvent used preferably is a high boiling point ether such as phenyl oxide, diglyme, triglyme and dimethylsulfoxide but also useful are high boiling point oils such as paraffin or vaseline. Preferably, the process is effected in another solvent such as phenyl oxide, diglyme, triglyme or dimethylsulfoxide, most preferably in phenyl oxide or triglyme.

The process may be effected at atmospheric pressure or under pressure at temperatures above 100° C., preferably above 150° C. for more than two hours. The reaction is preferably effected with cuprous oxide in triglyme at temperatures of 200° C. or higher for more than three hours.

The novel anti-androgenic compositions of the invention are comprised of an anti-androgenically effective amount of at least one compound of formula I and its non-toxic, pharmaceutically acceptable acid addition salts and an inert pharmaceutical carrier. The compositions may be in the form of tablets, dragees, capsules, syrups, suppositories, creams, pomades, lotions or injectable solutions prepared in the usual manner.

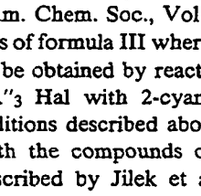
Examples of suitable excipients are aqueous or non-aqueous vehicles, arabic gum, lactose, starch, magnesium stearate, cocoa butter, fatty bodies of animal or vegetable origin, paraffinic derivatives, glycols, diverse wetting agents, dispersants or emulsifiers and preservatives.

The compositions inhibit the effect of androgens on peripherical receptors and have an anti-androgenic activity useful for therapy in adults without the certain effects of a chemical castration. The compositions are useful for the treatment of adenomas and neoplasies of the prostateas well as benign hypertrophia of the prostate as well as the treatment of benign or malignant tumors of cells containing androgen receptors. They are particularly useful for the treatment of breast, brain, skin and ovarian cancer and bladder, lymphatic system, liver and kidney cancers. They are equally useful for the treatment of hirsutism, acne, seborrhea, androgenic alopecia and hyperpilosity and in the veterinary field.

The compositions of the invention are useful in dermatology and can contain another ingredient such as an antibiotic such as derivatives of retinoids for the treatment of acne, or with a 5α-reductase inhibitor such as (5=, 17β)-1,1-dimethylethyl 3-oxo 4-aza-Δ^1-androstene-17 carboxamide (or Finasteride Merck, 11th ed.) or azelaic acid or a blocking agent of androgen receptors for the treatment of acne, alopecia or hirsutism, or with a product stimulating the growth of hair such as Minoxidil for the treatment of alopecia. The compositions can also be used in the veterinary domain and in the form of radioactive products, can also be used in diagnostics as specific labels for the androgen receptors. As radioactive products, the products labelled with tritium, with carbon 14 or also with iodine 125 can be used.

The novel method of the invention for inducing anti-androgenic activity in warm-blooded animals, including humans, comprises administering to warm-blooded animals an anti-androgenically effective amount of at least one compound of formula I and its non-toxic, pharmaceutically acceptable acid addition salts. The compounds may be administered parenterally, buccally, perlingually, rectally or topically and the usual daily dose is 0.133 to 6.66 mg/kg depending on the condition treated, the specific compound and the method of administration.

The starting compounds of formula II may be prepared by reacting phosgene when X is oxygen or thiophosgene when X is sulfur with an amine of the formula



A

A product of this type is described in French Patent No. 2,329,276. The amines of formula A are described in EP Patent No. 0,002,892 and French Patent No. 2,142,804.

The products of formula III or III' are known or can be prepared from the corresponding cyanhydrin by the process of J. Am. Chem. Soc., Vol 75 (1953), p. 4841. The compounds of formula III wherein R'3 is other than hydrogen may be obtained by reacting a compound of the formula R"3 Hal with 2-cyano-2-amino-propane under the conditions described above for reacting the said halide with the compounds of formula IV. An example is described by Jilek et al, Collect. Czech. Chem. Comm., Vol 54(8) (1989), p. 2248. The products of formula IV' are described in French Patent No. 2,329,276.

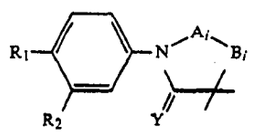
The compounds of formulae V and VI are commercially available known compounds and can be prepared by known methods.

The preparation of the compounds of formula VI are described in the following publications: Zhur Preklad Khim., Vol. 28 (1955), p. 969–75 (CA, Vol. 50 (1956), p 4881*a*); Tetrahedron, Vol. 43 (1987), p. 1753; J. Org. Chem., Vol. 52 (1987), p. 2407; Zh. Org. Khim., Vol. 21 (1985), p. 2006; J. Fluor. Chem., Vol. 17 (1981), p. 345; German Patent No. 637,318, European Patent No. 0,130,875 and Japanese Patent No. 81-121,525.

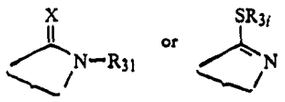
The products of formula VI which are derivatives of hydantoin are largely used and are known in the literature such as J. Pharm. Pharmacal., 67, Vol. 19(4) (1967), p. 209–16; J. Chem. Soc., Vol. 74(2) (1972), p. 219–221; Khim. Farm. Zh., Vol. 67(1)(5), p. 51–2; German Patent No. 2,217,914; European Patent No. 0,091,596 and J. Chem. Soc. Perkin. Trans. 1, Vol. 74(2), p. 48 and 219–221.

The novel intermediates of the invention are the compounds of the formula

IVi



wherein R_1, R_2 and Y have the above definitions and —Ai–Bi— is



wherein X is oxygen or sulfur and R_3, is R_3 with the reactive groups protected among which are —OH or $—NH_2$ protected as above for R_3.

In the following examples, there are described several preferred embodiments to illustrate the invention. However, it should be understood that the invention is not intended to be limited to the specific embodiments.

EXAMPLE 1

1-(4-nitro-3-trifluoromethyl-phenyl)-3,4,4-trimethyl-2,5-imidazolidinedione

A solution of 3.17 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl-imidazoline-2,5-dione (French Patent No. 2,329,276) and 32 ml of dimethylformamide were added at 23° C. to 26° C. to a 50% suspension of 492 mg of sodium hydride in oil and 3 ml of dimethylformamide and after stirring for 15 minutes, a solution of 0.7 ml of methyl iodide in 2 ml of dimethylformamide was added. The mixture was stirred for 25 minutes at 24° C. to 28° C. and was then poured into 200 g of a 1—1 water-ice mixture. The mixture was extracted with ether and the organic phase was washed with saturated aqueous sodium chloride, dried, filtered and evaporated to dryness under reduced pressure to obtain 3.6 g of the desired product melting at 116° C. An analytical sample was crystallized from isopropyl alcohol to obtain 2.73 g of the product melting at 116° C.

Analysis: $C_{13}H_{12}F_3N_3O_4$; molecular weight = 331.25

	% C	% H	% F	% N
Calculated:	47.14	3.65	17.20	12.68
Found:	47.0	3.5	17.1	12.5

IR Spectrum ($CHCl_3$):

C=O	1780, 1727 cm^{-1}
aromatics	1615, 1596, 1497 cm^{-1}
NO_2	1545, 1357 cm^{-1}

EXAMPLE 2

5,5-dimethyl-1-ethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazoline-2,5-dione prepared as in French Patent No. 2,329,276 was reacted with 0.37ml of ethyl iodide and a 50% suspension of 166 mg of sodium hydride in oil to obtain 1.19 g of the desired product melting at 110° C. to 111° C. which was crystallized from isopropanolto obtain 934 mg of the product melting at 110° C. to 111° C.

Analysis: $C_{14}H_{14}F_3N_3O_4$; molecular weight = 345.28

	% C	% H	% F	% N
Calculated:	48.70	4.09	16.51	12.17
Found:	48.6	4.0	16.8	12.1

IR Spectrum ($CHCl_3$):

C=O	1777, 1724 cm^{-1}
NO_2	1545, 1356 cm^{-1}
aromatics	1614, 1596, 1497 cm^{-1}

EXAMPLE 3

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-propyl-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazoline-2,5-dione was reacted with 0.35 ml of 1-iodopropane and a 50% suspension of 155mg of sodium hydride in oil to obtain after chromatography on silica with an eluant of acetone-methylene chloride (1–99), 3.087 g of raw product melting at 102° C. The product was crystallized from isopropanol to obtain 945 mg of the desired product melting at 102° C.

Analysis: $C_{15}H_{16}F_3N_3O_4$; molecular weight = 359.31

	% C	% H	% F	% N
Calculated:	50.14	4.49	15.86	11.69
Found:	50.1	4.4	15.9	11.5

IR Spectrum ($CHCl_3$):

C=O	1778, 1724 cm^{-1}
NO_2	1544, 1358 cm^{-1}
aromatics	1615, 1596, 1497 cm^{-1}

EXAMPLE 4

5,5-dimethyl-1-isopropyl-3-(4-nitor-3-trifluoromethyl-phenyl)-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazoline-2,5-dione was reacted with 0.4 ml of 2-iodopropane and a 50% suspension of 166 mg of sodium hydride in oil for 18 hours at 50° C. to obtain after chromatography over silica (eluant methylene chloride-acetone 99–1), 685 mg of product melting at 130° C. which after crystallization from isopropanol yielded 661 of the desired product melting at 130° C.

Analysis: $C_{15}H_{16}N_3F_3O_4$; molecular weight = 359.31

	% C	% H	% F	% N
Calculated:	50.14	4.49	15.86	11.69
Found:	50.1	4.4	16.2	11.6

IR Spectrum ($CHCl_3$):

C=O	1779, 1771, 1723 cm^{-1}

-continued

IR Spectrum ($CHCl_3$):	
NO_2	1544, 1361 cm^{-1}
aromatics	1615, 1596, 1497 cm^{-1}

EXAMPLE 5

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-(2-propenyl)-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-(henyl)-4,4-dimethyl imidazoline-2,5-dione was reacted with 0.35 ml of allyl bromide and a 50% suspension of 166 mg of sodium hydride in oil to obtain after chromatography over silica (eluant—methylene chloride-acetone (99-1)) 1.10 g of product which after crystallization from isopropanol yielded 1.01 g of the desired product melting at 105° C.

Analysis: $C_{15}H_{14}F_3N_3O_4$; molecular weight = 357.29				
	% C	% H	% F	% N
Calculated:	50.42	3.95	15.95	11.76
Found:	50.4	3.8	15.8	11.7

IR Spectrum ($CHCl_3$):	
C=O	1779, 1724 cm^{-1}
NO_2	1545, 1358 cm^{-1}
aromatics	1615, 1596, 1497 cm^{-1}
$CH=CH_2$	1643, 930 cm^{-1}

EXAMPLE 6

5,5-dimethyl-3-(3-trifluoromethyl-4-nitro-phenyl)-1-benzyl-2,4-imidazolidinedione

Using the procedure of Example 1, 2 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazolidine-2,5-dione was reacted with 0.71 ml of benzyl bromide and a 50% suspension of 332 mg of sodium hydride in oil to obtain after chromatography on silica and elution with 99-1 methylene chloride-acetone 2.375 g of the desired product which as crystallized from isopropanol to obtain 2.165 g of product melting at 99° C.

Analysis: $C_{19}H_{16}N_3F_3O_4$; molecular weight = 407.3				
	% C	% H	% F	% N
Calculated:	56.02	3.96	10.31	14.00
Found:	56.1	3.8	10.2	13.9

IR Spectrum ($CHCl_3$):	
C=O	1799, 1723 cm^{-1}
aromatics	1608 cm^{-1}
+	1594 cm^{-1} (m)
NO_2	1545 cm^{-1} (F)
	1497 cm^{-1}

EXAMPLE 7

4-(4,4-dimethyl-5-imino-2-oxo-1-imidazolidinyl)-2-trifluoromethylbenzonitrile

A solution of 10 g of 4-cyano-3-trifluoromethyl-aniline (described in European Paten No. 0,002,892) in 30 ml of ethyl acetate was added at 0 to 5° C. to 33.6 ml of a toluene solution of 1.93 M/1 of phosgene and after stirring at 0 to 5° C. for 30 minutes, the temperature was raised to 25° C. The mixture was distilled while introducing fresh toluene maintaining to constant level for compensate the distilled volume of toluene until a temperature of about 110° C. was reached. The mixture was held at reflux until the disengagement of hydrogen chloride ceased (4 ½ hours). The temperature returned to room temperature and the white solid was dried over sodium sulfate and was rinsed with toluene 3 times. The organic phase was evaporated to dryness under reduced pressure, heated at60° C. for one hour and then cooled under argon to obtain 11.6 g of 4-isocyanate of 2-trifluoromethyl-benzonitrile.

IR Spectrum:	
—NC=O	2268 cm^{-1}
—CN	2233 cm^{-1}

A solution of 6.6 g of 4-isocyanate of 2-trifluoromethyl-benzonitrile in 10 ml of dichloroethane was added at 5° C. to a solution of 2.63 g of 2-amino-2-cyano-propane and 36 ml of dichloroethane and 0.9 ml of triethylamine and after stirring 16hours at room temperature, the mixture was evaporated to dryness. The 7.7 g of residue were chromatographed on silica and eluted with a 85-15 methylene chloride-acetone mixture to obtain 3.54 g of the desired product melting at 228° C. An analytical sample was prepared by crystallizing 300 mg from isopropanol to obtain 267 mg of the product melting at 228° C.

Analysis: $C_{13}H_{11}F_3N_4O$; molecular weight = 296.25				
	% C	% H	% F	% N
Calculated:	52.71	3.74	19.24	18.91
Found:	52.7	3.6	19.1	18.6

IR Spectrum (Nujol):	
NH/OH	3340, 3290 cm^{-1}
CN	2240 cm^{-1}
C=O	1760 cm^{-1}
C=N	1655 cm^{-1}
aromatics	1606, 1570, 1502 cm^{-1}

EXAMPLE 8

4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-trifluoromethylbenzonitrile

A solution of 2.76 g of the product of Example 7 and 60 ml of 0.5 hydrochloric acid was refluxed for 35 minutes and was poured into 100 g of water and ice. The mixture was extracted with ethyl acetate and the organic phase was washed with water, dried and evaporated to dryness under reduced pressure to obtain 2.70 g of the desired product melting at 210° C. An analytical sample was obtained by crystallizing 440 mg of product from isopropanol to obtain 383 mg of product melting at 210° C. to 211° C.

Analysis: $C_{13}H_{10}F_3N_3O_2$; molecular weight = 297.24				
	% C	% H	% F	% N
Calculated:	52.53	3.39	19.17	14.14

-continued

Analysis: $C_{13}H_{10}F_3N_3O_2$; molecular weight = 297.24				
	% C	% H	% F	% N
Found:	52.4	3.2	19.4	13.9

IR Spectrum ($CHCl_3$):	
CN	2245 cm^{-1}
C=O	1788, 1722 cm^{-1}
aromatics	1610, 1572, 1502 cm^{-1}
NH (max)	3340 cm^{-1}

EXAMPLE 9

3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2,4-dioxo-1-imidazolidine acetic acid

A solution of 600 mg of the product of Example 8 in 6 ml of dimethylformamide was added with stirring over 15 minutes to a suspension of a 50% suspension of 210 mg of sodium hydride in oil in 3 ml of dimethylformamide and after the addition of 290 mg of bromoacetic acid, the mixture was stirred for 16 hours at room temperature. After another 105 mg of sodium hydride were added, 145 mg of bromoacetic acid were added to the mixture which was stirred for 30 minutes and then poured into a mixture of 50 ml of water and 5 ml of 2N hydrochloric acid. The mixture was extracted with ether and the organic phase was washed with saturated aqueous sodium chloride, dried, filtered and evaporated to dryness under reduced pressure. The 1.22 g of residue were chromatographed on silica and eluted with a 90-10-0.5 methylene chloride-methanol-acetic acid mixture to obtain 367 mg of the desired product.

IR Spectrum:	
CN	2238 cm^{-1}
C=O hydantoin & acid	1784, 1725, 1710 cm^{-1}
aromatic	1616, 1580, 1508 cm^{-1}

Ultra-violet Spectrum:		
ETOH - 0.1N HCl	max 258 nm	ϵ = 13,300
	inflex 277 nm	ϵ = 5,000
	inflex 285 nm	ϵ = 2,600
ETOH 0.1N NaOH	max 287 nm	ϵ = 19,100
	max 342 nm	ϵ = 1,900

EXAMPLE 10

Ethyl3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2,4-dioxo-1-imidazolidine-acetate

A solution of 600 mg of the product of Example 8 in6 ml of dimethylformamide was added to a 50% suspension of 100 mg of sodium hydride in oil and 3 ml of dimethylformamide and after stirring for 15 minutes, 0.25 ml of ethyl bromoacetate was slowly added at less than 30° C. The mixture was stirred for 30 minutes and then was poured into 50 g of a 1—1 ice-water mixture. 0.5 g of monopotassium phosphate was added and the mixture was extracted with ether. The organic phase was washed with water, dried and evaporated to dryness to obtain 1.1 g of residue which was chromatographed on silica and eluted with 97-3 methylene chloride-acetone to obtain 709 mg of the desired product melting at 152° C. An analytical sample was prepared by crystallization from isopropanol to obtain 667 mg of the desired product melting at 152° C.

Analysis: $C_{17}H_{16}N_3F_3O_4$; molecular weight = 383.33				
	% C	% H	% F	% N
Calculated:	53.21	4.21	14.83	10.96
Found:	53.3	4.0	14.9	10.8

IR Spectrum ($CHCl_3$):	
CN	2225 cm^{-1}
imidazolidine	1786, 1729 cm^{-1}
COOEt	1751 cm^{-1}
aromatics	1616, 1572, 1505 cm^{-1}

EXAMPLE 11

4-(5-imino-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

2.23 of 1-trifluoromethyl-4-amino-benzonitrile (described in European Patent No. 0,002,892)were slowly added to a solution of 22 ml of distilled water and 1 ml of thiophosgene and after stirring for one hour, the mixture was extracted with chloroform. The organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness under reduced pressure to obtain 3 g of isocyanate product which as used as is.

A mixture of the 3 g of product, 1.33 ml of 2-methylamino-2-cyano-propane, 23 ml of tetrahydrofuran and 0.23 ml of triethylamine was refluxed for 40 minutes and was evaporated to dryness. The 3.07 g of residue were chromatographed on silica and eluted with a 1—1 cyclohexane-ethyl acetate mixture and then a 95-5 methylene chloride-acetone mixture to obtain 2.83 g of product which was crystallized from isopropanol to obtain 2.63 g of the desired product melting at 173° C. to 174° C.

Analysis: $C_{14}H_{13}F_3N_4S$; molecular weight = 326.35					
	% C	% H	% F	% N	% S
Calculated:	51.53	4.01	17.17	17.46	9.82
Found:	51.7	3.9	17.2	17.2	9.9

IR Spectrum:	
C=NH	3308, 1679 cm^{-1}
C=S + aromatics	1608, 1575, 1505, 1488 cm^{-1}
CN	2230 cm^{-1}
CF_3	1185 cm^{-1}

EXAMPLE 12

4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

A mixture of 2.21 g of the product of Example 11and 44 ml of 0.5 N hydrochloric acid was refluxed with stirring for one hour and was then poured into 200 g of an ice-water (1—1) mixture. The mixture was extracted with methylene chloride and the organic phase was washed with saturated aqueous sodium chloride, dried and evaporated to dryness. The residue was chromatographed on silica and eluted with a 1—1cyclohexane-ethyl acetate mixture to obtain 2.1 g of product melting

at171° C. which was crystallized from isopropanol to obtain 1.99 g of the desired product melting at 171° C.

Analysis: $C_{14}H_{12}F_3N_3OS$; molecular weight = 327.33

	% C	% H	% F	% N	% S
Calculated:	51.37	3.69	12.84	17.41	9.79
Found:	51.4	3.5	12.7	17.6	10.79

IR Spectrum ($CHCl_3$):

C=O	1761, 1756 cm^{-1}
aromatics	1610, 1578, 1505 cm^{-1}
CN	2230 cm^{-1}
CF_3	1178 cm^{-1}

EXAMPLE 13

4-(2,5-dithioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

A mixture of 839 mg of the product of Example 12, 518 mg of Lawesson reagent and 4.7 ml of toluene was refluxed for 24 hours and was then evaporated to dryness under reduced pressure. The 1.36 g of residue were chromatographed on silica and eluted with a 99-1 methylene chloride-ethyl acetate mixture and then an 85-15 cyclohexane-ethylacetate mixture to obtain 783 mg of product which was crystallized from isopropanol to obtain 690 mg of the desired product melting at 211° C. to 212° C.

Analysis: $C_{14}H_{12}F_3N_3S_2$; molecular weight = 343.40

	% C	% H	% F	% N	% S
Calculated:	48.97	3.52	16.60	12.24	18.67
Found:	49.0	3.4	16.6	12.2	18.6

IR Spectrum ($CHCl_3$):

CN	2230 cm^{-1}
aromatics + conjugated system	1612, 1582, 1508 cm^{-1}
CF_3	1178 cm^{-1}

EXAMPLE 14

4-(4,4-dimethyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

1 g of 2-amino-2-cyano-propane and 1 ml of tetrahydrofuran were added with stirring to a mixture of 2.54 g of the isocyanate product of Example 11, 20 ml of tetrahydrofuran and 0.2 ml of triethylamine at room temperature and was then evaporated to dryness. The 3.5 g of residue were chromatographed on silica and eluted with a 7-3 ethyl acetate-cyclohexane mixture and then a 1—1 ethyl acetate-cyclohexane mixture to obtain 940 mg of the desired product. 300 g were crystallized from isopropanol to obtain 263 mg of product melting at296° C.

Analysis: $C_{13}H_{11}F_3N_4S$; molecular weight = 312.32

	% C	% H	% F	% N	% S
Calculated:	50.00	3.55	18.25	17.94	10.27

-continued

Analysis: $C_{13}H_{11}F_3N_4S$; molecular weight = 312.32

	% C	% H	% F	% N	% S
Found:	49.9	3.4	18.3	17.6	10.4

IR Spectrum (Nujol):

OH/NH	3260 cm^{-1}
CN	2230 cm^{-1}
C=S	1764 cm^{-1}
aromatic + C=C	1612, 1575, 1530, 1501 cm^{-1}

A new preparation was effected using 1,2-dichloroethane in place of tetrahydrofuran to obtain the product in a 60% yield.

EXAMPLE 15

4-(4,4-dimethyl-5-oxo-3-thioxo-1-imidazolidinyl)-1-trifluoromethyl-benzonitrile

A mixture of 635 mg of the product of Example 14 and 14 ml of 0.5 N hydrochloric acid was stirred for one hour at reflux and after cooling, 100 ml of water were added. The mixture was extracted with ethyl acetate and the organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness. The 600 mg of residue were chromatographed and eluted with a 95-5 methylene chloride-acetone mixture to obtain 590 mg of product melting at 190° C. to 191° C. The latter was crystallized from isopropanol to obtain 490 mg of product melting to 190° C. to 191° C.

Analysis: $C_{13}H_{10}F_3N_3OS$; molecular weight = 313.30

	% C	% H	% F	% N	% S
Calculated:	49.84	3.22	18.19	13.41	10.23
Found:	49.6	3.1	18.4	13.2	10.0

IR Spectrum ($CHCl_3$):

=C—NH	3430 cm^{-1}
CN	2230 cm^{-1}
C=O	1766 cm^{-1}
aromatics and conjugated system	1612, 1578, 1505 cm^{-1}

EXAMPLE 16

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-pentyl-2,4-imidazolidine

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazolidien-2,5-dione was reacted with 170 mg of sodium hydride and 0.47 ml of 1-bromo-pentane to obtain after chromatography on silica and elution with an 8-2 methylene chloride-cyclohexane mixture 1.23 g of product which as crystallized from isopropanol to obtain 995 mg of the desired product melting at 84° C.

Analysis: $C_{17}H_{20}O_4F_3N_3$; molecular weight = 387.35

	% C	% H	% F	% N
Calculated:	52.71	5.20	14.71	10.85
Found:	52.8	5.1	14.8	10.7

IR Spectrum ($CHCl_3$):	
C=O	1778, 1723 cm^{-1}
NO_2	1544, 1360 cm^{-1}

EXAMPLE 17

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-nonyl-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazolidine-2,5-dione was reacted with a 50% suspension of 170 mg of sodium hydride in oil and 0.7 ml of 1-bromononane to obtain after chromatography on silica 1.08 g of the desired product melting at 63° C.

Analysis: $C_{21}H_{28}O_4F_3N_3$; molecular weight = 443.46				
	% C	% H	% F	% N
Calculated:	56.87	6.36	12.85	9.48
Found:	57.0	6.5	12.8	9.5

IR Spectrum ($CHCl_3$):	
C=O	1788, 1723 cm^{-1}
NO_2	1544, 1359 cm^{-1}
C=O	1778, 1723 cm^{-1}
NO_2	1544, 1360 cm^{-1}

EXAMPLE 17

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-nonyl-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazolidine-2,5-dione prepared from a 50% suspension of 170 mg of sodium hydride in oil and 0.7 ml of 1-bromononane were reacted to obtain after chromatography on silica 1.08 g of the desired product melting at 63° C.

Analysis: $C_{21}H_{28}O_4F_3N_3$; molecular weight = 443.46				
	% C	% H	% F	% N
Calculated:	56.87	6.36	12.85	9.48
Found:	57.0	6.5	12.8	9.5

IR Spectrum ($CHCl_3$):	
C=O	1788, 1723 cm^{-1}
NO_2	1544, 1359 cm^{-1}

EXAMPLE 18

4-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 1, 300 mg of the product of Example 8 were reacted to obtain 275 mg of the desired product melting at 158° C.

IR Spectrum ($CHCl_3$):	
C=O	1780, 1727 cm^{-1}
aromatics	1615, 1574, 1505 cm^{-1}

-continued

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}

EXAMPLE 19

4-(5-thioxo-2-oxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (product A),
4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl benzonitrile (product B) and
4-(2,5-dithioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (product C)

A suspension of 230 mg of the product of Example 18, 1.4 ml of toluene and 78 mg of Lawesson reagent was refluxed for 9 hours and then returned to room temperature and evaporated to dryness. The 330 mg of residue was chromatographed on silica and eluted with a 99-1 methylenechloride-acetone mixture to obtain in the following order of elution 46 mg of product C with a melting point of 210° C. to 211° C. and a Rf=0.63 (identical to the product of Example 13), 26 mg of product B with a melting point of 170° C. to 171° C. and a Rf=0.49 (identical to the product of Example 12) and 42 mg of product A with a melting point of 194° C. and a Rf=0.34.

Analysis for Product A

IR Spectrum ($CHCl_3$):	
C=O	1760 cm^{-1}
CN	2235 cm^{-1}
aromatics	1615, 1580, 1508 cm^{-1}

UV Spectrum (ethanol):		
max	228 nm	ϵ = 19,400
	256 nm	ϵ = 12,100
	298 nm	ϵ = 8,600
	390 nm	ϵ = 70

EXAMPLE 20

4-(4,5-dihydro-4,4-dimethyl-2-methylthio-5-oxo-1H-imidazolidin-1-yl)-2-trifluoromethyl benzonitrile

A solution of 626 mg of the product of Example 15 in 6 ml of dimethylformamide was added to a 50% suspension of 108 mg of sodium hydride in oil and 1.8 ml of dimethylformamide and after rinsing with 0.3 ml of dimethylformamide, the mixture was stirred for 10 minutes after cessation of hydrogen evolution. A mixture of 0.19 ml of methyliodide in 1 ml of dimethylformamide was added dropwise and after 45 minutes of reaction, the mixture was poured into 50 g of an ice-water mixture containing 0.5 g of monosodium phosphate. The mixture was extracted4times with ether and the combined organic phases were washed with aqueous sodium chloride, dried over magnesium sulfate and evaporated to dryness. The 668 mg of residue were chromatographed on silica and eluted with a 95-5 dichloromethane-ethyl acetate mixture to obtain 640mg of the desired product which chromatographed again on silica. Elution with a 7-3 cyclohexane-ethyl acetate mixture yielded after taking up in ether 507mg of the desired product melting at62° C.

IR Spectrum:	
C=O	1747 cm^{-1}
C=N and aromatics	1614, 1581, 1563, 1503 cm^{-1}

UV Spectrum (ethanol):		
max	209 nm	ϵ = 26,000
inflex.	236 nm	ϵ = 11,500
inflex.	264 nm	ϵ = 8,700

EXAMPLE 21

4-(4,5-dihydro-4,4-dimethyl-5-oxo-2-benzylthio)-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile

A solution of 313 mg of 4-(4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile in 3 ml of dimethylformamide were added to a suspension of 53 mg of sodium hydride in oil and 0.5 ml of dimethylformamide and after stirring for 10 minutes, 0.1 ml of benzyl bromide were added. The mixture was stirred for 30 minutes and then poured into an ice-water mixture containing 500 mg of monosodium phosphate. The mixture was extracted with ether and the organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness. The 450 mg of residue were chromatographed on silica and eluted with a 97.5-2.5 methylene chloride-ethyl acetate mixture to obtain 316mg of the desired product with a RF=0.38.

	Analysis:			
	%C	%H	%F	%N
Calculated:	59.54	4.0	14.12	10.41
Found:	59.6	4.0	14.1	10.2

IR Spectrum ($CHCl_3$):	
C=O	1746 cm^{-1}
CN	2236 cm^{-1}
aromatics and conjugated system	1614, 1580, 1570, 1503, 1499 cm^{-1}

EXAMPLE 22

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-imino-2-thioxo-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile

8 ml of ethanoline were added dropwise at 20° C. to 30° C. to 12.3 ml of the cyanhydrin of acetone and after stirring for 18 hours, the mixture was distilled to obtain 2.3 g of a mixture of 2-(2-hydroxyethyl)-amino-2-methyl-propanenitrile and 2,2-dimethyloxazolidine which was used as is for the next step.

A mixture of 1.18 g of the said mixture, 2.11 g of the isothiocyanate of Example 11 and 20 ml of tetrahydrofuran and 0.5 ml of triethylamine was refluxed for 30 minutes and then evaporated to dryness. The residue was chromatographed on silica and eluted with a 95–5 methylene chloride-acetone mixture to obtain 1.26 g of the desired product and 686 mg of N-(4-cyano-2-trifluoromethyl-phenyl)-2,2-dimethyl-3-oxazolidine carbothioamide. The 686 mg were dissolved in 10 ml of ethyl acetate and after the addition of 30 ml of cyclohexane, the mixture was concentrated to 4 ml and vacuum filtered and dried to obtain another 518 mg of product. The raw product was dissolved in 20 ml of isopropanol and the solution was concentrated to 5 ml, vacuum filtered and dried to obtain 1.04 g of the desired product melting at 181° C.

	Analysis:				
	%C	%H	%F	%N	%S
Calculated:	50.55	4.24	16.00	15.72	9.00
Found:	50.4	4.1	15.9	15.6	9.0

IR Spectrum ($CHCl_3$):	
OH	3630 cm^{-1}
=NH	3314, 1677 cm^{-1}
CN	2230 cm^{-1}
aromatics	1611, 1576, 1504 cm^{-1}

EXAMPLE 23

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile (Product A) and 4-(4,4-dimethyl-2,5-dioxo-3-(2-mercaptoethyl) 1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (Product B)

A mixture of 680 mg of the product of Example 22, 7 ml of water and 7 ml of hydrochloric acid was refluxed for 10 minutes and after cooling to room temperature, the mixture was extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness. The residue was chromatographed on silica and eluted with a 1—1 cyclohexane-ethyl acetate mixture to obtain 119 mg of product B with a Rf=0.35 and 569 mg of product A with a Rf=0.14 and a melting point of ≃130° C.

Analysis: $C_{15}H_{14}F_3N_3O_2S$; molecular weight = 357.36					
	%C	%H	%F	%N	%S
Calculated:	50.42	3.95	15.95	11.76	8.97
Product A					
Found:	50.7	4.0	15.7	11.5	9.1
Product B					
Found:	50.6	3.8	15.9	11.6	9.1

IR Spectrum ($CHCl_3$):	
Product A:	
OH	3626 cm^{-1}
CN	2236 cm^{-1}
C=O	1763 cm^{-1}
aromatics	1615, 1578, 1504 cm^{-1}
Product B:	
Absence of OH	
CN	2228 cm^{-1}
C=O	1780, 1726 cm^{-1}
aromatics	1615, 1578, 1505 cm^{-1}

Using 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile of Example 8 and the appropriate reactants, the following products were prepared.

EXAMPLE 24

4-(4,4-dimethyl-2,5-dioxo-3-ethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile with a melting point of 100° C. to 101° C.

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Analysis: $C_{15}H_{14}F_3N_3O_2$; molecular weight = 325.29				
	%C	%H	%F	%N
Calculated:	55.39	4.34	17.52	12.92
Found:	55.7	4.3	17.6	12.8

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}
C=O	1777, 1724 cm^{-1}
aromatics	1617, 1575, 1505 cm^{-1}

EXAMPLE 25

4-(4,4-dimethyl-2,5-dioxo-3-(2-propenyl)-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 109° C. to 110° C.

Analysis: $C_{16}H_{14}F_3N_3O_2$; molecular weight = 337.35				
	%C	%H	%F	%N
Calculated:	56.97	4.18	16.90	12.46
Found:	57.0	4.1	16.2	12.3

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}
C=O	1728, 1725 cm^{-1}
$HC=CH_2$	1645 cm^{-1}
aromatics	1616, 1575, 1505 cm^{-1}

EXAMPLE 26

4-(4,4-dimethyl-2,5-dioxo-3-benzyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 98° C. to 99° C.

Analysis: $C_{20}H_{16}F_3N_3O_2$; molecular weight = 387.36				
	%C	%H	%F	%N
Calculated:	62.01	4.16	14.71	10.85
Found:	62.0	4.1	14.7	10.8

IR Spectrum ($CHCl_3$): C—NH: 3430 cm^{-1}	
CN	2238 cm^{-1}
C=O	1779, 1724 cm^{-1}
aromatics	1615, 1605, 1575, 1504, 1497 cm^{-1}

EXAMPLE 27

4-(4,4-dimethyl-2,5-dioxo-3-(4-fluorobenzyl)-1-imidazolidinyl-2-trifluoromethyl-benzonitrile melting at 101°° C. to 102° C.

Analysis: $C_{20}H_{15}F_4N_3O_2$; molecular weight = 405.35				
	%C	%H	%F	%N
Calculated:	59.26	3.73	18.75	10.37
Found:	59.1	3.5	18.9	10.3

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}
C=O	1780, 1724 cm^{-1}
aromatics	1615, 1612, 1505 cm^{-1}

EXAMPLE 28

4-(4,4-dimethyl-2,5-dioxo-3-(4-methoxybenzyl)-1-imidazolidinyl-benzonitrile melting at 95° C. to 96° C.

Analysis: $C_{21}H_{18}F_3N_3O_3$; molecular weight = 417.39				
	%C	%H	%F	%N
Calculated:	60.43	4.35	13.65	10.07
Found:	59.1	3.5	18.9	10.3

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}
C=O	1778, 1723 cm^{-1}
aromatics	1615, 1584, 1514, 1505 cm^{-1}

EXAMPLE 29

4-(4,4-dimethyl-2,5-dioxo-3-(4-trifluoromethyl-benzyl)-1-imidazolidinyl)-2-trifluoromethyl benzonitrile melting at ≈89° C. to 90° C.

Analysis: $C_{21}H_{15}F_6N_3O_2$; molecular weight = 313.30				
	%C	%H	%F	%N
Calculated:	55.39	3.32	25.03	9.23
Found:	55.2	3.2	25.3	9.2

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}
C=O	1615, 1505 cm^{-1}
aromatics	1615, 1505 cm^{-1}

EXAMPLE 30

4-(4,4-dimethyl-2,5-dioxo-3-(2-epoxymethyl)-1-imidazolidinyl 2-trifluoromethyl-benzonitrile melting at 112° C. to 113° C.

Analysis: $C_{16}H_{14}F_3N_3O_3$; molecular weight = 353.30				
	%C	%H	%F	%N
Calculated:	54.39	3.99	16.13	11.89
Found:	54.7	4.0	16.1	11.8

IR Spectrum ($CHCl_3$):	
CN	2235 cm^{-1}
C=O	1781, 1725 cm^{-1}
aromatics	1615, 1576, 1505 cm^{-1}

EXAMPLE 31

4-(4,4-dimethyl-2,5-dioxo-3-propyl-1H-imidazolidinyl)-2-trifluoromethyl benzonitrile melting at 113° C. to 114° C.

Analysis: $C_{16}H_{16}F_3N_3O_2$; molecular weight = 339.32				
	%C	%H	%F	%N
Calculated:	56.64	4.75	16.80	12.38
Found:	56.7	4.7	16.7	12.2

IR Spectrum ($CHCl_3$):	
CN	2236 cm^{-1}
C=O	1778, 1725 cm^{-1}
aromatics	1616, 1505 cm^{-1}

EXAMPLE 32

4-(4,4-dimethyl-2,5-dioxo-3-isopropyl-1-imidazolidinyl)-2-trifluoromethyl benzonitrile melting at 138° C. to 139° C.

Analysis: $C_{16}H_{16}F_3N_3O_2$; molecular weight = 339.32				
	%C	%H	%F	%N
Calculated:	56.64	4.75	16.80	12.38
Found:	56.5	4.7	17.1	12.3

IR Spectrum ($CHCl_3$):	
CN	2236 cm^{-1}
C=O	1778, 1724 cm^{-1}
aromatics	1616, 1575, 1505 cm^{-1}

Using 4-(4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile of Example 15 and the appropriate reactants, the following compounds were prepared:

EXAMPLE 33

4-(4,5-dihydro-4,4-dimethyl-2-nonylthio-5-oxo-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile were a Rf=0.35 (97.5–2.5 methylene chloride-ethyl acetate eluant).

EXAMPLE 34

4-(4,5-dihydro-4,5-dimethyl-2-(3-hydroxypropylthio)-5-oxo-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile with a Rf=0.17 (8–2 methylene chloride-ethyl acetate eluant).

EXAMPLE 35

Ethyl [1-(4-cyano-3-trifluoromethyl-phenyl)-4,5-dihydro-4,4-dimethyl-5-oxo-1H-imidazol 2-yl)-thio]-acetate with a Rf=0.20 (65–35 cyclohexane-ethyl acetate eluant).

Using the isocyanate of Example 11 and the appropriate reactants, the following compounds were prepared.

EXAMPLE 36

4-(4,4-dimethyl-3-ethyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile with a Rf=0.16 (95-5 methylene chloride-acetone eluant).

EXAMPLE 37

4-(4,4-dimethyl-5-imino-3-pentyl-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile with a RF=0.35 (8-2 ethyl acetate-cyclohexane eluant)

Using the 4-(4,4-dimethyl-3-ethyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile of Example 36 and the 4-(4,4-dimethyl-5-imino-3-pentyl-2-thioxo-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile of Example 37 and 0.5 N hydrochloric acid, the following compounds were prepared.

EXAMPLE 38

4-(4,4-dimethyl-3-ethyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile with a Rf=0.38 (1—1 ethyl acetate-cyclohexane eluant).

EXAMPLE 39

4-(4,4-dimethyl-5-oxo-3-pentyl-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile with a melting point of 78° C. and a Rf=0.66 (8-2 ethyl acetate-cyclohexane eluant)

Using 4-(4,5-dihydro-4,4-dimethyl-2-methylthio-5-oxo-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile of Example 20 and 4-(4,5-dihydro-4,4-dimethyl-5-oxo-2-benzylthio-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile of Example 21 and the Lawesson reagent, the following compounds were prepared.

EXAMPLE 40

4-(4,5-dihydro-4,4-dimethyl-2-methylthio-5-thioxo-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile with a Rf=0.36 (97.5-2.5 methylene chloride-ethyl acetate eluant).

EXAMPLE 41

4-(4,5-dihydro-4,4-dimethyl-2-benzylthio-5-thioxo-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile with a Rf=0.62 (98-2 methylene chloride-ethyl acetate eluant).

EXAMPLE 42

3-(4-cyano-3-trifluoromethyl-penyl)-5,5-dimethyl-2,4-dioxo-N-methyl-N-isopropyl-1-imidazolidine acetamide

0.1 ml of N-methyl-morpholine was added to a suspension of 3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2,4-dioxo-1-acetic acid in 4 ml of methylene chloride and after cooling the solution to −10° C., 0.1 ml of isobutyl chloroformate was added dropwise. After stirring for 25 minutes at −10° C., 0.15 ml of N-methyl-N-isopropylamine was added and the mixture was allowed to return to room temperature over 40 minutes. 5 ml of an aqueous saturated sodium bicarbonate solution were added and after stirring for 30 minutes, the mixture was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The residue was chromatographed on silica and eluted with a 96-4 methylene chloride-acetone mixture to obtain 147 mg of the desired product.

IR Spectrum ($CHCl_3$):	
CN	2236 cm^{-1}
hydantoin C=O	1783, 1728 cm^{-1}
amide C=O	1661 cm^{-1}

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-continued

IR Spectrum ($CHCl_3$):	
aromatics	1615, 1575, 1505 cm^{-1}

EXAMPLE 43

4-(4,4-dimethyl-2,5-dioxo-3-(2-hydroxyethyl)-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile

Using the procedure of Example 9, 900 mg of the product of Example 8 and 1.91 g of 2-bromoethane tert.-butyldimethylsilyl ether were reacted to obtain 1 g of the silyloxy ether derivative melting at 86° C. to 87° C. after chromatography on silica and elution with a 7 g cyclohexane-ethyl acetate mixture.

1 ml of 2 N hydrochloric acid were added to a mixture of 380 mg of the silyloxy ether, 4 ml of methanol and 1 ml of methylene chloride and after stirring for 40 minutes at room temperature,the mixture was poured into 15 ml of water and was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness and the residue was chromatographed on silica. Elution with a 7-3 methylene chloride-ethyl acetate mixture yielded the desired product which after crystallization from isopropanol melted at 109° C. to 110° C. and had a Rf=0.9.

	Analysis:			
	%C	%H	%F	%N
Calculated:	52.79	4.23	16.70	12.31
Found:	52.5	4.2	16.7	12.1

EXAMPLE 44

Using the procedure of Example 43, 2-bromopropanol tert.-butyldimethylsilyl ether was reacted to obtain 4-(4,4-dimethyl-2,5-dioxo-3-(3-hydroxypropyl) 1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 131° C. to 132° C. and a Rf=0.13 (3-1 methylene chloride-ethyl acetate eluant).

EXAMPLE 45

4-[3-(2-acetyloxyethyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]2-trifluoromethyl-benzonitrile

A mixture of 215 mg of the product of Example 43, 15 mg of 4-dimethylamino-pyridine, 1 ml of pyridine and 0.5 ml of acetic acid anhydride was stirred at room temperature for 30 minutes and was then poured into 20 ml of a saturated aqueous sodium bicarbonate solution. After stirring for 20 minutes, the mixture was extracted with ethyl acetate. The organic phase was washed with water and evaporated to dryness and the pyridine and residual acetic acid were distilled. The residue was chromatographed on silica and eluted with a 65-35 methylene chloride-ethyl acetate mixture. The residue with a Rf=0.35 was taken up in isopropanol, partially concentrated, iced and vacuum filtered to obtain after drying 210 mg of the desired product melting at 99° C. to 100° C.

	Analysis:			
	%C	%H	%F	%N
Calculated:	53.27	4.21	14.87	10.96
Found:	53.5	4.3	15.2	10.9

Using the above procedure, the following products were prepared.

EXAMPLE 46

4-(4,4-dimethyl-2,5-dioxo-3-(5-hydroxypentyl)-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile melting at 101° C. to 102° C.

EXAMPLE 47

4-(4,4-dimethyl-2,5-dioxo-3-(2-methoxyethyl)-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile melting at 68° C. to 69° C.

EXAMPLE 48

4-(4,4-dimethyl-2,5-dioxo-3-cyanomethyl-1-imidazolidinyl)-2-trifluoromethyl benzonitrile melting at 186° C. to 187° C.

EXAMPLE 49

4-(4,4-dimethyl-2,5-dioxo-3-[(1,3-dioxolan-2-yl)-methyl]-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile melting at 135° C. to 136° C.

EXAMPLE 50

4-(4,4-dimethyl-2,5-dioxo-3-(2-chloroethyl)-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile melting at 120° C. to 121° C.

EXAMPLE 51

1-(3,4-dichlorophenyl)-5-imino-3,4,4-trimethyl-2-imidazolidine thione

A mixture of 2.4 g of the isocyanate of 3,4-dichlorophenyl, 1.3 ml of 2-methylamino-2-cyano-propane, 23 ml of tetrahydrofuran and 0.23 ml of triethylamine was refluxed for 16 hours and then evaporated to dryness under reduced pressure. The residue was chromatographed on silica and eluted with a 96-4 methylene chloride-acetone mixture to obtain after crystallization from ether, 2.54 g of the desired product melting at 133° C.

EXAMPLE 52

3-(3,4-dichlorophenyl)-2-thioxo-1,5,5-trimethyl-1-imidazolidinone

A suspension of 1.88 g of the product of Example 51 in 14 ml of 6 N hydrochloric acid was refluxed for 45 minutes and after the addition of another 14 ml of 6 N hydrochloric acid, the mixture was refluxed for 2 more hours. Another 4 ml of 6 N hydrochloric acid were added and the mixture was refluxed for 90 minutes and then returned to room temperature. 100 g of ice were added and the mixture was extracted with ethyl acetate. The organic phase was washed with water, dried and evaporated to dryness. The residue was chromatographed on silica and eluted with a 1—1 cyclohexane-ethyl acetate mixture to obtain 1.84 g of the desired product melting at 129° C. after crystallization from isopropanol.

Analysis: $C_{12}H_{12}Cl_2N_2OS$; molecular weight = 303.21					
	%C	%H	%Cl	%N	%S
Calculated:	47.54	3.99	23.38	9.24	10.57
Found:	47.5	3.8	23.2	9.3	10.5

IR Spectrum ($CHCl_3$):	
C=O	1753 cm^{-1}
C=S + aromatics	1595, 1570, 1496 cm^{-1}

Using the above procedures, the following compounds were prepared:

EXAMPLE 53

3-(3,4-dichlorophenyl)-3,5-dihydro-5,5-dimethyl-2-methylthio-4H-imidazol 4-one melting at 110° C.

EXAMPLE 54

1-(3,4-dichlorophenyl)-3,4-4-trimethyl-2,5-imidazolidine-dithione melting at ≈146° C.

EXAMPLE 55

1-(4-chloro-3-trifluoromethyl-phenyl)-4,4-dimethyl-2-thioxo-5-imidazolidinone melting at 176° C.

EXAMPLE 56

1-(4-chloro-3-trifluoromethyl-phenyl)-4,4-dimethyl-5-imino-2-imidazolidinethione melting at 173° C. to 174° C.

EXAMPLE 57

3-(3,4-dichlorophenyl)-3,5-dihydro-5,5-dimethyl-2-benzylthio 4H-imidazol-4-one

IR Spectrum ($CHCl_3$):	
C=O	1736 cm^{-1}
CN + aromatics	1578, 1496 cm^{-1}

EXAMPLE 58

4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxy butyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

a) Condensation

600 mg of 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl) benzonitrile obtained as in Example 8—in 5 ml of dimethylformamide were added to a suspension of 104 mg of sodium hydride in 0.8 ml of dimethylformamide, while maintaining the temperature below 20° C. After 10 minutes of stirring, 445 mg of 4-chloro-t-butyl-dimethylsilylether and 300 mg of sodium iodide were added. The mixture was heated for 16 hours at 50° C. and then, cooled to ambient temperature. 87 mg of sodium hydride were added followed by another 400 mg of the chlorinated ether and 267 mg of sodium hydride were added. The mixture was heated for another hour and then, returned to ambient temperature, and poured into 60 ml of water containing 600 mg of monopotassium phosphate. Extraction was carried out with ether and the organic phase was washed with water, dried and the solvent was evaporated. The residue was chromatographed on silica (eluant: methylene chloride—acetone (99-1)) to obtain 526 mg of product which as used as is for the stage following the cleavage.

The said product was mixed in 5 ml of methanol and 1.5 ml of 2 N hydrochloric acid and the mixture was stirred for 40 minutes at ambient temperature. The mixture was poured into 30 ml of water and was extracted with methylene chloride. The organic phase was washed with water, dried and the solvent was evaporated. After chromatographing the residue on silica (eluant methylene chloride—acetone (9-1), the fractions with a Rf=0.15, were recovered, and after crystallization from isopropyl ether, 307 mg of the expected product melting at 102°-103° C. were obtained.

Analysis: $C_{17}H_{18}F_3N_3O_3$; molecular weight = 369.35				
	C%	H%	F%	N%
Calculated	55.28	4.91	15.43	11.38
Found	55.2	4.9	15.3	11.1

IR Spectrum ($CHCl_3$);	
OH	3628 cm^{-1}
C≡N	2236 cm^{-1}
C=O	1778-1724 cm^{-1}
Aromatics	1615-1575-1505 cm^{-1}

Preparation of the 4-chloro t-buryl dimethylsilylether used at the start of Example 58.

9.9 ml of 4-chloro-1-butanol and 24.3 g of imidazole in 50 ml of tetrahydrofuran were stirred and 2.82 g of terbutyldimethylsilyl chloride in 20 ml of tetrahydrofuran were added dropwise at a temperature of less than 20° C. The mixture was stirred for 18 hours at ambient temperature, followed by separating, rinsing with tetrahydrofuran and eliminating the solvent under reduced pressure. The residue was purified by chromatography on silica (eluant: cyclohexane—ethyl acetate (95-5)) to obtain 17.5 g of the expected product.

EXAMPLE 59

(1,1-dimethyl) ethyl 3-(4-cyano 3-trifluoro-methyl-phenyl)5,5-dimethyl 2,4-dioxo-1-imidazolidine acetate

450 mg of the product of Example 8—in solution in 4 ml of dimethylformamide were added to a suspension of 78 mg of sodium hydride at 50% in oil and 0.5 ml of dimethylformamide. The mixture was stirred for 15 minutes and then without exceeding 30° C., 0.22 ml of terbutyl bromoacetate were slowly added. The mixture was stirred for 16 hours and then, was poured into 50 g of a water and ice mixture (1—1). 0.5 g of monopotassium phosphate were added and extraction was carried out with ether. The organic phase was washed with water, dried and evaporated to dryness. The 1.1 g of crude product was chromatographed on silica (eluant: methylene chloride—acetone (99-1)) to obtain 425 mg of the expected product melting at 122°-123° C. with a Rf=0.28 (eluant: methylene chloride—acetone (99-1))

IR Spectrum ($CHCl_3$);	
C=O	1788-1729 cm^{-1} (hydantoin) 1745 cm^{-1} (ester)
C≡N	2235 cm^{-1}
Aromatics	1616-1505 cm^{-1}

UV Spectrum (EtOH)
Max. 258 nm = 16100
Infl. 277 nm = 6000
Infl. 285 nm = 3000

EXAMPLE 60

cyclopentyl 3-(4-cyano-3-trifluoromethyl phenyl)-5,5-dimethyl 2,4-dioxo 1-imidazolidine acetate

A solution of 355 mg of the product of Example 9,—49 mg of 4-dimethylamino-pyridine 130 mg of cyclopentanol and 6.5 ml of methylene chloride was cooled to −10° C. and then 226 mg of dicyclohexylcarbodiimide in 2 ml of methylene chloride were added. The mixture was allowed to return to ambient temperature, stirred for 25 minutes, heated at reflux for 2 hours, returned to ambient temperature, filtered and the solvent was evaporated. The residue was chromatographed on silica (eluant: methylene chloride—acetone (99-1)) to obtain 281 mg of the expected product with a Rf=0.25 (eluant: methylene chloride—acetone (99-1))

IR Spectrum ($CHCl_3$);	
C=O	1786-1729 cm^{-1} (hydantoin) 1748 cm^{-1} (ester)
C≡N	2235 cm^{-1}
Aromatics	1615-1602-1576-1505 cm^{-1}

UV Spectrum (EtOH)
Max. 258 nm = 16800
Infl. 276 nm = 5800
Infl. 286 nm = 3000

EXAMPLE 61

ethyl 3-(4-cyano 3-(trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoate

Using the procedure of Example 59, the product of Example 8—and ethyl 4-bromobutyrate were reacted to obtain the expected product melting at 66°–67° C. with a Rf=0.16 (eluant: methylene chloride—acetone (99-1))

IR Spectrum ($CHCl_3$);	
C=O	1770-1726 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1616-1576-1505 cm^{-1}

UV Spectrum (EtOH)
Max. 260 nm = 15500
Infl. 277 nm = 7000
Infl. 286 nm = 3600

EXAMPLE 62

3-(4-cyano 3-trifluoromethyl-phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidine butanoic acid

1 g of the product of Example 61 in 20 ml of methanol was stirred for 3 hours at ambient temperature in the presence of 3 ml of 2 N sodium hydroxide and the mixture was poured into 20 ml of water and acidified to pH=1 using 7 ml of N hydrochloric acid. The mixture was extracted with ether and the extracts were washed with water and dried and the solvents were eliminated under reduced pressure to obtain 863 mg of crude product melting at 179°–180°C. which was purified by chromatography on silica (eluant: methylene chloride—methanol (92.5-7.5)). After crystallization from isopropanol, 614 mg of the expected product melting at 184°–185° C. and with a Rf=0.25 (eluant: methylene chloride—methanol (92.5-7.5)) were obtained.

IR Spectrum (nujol);	
C=O	1770-1753-1735-1712-1690-1645 cm^{-1}
C≡N	2230 cm^{-1}
Aromatics	1613-1587-1533-1502 cm^{-1}

EXAMPLE 63

(1,1-dimethyl) ethyl 3-(4-cyano 3-trifluoro-methyl-phenyl)-5,5-dimethyl 2,4-dioxo-1-imidazolidine-butanoate

By carrying out the esterification of the product of Example 62, with terbutanol in the presence of dicyclohexylcarbodiimide and 4-dimethylamino-pyridine as in Example 60, the expected product melting at 96°–97° C. with a Rf=0.32 (eluant: methylene chloride—acetone (98-2)) was obtained.

IR Spectrum ($CHCl_3$);	
C=O	1779-1725 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1616-1576-1505 cm^{-1}

UV Spectrum (EtOH)
Max. 261 nm = 15600
Infl. 276 nm = 7800
Infl. 286 nm = 3700

EXAMPLE 64

cyclopentyl 3-(4-cyano 3-trifluoromethyl-phenyl) 5,5-dimethyl-2,4-dioxo-1-imidazolidine butanoate

Using the procedure of Example 63, cyclopentanol was reacted to obtain the expected product melting at 85°–86° C. with a Rf=0.33 (eluant: methylene chloride—acetone (98-2)).

IR Spectrum ($CHCl_3$)	
C=O	1779-1728 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1616-1578-1505 cm^{-1}

UV Spectrum (EtOH)
Max. 261 nm = 16000
Infl. 277 nm = 7600
Infl. 286 nm = 3700

EXAMPLE 65

4-(4,4-dimethyl-2,5-dioxo 3-(2-(4-fluorophenylthio) ethyl)-1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile

a) Formation of the phenolate

0.16 ml of 4-fluorothiophenol in 1.6 ml of dimethylformamide were added at a temperature of less than 28° C. to a suspension of 80 mg of sodium hydride in 0.5 ml of dimethylformamide, and the solution was stirred for 10 minutes.

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b) Substitition

548 mg of 4-[4,4-dimethyl-2,5-dioxo-3-(2-chloroethyl) 1-imidazolidinyl]-2-(trifluoromethyl) benzonitrile (Example 50—in solution in 4 ml of dimethylformamide were added to the solution of a) and the mixture was stirred for 2 hours, poured into 50 ml of water with 0.5 g of monopotassium phosphate. Extraction was carried out with ether and the organic phase was washed with water and dried and the solvent was evaporated. After chromatographing the residue on silica (eluant: cyclohexane—ethyl acetate (75-25)), 570 mg of the expected product melting at 93°–94° C. with a Rf=0.29 (eluant: cyclohexane—ethyl acetate (75-25)) were obtained.

IR Spectrum ($CHCl_3$)	
C=O	1780-1726 cm^{-1}
C≡N	2238 cm^{-1}
Aromatics	1616-1579-1506 cm^{-1}
(fluorophenyl) thio	1591-1492 cm^{-1}

UV Spectrum (EtOH)
Max. 254 nm = 18600
Infl. 277 nm = 7500
Infl. 286 nm = 4200

EXAMPLE 66

4-(4,4-dimethyl-2,5-dioxo-3-(2-(4-fluorophenyl sulfonyl) ethyl)-1-imidazolidinyl-2-(trifluoromethyl) benzonitrile

1.21 g of metachloroperbenzoic acid in 24 ml of methylene chloride were added dropwise at a temperature of less than 29° C. to 222 mg of the product of Example 65 in 4.4 ml of methylene chloride. After 30 minutes of stirring, the mixture was poured into 30 ml of sodium thiosulfate (0.5 M/1). The mixture was stirred for 10 minutes, followed by decanting and extracting with methylene chloride. The organic phase was washed with a saturated aqueous solution of sodium bicarbonate, then with water, dried, and the solvent was evaporated. After chromatographing the residue on silica (eluant: cyclohexane—ethyl acetate (1—1)), 220 mg of product were obtained which was crystallized from isopropanol to obtain 196 mg of the expected product melting at 155°–156° C. with a Rf=0.22 (eluant: ethyl acetate—cyclohexane (1—1)).

IR Spectrum ($CHCl_3$);	
C=O	1783-1727 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1615-1593-1505-1497 cm^{-1}
SO_2	1314-1150 cm^{-1}

UV Spectrum (EtOH)
Max. 258 nm = 16700
Infl. 286 nm

EXAMPLE 67

4-(4,4-dimethyl 2,5-dioxo 3-(2-((4-fluorophenyl) sulfinyl) ethyl) 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile

222 mg of the product of Example 65 in 15 ml of methanol were stirred for 30 minutes at ambient temperature in the presence of 5 ml of an aqueous solution of sodium metaperiodate (0.1 M/1). The suspension was heated for one hour at 40° C. and 10 ml of methanol and 5 ml of oxidizing solution were added. The methanol was evaporated off and after 10 ml of a saturated solution of sodium chloride were added, extraction was carried out with ethyl acetate. The organic phase was washed with salt water, dried, and the solvent was evaporated. After chromatographing the residue on silica (eluant: methylene chloride—acetone (9-1)), 205 mg of product were obtained which was crystallized from isopropanol to obtain 180 mg of the expected product melting at 145°–146° C. with a Rf=0.10 (eluant: methylene chloride—acetone (9-1)).

IR Spectrum ($CHCl_3$);	
C=O	1782-1727 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1615-1592-1505-1493 cm^{-1}

UV Spectrum (EtOH)	
Max. 258 nm	ε = 17600
Infl. 285 nm	

Using the procedure of the preceding examples, 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile of Example 8—and the appropriate reagents, the compounds of the following examples were obtained:

EXAMPLE 68

4-(4;4-dimethyl 2,5-dioxo 3-((3-methoxyphenyl) methyl) 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile Melting at 88°–89° C. with a Rf=0.21 (eluant: cyclohexane—ethyl acetate (7-3))

IR Spectrum ($CHCl_3$)	
C=O	1779-1724 cm^{-1}
C≡N	2238 cm^{-1}
Aromatics	1614-1602-1588-1575-1504-1491

UV Spectrum (EtOH)	
Max. 260 nm	ε = 16800
Infl. 210 nm	ε = 28500
Infl. 280 nm	ε = 8900

EXAMPLE 69

4-(4,4-dimethyl 2,5-dioxo 3-(2-(4-morpholinyl) ethyl) 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile with a Rf=0.20 (eluant: methylene chloride—acetone (70-30))

IR Spectrum ($CHCl_3$)	
C=O	1779-1725 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1616-1576-1505 cm^{-1}
morpholinyl	1117 cm^{-1}

UV Spectrum (EtOH)	
Max. 261 nm	ϵ = 14000
Infl. 277 nm	ϵ = 6900
Infl. 286 nm	ϵ = 3600

EXAMPLE 70

4-(4,4-dimethyl 3-(2-hydroxyethyl) 5-imino 2-thioxo 1-inidazolidinyl) 2-(trifluoromethyl)-benzonitrile

a) Preparation of the isothiocyanate

2.23 g of 1-trifluoromethyl-4-amino benzonitrile (prepared accord to EP 0002892) were added slowly to a solution of 22 ml of distilled water and 1 ml of thiophosgene and the mixture was stirred for one hour and then extracted with chloroform. The extracts were washed with salt water, dried and evaporated to dryness under reduced pressure to obtain 3 g of product which was used as is for obtaining the imine.

b) Obtaining the imine

5 g of the said isothiocyanate were mixed with 37 ml of tetrahydrofuran in the presence of 1.5 ml of triethylamine and 2.8 g of 2-[(2-hydroxy ethyl) amino] 2-methyl propane nitrile (prepared in Example 22)—in solution in 10 ml of tetrahydrofuran were added all at once. The temperature spontaneously increased to 34° C. and the resultant mixture was allowed to return to ambient temperature while stirring for one hour. The solvent was evaporated off and the residue was chromatographed on silica (eluant: methylene chloride—methanol (7-3)) to obtain 5.87 g of the expected product melting at 181° C., after crystallization from isopropanol.

EXAMPLE 71

4-(4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

4.6 g of the product of Example 70 in 65 ml of methanol was refluxed for one hour in the presence of 10 ml of 2 N hydrochloric acid. The mixture was cooled to ambient temperature and poured into 300 ml of ice-cooled water. Extraction was carried out with ethyl acetate and the organic phase was washed with salt water, dried, and the solvent was evaporated off. The residue was chromatographed on silica (ethyl acetate—cyclohexane (1—1)) and the fractions were collected with a Rf=0.14. After crystallization from methylene chloride and cyclohexane, 4.37 g of the expected product melting at 130° C. were obtained

Analysis; $C_{15}H_{14}F_3N_3O_2S$; molecular weight = 357.36					
	C %	H %	F %	N %	S %
Calculated	50.42	3.95	15.95	11.76	8.97
Found	50.3	3.9	15.9	11.6	8.9

IR Spectrum ($CHCl_3$);	
OH	3626 cm^{-1}
C≡N	2236 cm^{-1}
C=O	1763 cm^{-1}
Aromatics	1615-1578-1504 cm^{-1}

EXAMPLE 72

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-imino-2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl)-5-^{3}H-benzonitrile

a) Preparation of the tritiated benzonitrile

15 mg of 2-trifluoromethyl 4-amino 5-bromo benzonitrile were mixed with 200 µl of ethyl acetate in the presence of 6.5 µl of triethylamine and 2 mg of palladium on activated charcoal and then tritium (1.42 bar) was introduced. After filtering, rinsing with ethyl acetate and evaporating to dryness at ambient temperature, approximately 66.6 G.Bq (1.8 Ci) of product were obtained.

b) Preparation of the tritiated isothiocyanate

150 µl of a 10% solution of thiophosgene in chloroform were added to the above product, in 150 µl of water and the mixture was stirred for 45 minutes at ambient temperature. Dilution was carried out with 0.5 ml of water and 1 ml of chloroform, followed by extraction with chloroform. The solvent was evaporated off under reduced pressure and the residue was taken up in toluene to obtain 50.7 G.Bq (1.37 Ci) of the expected product which was kept at −80° C.

c) Preparation of the tritiated imine

Having eliminated the toluene from the above mixture under reduced pressure, 130 µl of tetrahydrofuran with 1% triethylamine were added and 13 µl of 2-[(2-hydroxyethyl)-amino] 2-methylpropane-nitrile (Example 22)—were added. Then, another 130 µl of tetrahydrofuran with 1% triethylamine were added and the mixture was stirred for 30 minutes at ambient temperature and the solvents were eliminated under reduced pressure.

Preparation of the 2-trifluoromethyl 4-amino 5-bromo benzonitrile used in Example 72.

A solution of 2-trifluoromethyl 4-amino benzonitrile (prepared according to EP 0002892) (5 moles) in 25 ml of methanol was cooled to 0° C. and bomine was added (5.2 moles). The mixture was allowed to return to ambient temperature, stirred for 3 hours, alkalinized with triethylamine and then an aqueous solution of sodium thiosulfate was added. The solvents were eliminated and extraction was carried out with chloroform. The organic phase was washed with water, dried, and the solvent was evaporated to obtain the product which was used as is for the following stage.

IR Spectrum ($CHCl_3$);	
NH_2	3612-3408 cm^{-1}
C≡N	2230 cm^{-1}
Aromatics	1621-1556-1506 cm^{-1}

EXAMPLE 73

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo 1-imidazolidinyl)-2-(trifluoromethyl) 5-^{3}H-benzonitrile

The product of Example 72 in 180 µl of water was heated to 100° C. and 60 µl of 2 N hydrochloric acid was added. The mixture was stirred for 5 minutes at reflux and then approximately 600 mg of ice were added. Extraction is carried out with ethyl acetate and the extracts were washed with salt water and dried to obtain 34.7 G.Bq (937 mCi) of product. After chromatography on silica (eluant: cyclohexane—ethyl acetate (60-40)), 19 G.Bq (513 mCi) of the expected product were obtained.

EXAMPLE 74

4-(4,4-dimethyl-3-hydroxypropyl)-5-imino-2-thioxo-1-imidazolidinyl) 2-(trifluoromethyl)-benzonitrile

Using the procedure of Example 22—2 g of the isothio-cyanate of Example 70 (a) and 1.2 g of the appropriate aminonitrile were reacted to obtain 1.70 g of the expected product with a Rf=0.25 (methylene chloride—acetone (65-35)).

IR Spectrum ($CHCl_3$);	
OH	3630 cm^{-1}
=NH	3314-1676 cm^{-1}
C≡N	2235 cm^{-1}

EXAMPLE 75

4-(4,4-dimethyl-3-(3-hydroxypropyl)-5-oxo-2-thioxo-1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 71, 240 mg of the product of Example 74 were reacted to obtain 226 mg of the expected product melting at 149°-150° C. with a Rf=0.32 (eluant; methylene chloride—acetone (75-25)).

IR Spectrum ($CHCl_3$);	
OH	3626 cm^{-1}
C=O	1763 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1615-1580-1504-1483 cm^{-1}

EXAMPLE 76

4-(4,4-dimethyl 3-(4-hydroxybutyl)-5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 22,—2 g of isothiocyanate and 1.38 g of the appropriate aminoitrile were reacted to obtain 2.08 g of the expected product with a Rf=0.25 (methylene chloride—acetone (65-35)).

IR Spectrum ($CHCl_3$);	
OH	3630 cm^{-1}
=NH	3314-1675 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1614-1577-1504 cm^{-1}

EXAMPLE 77

4-(4,4-dimethyl 3-(4-hydroxybutyl)-5-oxo 2-thioxo-1-imidazolidinyl) 2-(trifluoromethyl) benzonitile

Using the procedure of Example 71, 300 mg of the product of Example 76 were reacted to obtain 236 mg of the expected product melting at 78°-79° C. with a Rf=0.31 (eluant: methylene chloride—acetone (75-25)).

IR Spectrum ($CHCl_3$);	
OH	3624 cm^{-1}
C=O	1762 cm^{-1}
C≡N	2237 cm^{-1}
Aromatics	1615-1580-1504 cm^{-1}

UV Spectrum (EtOH)	
Max. 232 nm	ε = 19500
Max. 254 nm	ε = 24000
Infl. 266 nm	

EXAMPLE 78

4-(4,4-dimethyl 3-(2-methoxyethyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 22,—2.5 g of isothiocyanate and 1.56 g of the appropriate aminoitrile were reacted to obtain 2.36 g of the expected product with a Rf=0.23 (methylene chloride—acetone (92.5-7.5)).

IR Spectrum ($CHCl_3$);	
=NH	3314 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1614-1578-1504 cm^{-1}
C=N	1675 cm^{-1}

EXAMPLE 79

4-(4,4-dimethyl 3-(2-methoxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 71, the product of Example 78 was reacted to obtain the expected product melting at 98°-99° C. with a Rf=0.32 (eluant: methylene chloride—acetone (99-1))

IR Spectrum ($CHCl_3$);	
C=O	1757 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1615-1580-1504 cm^{-1}

UV Spectrum (EtOH)	
Max. 232 nm	ε = 18200
Max. 254 nm	ε = 22400
Infl. 265 nm	

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EXAMPLE 80

4-(4,4-dimethyl 3-(1-methylethyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 22,—2.5 g of the isothiocyanate and 1.32 g of the appropriate aminonitrile were reacted to obtain 880 mg of the expected product with a Rf=0.20 (eluant: methylene chloride—acetone (96-4)).

IR Spectrum ($CHCl_3$);	
=NH	3310-1675 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1614-1580-1504 cm^{-1}

EXAMPLE 81

4-(4,4-dimethyl 3-(1-methylethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 71, 880 mg of the product of Example 80 and 35 ml of 6 N hydrochloric acid were reacted to obtain after extraction with chloroform, 744 mg of the expected product melting at 203°-204° C. with a Rf=0.45 (eluant: cyclohexane—ethyl acetate (1—1)).

IR Spectrum ($CHCl_3$);	
OH	3626 cm^{-1}
C=O	1753 cm^{-1}
C≡N	2232 cm^{-1}
Aromatics	1615-1580-1504 cm^{-1}

UV Spectrum (EtOH)	
Max. 232 nm	ε = 18900
Max. 235 nm	ε = 22500
Infl. 273 nm	

EXAMPLE 82

3-(3,4-dichlorophenyl 5,5-dimethyl 1-(3-hydroxypropyl) 4-imino 2-imidazolidine thione

Using the procedure of Example 51,—2.4 g of 3,4-dichlorophenyl isocyanate and 1.6 g of the appropriate aminonitrile were reacted to obtain, after chromatography on silica (eluant: methylene chloride—acetone (6-4)), 2.16 g of expected product with a Rf=0.25

IR Spectrum ($CHCl_3$);	
OH	3630 cm^{-1} + associated
C=NH	3294-1676 cm^{-1} (F)
Aromatics	1595-1569-1482 cm^{-1}

EXAMPLE 83

3-(3,4-dichlorophenyl 5,5-dimethyl 1-(3-hydroxypropyl) 2-thioxo 4-imidazolidinone

Using the procedure of Example 52,—0.88 g of the product of Example 82 and 35 ml of 6 N hydrochloric acid were reacted to obtain, after extraction with chloroform, 0.79 g of the expected product melting at 202°-203° C.

IR Spectrum ($CHCl_3$);	
C=O	1753 cm^{-1}
C≡N	2232 cm^{-1}
Aromatics	1615-1580-1504 cm^{-1}

UV Spectrum (EtOH)	
Max. 232 nm	ε = 18900
Max. 235 nm	ε = 22500
Infl. 273 nm	

EXAMPLE 84

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

a) 4-amino 2-(trifluoromethyl) (5-^{3}H) benzonitrile

The following were cooled to −180° C. and mixed under an inert atmosphere: 16 mg of 2-trifluoromethyl 4-amino 5-bromo benzonitrile, 2 mg of palladium on activated charcoal, 200 µl of ethyl acetate and 6.5 µl of triethylamine. Then the mixture was left under a tritium atmosphere and taken to 20° C. and the pressure was then 1.68 bar. The mixture was stirred until absorption was complete (p=0.42 bar), followed by cooling to −180° C. The excess tritium was recovered, taken to 20° C. and then filtered. The filtrate was rinsed with ethyl acetate and concentrated at 40° C. under reduced pressure to obtain 68 G.Bq of the expected product.

b) 4-thioisocyanate 2-(trifluoromethyl) (5-^{3}H) benzonitrile

The following were mixed under an argon atmosphere: 34 G.Bq of the above tritiated amino derivate, 150 µl of demineralized water and 150 µl of 10% thiophosgene solution in chloroform. The mixture was stirred at 20° C. for 45 minutes, decanted and reextraction was carried out with chloroform. The extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The thioisocyanate obtained was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

The following were mixed under an argon atmosphere with the thioisocyanate of stage b): 350 µl of tetrahydrofuran with 1% triethylamine and 20 µl of propanonitrile prepared as indicated below. The mixture was stirred for 2 hours at 20° C., followed by concentration at 20° C. under reduced pressure. The imine was used as is for the following stage. Preparation of the 2-(4-hydroxybutylamino) 2-methylpropano-nitrile used in stage c)

550 µl of acetone cyanohydrin and 500 µl of 4-amino 1-butanol were mixed together and the mixture was stirred for 16 hours at 20° C. to obtain the desired product which was used as is for the following stage.

EXAMPLE 85

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

200 µl of 2 N hydrochloric acid were added to the imine of Example 84 and the mixture was refluxed for 5 minutes, then returned to 20° C. and diluted with 1 ml of water. Extaction was carried out with ethyl acetate and the extracts were washed with water and concentrated under reduced pressure. The crude product was purified by chromatography on silica (eluant: cyclohexane—ethyl acetate (6-4)) to obtain 2.8 G.Bq of the expected product.

EXAMPLE 86

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

a) 4-amino 2-(trifluoromethyl) benzo (^{14}C) nitrile

377 mg of cuprous cyanide ^{14}C (9 G.Bq) and 1.0732 g of 4-bromo 3-(trifluoromethyl) benzenamine were mixed together under a nitrogen atmosphere in 8 ml of dimethylformamide and the mixture was refluxed for 4 hours, then cooled to 0° C. and diluted with 20 ml of acetone. The insoluble part was filtered off and the filtrate was concentrated at 70° C. under reduced pressure. The residue was taken up in methylene chloride, filtered and the filtrate was concentrated under reduced pressure. The benzonitrile (^{14}C) was purified by chromatography on silica (eluant: methylene chloride—cyclohexane (70-30)) to obtain 0.558 g (6.62 G.Bq) of the expected product.

b) 4-thioisocyanate 2-(trifluoromethyl) benzo (^{14}C) nitrile

The following were mixed under a nitrogen atmosphere: 189 mg of benzonitrile (^{14}C) of stage a), 2.7 ml of water and 85 µl of thiophosgene. The mixture was agitated vigorously stirred for 5 minutes, and after 30 µl of thiophosgene were added, stirring was continued for one hour at 20° C. Then extraction was carried out with chloroform and the extracts were washed with water, dried and concentrated under reduced pressure. The thioisocyanate obtained was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

2 ml of tetrahydrofuran, the propanonitrile prepared below in solution in 1.5 ml of methylene chloride and 150 µl of triethylamine were added under a nitrogen atmosphere to the thioisocyanate of stage b). The mixture was heated for 30 minutes under reflux and concentrated under reduced pressure to obtain the imine which was used as is for the following stage.

Preparation of the 2-(4-hydroxybutylamino) 2-methylpropano-nitrile of stage c

220 µl of acetone cyanohydrin and 200 µl of 4-amino 1-butanol were mixed together with stirring for 16 hours at 20° C. and then was diluted with 2 ml of methylene chloride, dried, filtered and the filtrate was concentrated under reduced pressure to obtain the propanonitrile which was used as is for the following stage.

EXAMPLE 87

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

6 ml of methanol and 1.6 ml of 2 N hydrochloric acid were added to the imine of Example 86 and the mixture was refluxed for 45 minutes, cooled to 20° C. and diluted with 10 ml of water. Extraction was carried out with methylene chloride and the extracts were washed with water and concentrated under reduced pressure. The crude product was purified by chromatography on silica (eluant: ether—acetonitrile—cyclohexane (50-15-35)) to obtain 328 mg of the expected product.

EXAMPLE 88

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

a) 4-amino 2-(trifluoromethyl) (5-^{3}H) benzonitrile

Using the procedure of stage a) of Example 84, 16 mg of 4-amino 5-bromo 2-trifluoromethyl benzonitrile, 2 mg of palladium on activated charcoal, 200 µl of ethyl acetate and 6.5 µl of triethylamine were reacted to obtain 68 G.Bq of the expected product.

b) 4-isocyanate 2-(trifluoromethyl) (5-^{3}H) benzonitrile

34 G.Bq of tritiated amino derivate of step a) and 100 µl of 20% phosgene in toluene were mixed together under an argon atmosphere and the mixture was taken to 80° C. for one hour. A further 100 µl of phosgene were added and the mixture heated for one hour at 80° C. This operation was repeated one more time, then concentration was carried out at 20° C. under reduced pressure to obtain the isocyanate which was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

The following were added under an argon atmosphere to the isocyanate of stage b): 200 µl of methylene chloride, 50 µl of the propanonitrile chloromethylene solution prepared as below and 20 µl of triethylamine and the mixture was stirred for 30 minutes. A further 50 µl of the propanonitrile solution were added and stirring was continued for 30 minutes followed by concentration at 20° C. under reduced pressure. The imine was used as is for the following stage. Preparation of the 2-(4-hydroxybutylamino) 2-methyl propano-nitrile, of stage c)

220 µl of acetone cyanohydrin and 200 µl of 4-amino 1-butanol were mixed together and the mixture was stirred for 16 hours at 20° C., then diluted with 3 ml of methylene chloride and dried over magnesium sulfate. The decanted solution was used as is for the following stage.

EXAMPLE 89

4-(4,4-dimethyl2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

200 µl of methanol and 50 µl of 2 N hydrochloric acid were added to the imine of Example 88 and the mixture was refluxed for 45 minutes, then returned to 20° C. and diluted with 1 ml of water. Extraction was carried out with methylene chloride and the extracts were washed

with water and concentrated at 20° C. under reduced pressure. The crude product was purified by chromatography on silica (eluant: methylene chloride—ethyl acetate (7-3 then 5—5)) to obtain 16 G.Bq of the expected product.

EXAMPLE 90

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

a) 4-amino 2-(trifluoromethyl) benzo (^{14}C) nitrile

Using the procedure of Example 86, stage a), 377 mg of cuprous cyanide ^{14}C, 1.0732 g of 4-bromo 3-trifluoromethyl benzenamine and 8 ml of dimethylformamide were reacted to obtain 0.558 g (6.62 G.Bq) of the expected product.

b) 4-isocyanato 2-(trifluoromethyl) benzo (^{14}C) nitrile

182.4 mg of benzonitrile (^{14}C) (0.97 mmole), 2 ml of dioxane and 1 ml of 20% phosgene in toluene were mixed together under a nitrogen atmosphere and the solution was heated at 60° C. for 22 hours, then concentrated at 60° C. under reduced pressure. The isocyanate was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

1.5 ml of methylene chloride (on siliporite NK 30), the propanonitrile of Example 88 in solution in 1.5 ml of methylene chloride, and 150 µl of triethylamine were added under a nitrogen atmosphere to the isocyanate of stage b). The mixture was stirred for one hour at 20° C. and concentrated under reduced pressure. The imine was used as is for the following stage.

EXAMPLE 91

4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

5 ml of methanol and 1.2 ml of 1 N hydrochloric acid were added to the imine of Example 90 and the mixture was refluxed for 40 minutes, then returned to 20° C. and diluted with 10 ml of water. Extraction was carried out with methylene chloride and the extracts were washed with water and concentrated under reduced pressure. The crude product was purified by chromatography on silica (eluant: ether—acetonitrile—cyclohexane (50-15-35)) to obtain 289 mg (1.26 G.Bq) of the expected product.

EXAMPLE 92

4-(2,5-dioxo 4,4-dimethyl 3-(4-triphenylmethoxy-butyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

370 mg of the product of Example 58, 307 mg of trityl chloride in the presence of 10 mg of 4-dimethylaminopyridine, 0.25 ml of triethylamine and 4 ml of dimethylformamide were stirred at ambient temperature for 16 hours. The mixture was heated to 40° C. for 4 hours, poured into water and extraction was carried out with ether. The extracts were washed with water and dried and the solvent was eliminated under reduced pressure. The residue was chromatographed on silica (eluant: cyclohexane—ethyl acetate 75-25) to obtain 467 mg of the expected product with a Rf=0.25.

IR Spectrum ($CHCl_3$);	
C=O	1778, 1725 cm^{-1} (F)

-continued

IR Spectrum ($CHCl_3$);	
C≡N	2235 cm^{-1}
Aromatics	1615, 1597, 1505, 1490 cm^{-1}

EXAMPLE 93

4-(2,5-dioxo 4,4-dimethyl 3-(4-phenylmethoxy-butyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

48 mg of sodium hydride were added in several lots to 370 mg of the product of Example 58 in solution in 4 ml of dimethylformamide and the mixture was stirred for 30 minutes. Then, 0.12 ml of benzyl bromide and 40 mg of tetrabutylammonium iodide were added and after 90 minutes of reaction, the same amount of each reagent was added. The mixture was stirred for one hour and the reaction medium was poured into an ice-cooled aqueous solution of monopotassium phosphate. Extraction was carried out with ether and the extracts were washed with water and dried. The solvent was eliminated under reduced pressure and the residue was chromatographed on silica (eluant: methylene chloride—acetone 99-1) to obtain 140 mg of the expected product melting at 75°–76° C.

IR Spectrum ($CHCl_3$);	
C=O	1779, 1725 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1615, 1580, 1505, 1497 cm^{-1}

EXAMPLE 94

4-[4,4-dimethyl 2,5-dioxo 3-(4-methoxybutyl) 1-imidazolidinyl] 2-(trifluoromethyl)-benzonitrile

50 mg of sodium hydride were added in several lots to 370 mg of the product of Example 58 in solution in 3 ml of dimethylformamide and the mixture was stirred for 20 minutes. 0.06 ml of methyl iodide were added and the mixture was stirred for one hour. A further 50 mg of sodium hydride were added and then after 20 minutes, 0.06 ml of methyl iodide were added. The reaction medium was poured into water and extracted with ether. The extracts were washed with water, dried and the solvent was evaporated. The residue was chromatographed on silica (eluant: methylene chloride—acetone 98-2) to obtain 135 mg of the expected product melting at 80°–81° C.

IR Spectrum ($CHCl_3$);	
C=O	1779, 1725 cm^{-1} (F)
C≡N	2234 cm^{-1}
Aromatics	1616, 1576, 1505 cm^{-1}
OCH_3 approx.	2830 cm^{-1}

EXAMPLE 95

4-[3-(4-chlorobutyl) 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrile

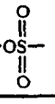
Using the procedure of Example 59, 600 mg of the product of Example 8—and 660 mg of 1-chloro 4-iodobutane in solution in 1 ml of dimethylformamide cooled down to +5° C. were reacted to obtain 604 mg of the expected product melting at 80°–81° C.

IR Spectrum ($CHCl_3$);	
C=O	1779, 1725 cm^{-1} (F)
C≡N	2238 cm^{-1}
Aromatics	1616, 1575, 1505 cm^{-1}

EXAMPLE 96

4-[3-[4-[(methylsulphoneyl) oxyl] butyl] 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrile

0.17 ml of methanesulfonyl chloride were added to 740 mg of the product of Example 58 in solution in 7.4 ml of pyridine and 24 mg of 4-dimethylamino-pyridine and the mixture was stirred for one hour. The mixture was poured into ice-cooled water and extraction was carried out with methylene chloride. The extracts were washed with water and the residual pyridine was eliminated by distillation. The residue was chromatographed on silica (eluant: methylene chloride—ethyl acetate 8-2) to obtain 771 mg of the expected product.

IR Spectrum ($CHCl_3$);	
C=O	1779, 1725 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1615, 1575, 1505 cm^{-1}
	1361, 1175 cm^{-1}

UV Spectrum (EtOH)		
max.	261 nm	ϵ = 14900
infl.	279–297 nm	

EXAMPLE 97

4-(3-acetyl 4,4-dimethyl 2,5-dioxo 1-imidazo-lidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 59, 420 mg of the product of Example 8—and two lots of 0.1 ml of acetyl chloride were reacted to obtain after chromatography on silica (eluant: methylene chloride—ethyl acetate 98-2), 334 mg of the expected product melting at 129°–130° C.

IR Spectrum ($CHCl_3$);	
C=O	1800, 1740, 1717 cm^{-1}
C≡N	2240 cm^{-1}
Aromatics	1616, 1505 cm^{-1}

UV Spectrum (EtOH)		
max	250 nm	ϵ = 12000
infl.	274–284 nm	

EXAMPLE 98

4-(3-benzoyl 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 59, 300 mg of the product of Example 8—and two lots of 0.12 ml of benzoyl chloride in solution in 0.5 ml of dimethylformamide were reacted to obtain after chromatography on silica (eluant: cyclohexane—ethyl acetate 8-2), 285 mg of the expected product melting at 179°–180° C.

IR Spectrum ($CHCl_3$);	
C=O	1800, 1780, 1746, 1699 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1617, 1600, 1580, 1504 cm^{-1}

UV Spectrum (EtOH)	
max. 250 nm	ϵ = 28500
infl. 275 nm	ϵ = 6500
infl. 263 nm	ϵ = 3850

EXAMPLE 99

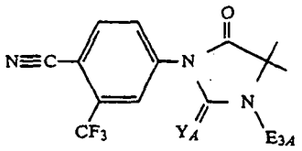
4-[3-[dimethyl (1,1-dimethylethyl) silyl] 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrle

Using the procedure of Example 59, 450 mg of the product of Example 8—and 300 mg of dimethyl t-butylsilyl chloride in 2 ml of dimethylformamide were reacted to obtain after chromatography on silica (eluant: methylene chloride—acetone 99-1), 527 mg of the expected product melting at 147°–148° C.

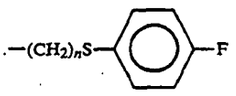
IR Spectrum ($CHCl_3$);	
C≡N	2236 cm^{-1}
Aromatics	1615, 1579, 1505 cm^{-1}

UV Spectrum (EtOH)	
max. 258 nm	ϵ = 17000
infl. 275–285 nm	

In addition to the products described above, the following products are products which can be obtained within the scope of the present invention, namely the products of the formula:



in which Y_A is oxygen or sulfur and R_{3A} has the following values:



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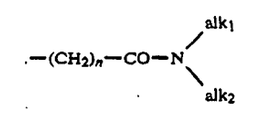
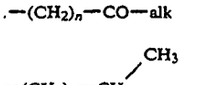
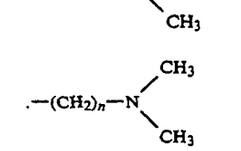
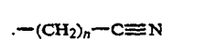
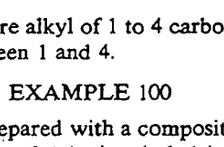
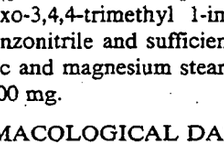


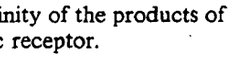












alk, alk_1 and alk_2 are alkyl of 1 to 4 carbon atoms and n is an integer between 1 and 4.

EXAMPLE 100

Tablets were prepared with a composition of 100 mg of 4-(5-oxo-2-thioxo-3,4,4-trimethyl 1-imidazolinyl)-2-trifluoromethyl-benzonitrile and sufficient excipient of lactose, starch, talc and magnesium stearate for a final tablet weight of 300 mg.

PHARMACOLOGICAL DATA

Study of the affinity of the products of the invention for the androgenic receptor.

1) Androgenic receptor

Male rats of the Sprague Dawley EOPS strain weighing 180 to 200 g, castrated 24 hours previously, were killed and the prostrate was removed, weighed and homogenized at 0° C. with a potter glass in a buffered solution (Tris 10 mM, saccharose 0.25 M, PMSF (phenyl methane sulfonyl fluoride) 0.1 mM, sodium molybdate 20 mM, HCl pH 7.4 into which was added extemporaneously 2 M of DTT (DL dithiothreitol) at a rate of 1 g of tissue per 8 ml of buffer solution. The homogenate was then ultracentrifuged at 0° C. for 45 minutes at 105,000 g and the aliquots of supernatant (=cytosol) were incubated for 30 minutes and 24 hours with a concentration (T) of tritiated testosterone and in the presence of increasing concentrations (0 to 2500.10^{-9}M) of cold testosterone or the test products. The concentration of bound tritiated Testostrone (B) was then measured for each incubate by adsorption method of carbon-dextran. The relative affinity of bonding (RBA) was calculated.

The following two curves were graphed: the percentage of the bound tritiated hormone B/T as a logarithm function of the concentration of the cold hormone and B/T as a logarithm function of the concentration of the tested cold product. The line of the equation

$$I_{50} = \frac{(B/T\max + B/T\min)}{2}$$

was determined. B/T max=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T). B/T min=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T) in the presence of a large excess of cold hormone ($2,500\times10^{-9}$M).

The intersections of the straight line I_{50} and the curves permit an evaluation of the concentrations of the cold reference hormones (CH) and the cold test product (CX) which inhibit by 50% the bonding of the tritiated hormone on the receptor. The RBA 9of the test product was determined by the equation

$$RBA=(CH)/(CX)$$

and the following results expressed in ARL were obtained with testosterone=100.

	Incubation 30 minutes	Incubation 24 hours
Product Example 1	27.5	3
Product Example 2	22	6
Product Example 4	21	5
Product Example 11	28	8
Product Example 12	128	92
Product Example 13	31	39
Product Example 14	27	7
Product Example 15	69	24

2) Study of the affinity of the products of the invention for the androgen receptor.

Male rats of the Sprague Dawley EOPS strain weighing 180 to 200 g, castrated 24 hours previously, were killed and the prostate was removed, weighed and homogenized at 0° C. with a potter glass in a buffered solution (Tris 10 mM, saccharose 0.25 M, PMSF (phenyl methane sulfonyl fluoride) 0.1 mM, sodium molybdate 20 mM, HCl pH 7.4 into which was added extemporaneously 2 mM of DTT (DL dithiothreitol) at a rate of 1 g of tissue per 8 ml of buffer solution. The homogenate was then ultracentrifuged at 0° C. for 30 minutes at 209,000 g and the aliquots of supernatant (=cytosol) were incubated for 30 minutes and 24 hours with a concentration (T) of tritiated testosterone and in the presence of increasing concentrations (0 to 2500.10^{-9}M) of cold testosterone or the test products. The concentration of bound tritiated Testostrone (B) was then measured for each incubate by adsorption method of carbon-dextran. The relative affinity of bonding (RBA) was calculated.

The following two curves were graphed: the percentage of the bound tritiated hormone B/T as a logarithm function of the concentration of the cold hormone and B/T as a logarithm function of the concentration of the tested cold product. The line of the equation

$$I_{50} = \frac{(B/T\max + B/T\min)}{2}$$

was determined. B/T max=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T). B/T min=% of the bound tritiated hormone for an incubation of this tritiated hor-

mone at the concentration (T) in the presence of a large excess of cold hormone ($2{,}500 \times 10^{-9}$M).

The intersections of the straight line I_{50} and the curves permit an evaluation of the concentrations of the cold reference hormones (CH) and the cold test product (CX) which inhibit by 50% the bonding of the tritiated hormone on the receptor. The RBA of the test product was determined by the equation

$$RBA = 100(CH)/(CX)$$

and the following results expressed in RBA were obtained with testosterone = 100.

	Incubation 24 hours
Example 59	31
Example 71	163
Example 77	300
Example 79	81
Example 81	28

3) Determination of the androgen or anti-androgen activity by the dosage of ornithine carboxylase.

Six week old male Swiss mice castrated 24 hours receive oral does of the test products as a 0.5% suspension in methyl cellulose simultaneously with a subcutaneous injection of 3 mg/kg of testosterone propionate in solution in sesame oil containing 5% of benzyl alcohol to determine the anti-androgen activity. Active agonists were determined in the absence of testosterone propionate. The test compounds as well as testosterone were administered in a volume of 10 ml/kg. 16 hours after the treatments, the animals were killed, the kidneys were removed and then homogenized at 0° C. with a teflon-glass grinding apparatus in 10 volumes of buffer Tris-HCl 50 mM at a pH 7.4 containing 250 mM of pyridoxal phosphate, 0.1 mM EDTA and 5 mM of dithiothreitol. The homogenate was centrifuged at 105,000 g for 45 minutes.

At 37° C., renal ornithine decarboxylase transforms an isotropic mixture of cold ornithine and tritiated ornithine in cold putrescine and tritiated putrescine. The putrescine was then collected on selective ion-exchange papers. After drying, excess non-transformed cold and tritiated ornithine were eliminated by washing 3 times with 0.1 M ammonium hydroxide. The papers were dried and the radioactivity was determined after addition of an Aqualite sample. The results expressed in fmoles (10^{-15}M) of tritiated putrescine formed per hour mg of protein are reported in the following Table

PRODUCT OF EXAMPLE	ANTAGONISM IN MG/KG	PERCENT
11	3	83
12	0.1	12
	0.3	36
	1	68
	3	94
	10	99
12	(Agonism) 10	0
14	Antagonism 3	87
15	0.3	4
	1	82

4) Determination of the androgen or anti-androgen activity by the dosage of ornithine carboxylase.

Swiss six week old male mice castrated24 hours received oralor percutaneous doses of the test products as a 0.5% suspension in methyl cellulose or in ethanol simultaneously with a sub-cutaneous injection of 3 mg/kg of testosterone propionate in solution in corn oil to determine the anti-androgen activity. Active agonists were determined in the absence of testosterone propionate. The test compounds as well as testosterone were administered in a volume of 10 ml/kg. 20 hours after the treatments, the animals were killed, the kidneys were removed and then homogenized at 0° C. with a teflon-glass grinding apparatus in 10 volumes of buffer Tris-HCl 50 mM at a pH 7.4 containing 250 mM of pyridoxal phosphate, 0.1 mM EDTA and 5 mM of dithiothreitol. The homogenate was centrifuged at 209,000 g for 45 minutes.

Principle of dosage

At 37° C., renal ornithine decarboxylase transforms an isotopic mixture of cold ornithine and tritiated ornithine in cold putrescine and tritiated putrescine. The putrescine was then collected on selective ion-exchange papers. After drying, excess non-transformed cold and tritiated ornithine were eliminated by washing 3 times with 0.1 M ammonium hydroxide. The papers were dried and the radioactivity was determined after addition of an Aqualite sample. The results expressed in fmoles (10^{-15}M) of tritiated putrescine formed per hour/mg of protein are reported in the following Table.

The same test were repeated with the following changes:

Test A: the products were administered percutaneously at 1.5 mg/kg at a volume of 10 μl.

Test B: the products were administered orally at 1 mg/kg.

Test C: the products are administered orally at 3 mg/kg. The results are in the following Table.

The results are expressed in % of inhibition of the ODL the samples receiving only the testosterone propionate:

Products of example	ODL		
	Test A	Test B	Test C
58	40	36	
71	32		67
75	41		
78	78		
80	62		
81	35		
83	58		

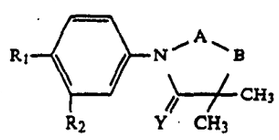
CONCLUSION

The tests show that the tested compounds of the invention possess a strong anti-androgen activity and do not have agonist activity.

Various modifications of the compounds and method of the invention may be made without departing from the spirit or scope thereof and it is to be understood that the invention is intended to be limited only as defined in the appended claims.

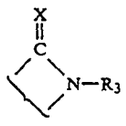
We claim:

1. A compound selected from the group consisting of a compound of the formula

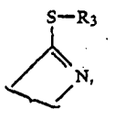


I

wherein R_1 is selected from the group consisting of —CN, —NO_2 and halogen, R_2 is —CF_3 or halogen, —A–B is



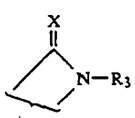
or



X is —O— or —S—, R_3 is selected from the group consisting of a) hydrogen, b) alkyl, alkenyl and alkynyl of up to 12 carbon atoms, c) phenyl and phenylalkyl unsubstituted or substituted with at least one member of the group consisting of —OH, halogen, —OCH_3, —CN and haloalkyl, d) acyl of an organic carboxylic acid of up to 7 carbon atoms, e) free or salified carboxy, carboxy esterified with alkyl and amidified carboxy, f) amino and mono and dialkylamino of 1 to 4 carbon atoms and g) —S—phenyl unsubstituted or substituted with at least one member of the group consisting of—CF_3 and alkyl, alkenyl, alkoxy, alkenyloxy, alkynyl and alkynyloxy of up to 12 carbon atoms with the sulfur unoxidized or oxidized to sulfone or sulfoxide, the alkyl, alkenyl and alkynyl being uninterrupted or interrupted with oxygen, sulfur or nitrogen and Y is —O—, —S— or —NH— with the provisos that when X is oxygen, R_3 is hydrogen and Y is —O— or —NH—, then R_1 is NO_2 or —CN and when X is sulfur and Y is —O— then at least one of the following conditions is satisfied, R_1 is —CN and R_2 is —CF_3 and their non-toxic, pharmaceutically acceptable acid addition salts.

2. A compound of claim **1** wherein Y is oxygen.

3. A compound of claim **1** wherein —A–B— is



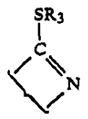
and X is sulfur.

4. A compound of claim **3** wherein R_3 is hydrogen or alkyl of 1 to 4 carbon atoms optionally substituted with a —OH or methoxy.

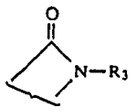
5. A compound of claim **1** wherein R_1 is —CN or halogen.

6. A compound of claim **1** wherein R_1 wherein R_1 is chlorine.

7. A compound of claim **1** wherein —A–B— is



or



and R_3 is alkyl or alkenyl of up to 6 carbon atoms unsubstituted or substituted or uninterrupted or interrupted by oxygen or unoxidized or oxidized sulfur or unsubstituted or substituted aralkyl or acylor trialkylsilyl.

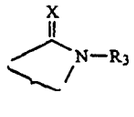
8. A compound of claim **7** wherein R_3 is alkyl of 1 to 6 carbon atoms unsubstituted or substituted by at least one member of the group consisting of halogen, —OH, —O acyl, carboxy, carboxy esterified with alkyl, a heterocycle, O-alkyl and unoxidized or oxidized S-aryl with the aryl unsubstituted or substituted with at least one member of the group consisting of halogen and alkoxy.

9. A compound of claim **8** wherein R_3 is alkyl of 2 to 4 carbon atoms substituted by a member selected from the group consisting of chlorine, ethoxycarbonyl, tertbitoxy carbonyl, cyclopentyloxycarbonyl, unoxidized or oxidized 4-fluorophenylthio, morpholino, phenylmethoxy, triphenylmethoxy and methylsulfonyloxy.

10. A compound of claim **7** wherein R_3 is acetyl or benzoyl or (1,1-dimethylethyl)dimethylsilyl.

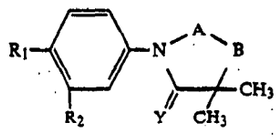
11. A compound of claim **1** selected from the group consisting of 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl-5-oxo-2-thioxo 1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl 2-(trifluoromethyl)-benzonitrile, 3-(3,4-dichlorophenyl)-2-thioxo--1,5,5-trimethyl-4-imidazolidinone, 1-(4-nitro-3-(trifluoromethyl) phenyl-3,4,4-trimethyl-2,5-imidazolidinedione, 4-4,5-dihydro4,4-dimethyl-5-oxo-2-(phenylmethyl) thio-1H-imidazol-1-yl-2-(trifluoromethyl) benzonitrile, 4 4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile, 3-(4-cyano 3-trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoic acid and 4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl benzonitrile.

12. A compound of claim **1** wherein Y is —O— except the compounds wherein the —A–B— group is

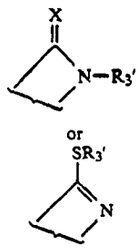


in which X is oxygen and R_3 is hydrogen, R_2 is halogen or trifluoromethyl and R_1 is nitro or halogen.

13. A compound of the formula



wherein R_1, R_2 and Y have the definitions of claim 1, —A—$_i$—B_1 is



Y is oxygen or sulfur and R'_3 is R_3 with any reactive functions protected.

14. An anti-androgenic composition comprising an anti-androgenically effective amount of at least one compound of claim 1 and an inert pharmaceutical carrier.

15. A composition of claim 14 wherein the active compound is selected from the group consisting of 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl) 2-(trifluoromethyl)-benzonitrile, 4-(4,4-dimethyl-5-oxo-2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl)-benzoitrile, 4-4.4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo 1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile, 3-(3,4-dichlorophenyl) 2-thioxo--1,5,5,-trimethyl-4-imidazolidinone, 1-(4-nitro-3-(trifluoromethyl)-phenyl-3,4,4-trimethyl-2.5-imidazolidinedione, 4-4,5-dihydro4,4-dimethyl-5-oxo-2-(phenylmethyl)thio-1H-imidazol 1-yl)2-(trifluoromethyl) benzonitrile-4,4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile-3-(4-cyano 3-trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-dioxo 3-(4-hydroxybutyl) 1- imidazolidinyl) 2-(trifluoromethyl) benzonitrile.

16. A method of inducing anti-androgenic activity in warm-blooded animals comprising administering to warm-blooded animals an anti-androgenically effective amount of at least one compound of claim 1.

17. A method of claim 16 wherein Y is oxygen.

18. A method of claim 16 wherein R_1 is —CN or halogen.

19. A method of claim 16 wherein R_1 is chlorine.

20. A method of claim 14 wherein the active compound is selected from the group consisting of 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl) 2-(trifluoromethyl)-benzonitrile, 4-(4,4-dimethyl-5-oxo-2-thioxo 1-imidazolidinyl)-2-(trifluoromethyl)-benzoitrile, 4-4,4-dimethyl-3-(2-hydroxyethyl) 5-oxo-2-thioxo-1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile, 3-(3,4-dichlorophenyl)-2-thioxo--1,5,5-trimethyl-4-imidazolidinone, 1-(4-nitro-3-(trifluoromethyl)-phenyl-3,4,4-trimethyl-2,5-imidazolidinedione, 4-4,5-dihydro4,4-dimethyl-5-oxo-2-(phenylmethyl)-thio-1H-imidazol-1-yl-2-(trifluoromethyl) benzonitrile-4,4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile, -4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile-3-(4-cyano 3-trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoic and acid and 4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile.

* * * * *

Annexure V

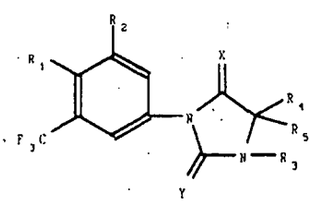
(21) Application 2440/DEL/1996 A (22) Date of filing of 11-Jun-1996

(54) Title of the New preparation process for phenylimidazolidine derivatives.

(51) International	(71) Name of the Applicant : ROUSSEL UCLAF (71) Address of the Applicant : 102 Route de Noisy, F-93230 Romainville, F
(30) Priority Data :	
(31) Document	
(32) Date : 16/11/1995	
(33) Name of convention country : FRANCE	(72) Name of the Inventors :
(66) Filed U/s 5(2) : YES	1. RAPHAEL BOUCHET 2. MICHEL DELTHIL 3. DANIEL GUILMARD 4. PHILIPPE MACKIEWICZ
(61) Patent of addition to	
(62) Filed on :	
(63) Divisional to Application	
(62) Filed on :	

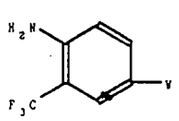
(57) Abstract :

A subject of the invention is a preparation process for the products of formula (I):



(I)

in which R_1 and R_2 represent in particular hydrogen, cyano, halogen or amino, R_3 represents in particular hydrogen or hydroxyl alkyl,
R_4 and R_5 represent in particular optionally substituted alkyl,
X and y represent oxygen or sulphur,
characterized in that a product of formula (A):



(A)

is prepared in which W represents a halogen atom or a hydantoin derivative,
which is subjected to various reactions in order to obtain the products of formula (I), all their isomers and their salts.

THE PATENTS ACT, 1970

2440 DEL 96

COMPLETE

SPECIFICATION
Section 10

- 6 NOV 1996

"NEW PREPARATION PROCESS FOR PHENYLIMIDAZOLIDINE DERIVATIVES"

ORIGINAL

ROUSSEL UCLAF, a French company, of 102, route de Noisy, F-93230 Romainville, France.

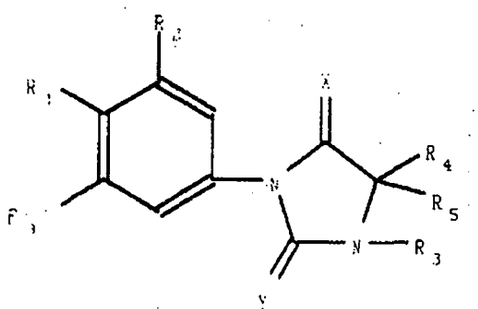
The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:-

358

~~New preparation process for phenylimidazolidine derivatives.~~

The present invention relates to a new preparation process for phenyl imidazolidine derivatives.

Therefore a subject of the present invention is a new preparation process for the products of formula (I):



(I)

in which:

R_1 and R_2, identical or different, are chosen from the hydrogen atom, halogen atoms and the following radicals: alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, phenyl, phenoxy, nitro, trifluoro-methyl, acyl, cyano, amino, monoalkylamino, dialkylamino, free, esterified, amidified or salified carboxy,

R_3 is chosen from the hydrogen atom and alkyl, alkenyl, alkynyl, aryl and arylalkyl radicals, all these radicals being optionally substituted by one or more substituents chosen from halogen atoms, the following radicals: optionally esterified, etherified or protected hydroxyl, alkoxy, alkenyloxy, alkynyloxy, trifluoromethyl, mercapto, cyano, acyl, acyloxy, free, esterified, amidified or salified carboxy, amino, mono- and dialkylamino, arylthio and cyclic radicals containing 3 to 6 members, the alkyl, alkenyl or alkynyl radicals being more optionally interrupted by one or more oxygen, nitrogen or sulphur atoms,
all the sulphur atoms being optionally oxidized in the form of the sulphoxide or sulphone,
the aryl and aralkyl radicals being moreover optionally substituted by an alkyl, alkenyl or alkynyl radical,

R_4 and R_5:
either are identical or different and represent a hydrogen

atom or an alkyl radical, optionally substituted by one or more substituents chosen from halogen atoms, the optionally esterified, etherified or protected hydroxyl radical and phenylthio and alkylthio radicals, in which the sulphur atom can be oxidized into the sulphoxide or sulphone and being optionally substituted by one or more radicals chosen from halogen atoms and optionally esterified, etherified or protected hydroxyl radicals, free, esterified, amidified or salified carboxy radicals, amino, mono- and dialkylamino radicals,

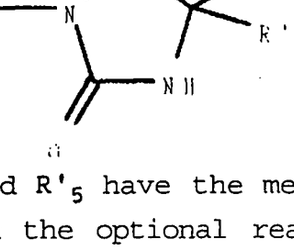
or form together a heterocyclic radical with 4 to 6 members containing an oxygen or sulphur atom,

X and Y, identical or different, represent an oxygen or sulphur atom,

said products of formula (I) being in all possible racemic, enantiomeric or diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or mineral and organic bases of said products of formula (I),

characterized in that:

a) a product of formula (A):

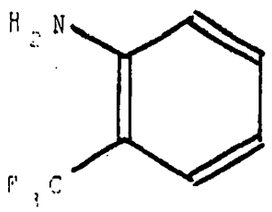


(A)

is prepared, in which W represents a halogen atom or a hydantoin derivative of formula:

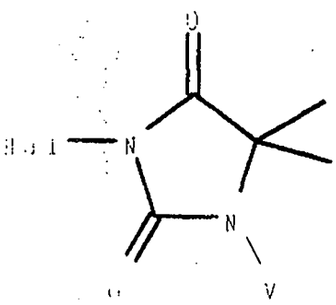
in which R'_4 and R'_5 have the meanings indicated above for R_4 and R_5 in which the optional reactive functions are optionally protected,

by reacting on the compound of formula (II):



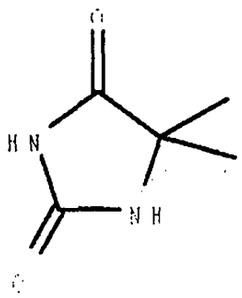
(II)

either first of all, a compound of formula (III):



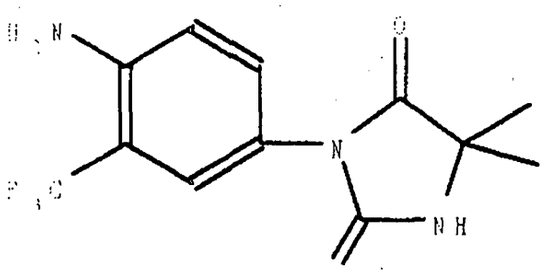
(III)

in which Hal represents a halogen atom and V represents a hydrogen atom or a halogen atom, then the compound of formula (B):



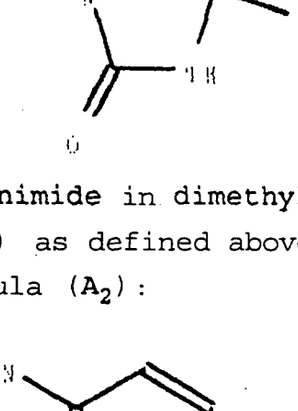
(B)

in order to obtain the product of formula (A_1):

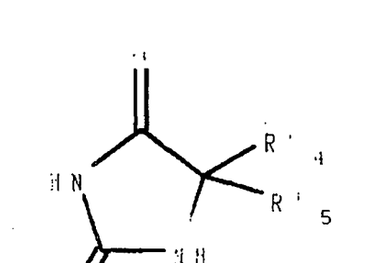


(A_1)

corresponding to the product of formula (A) in which W represents the dimethylhydantoin radical:

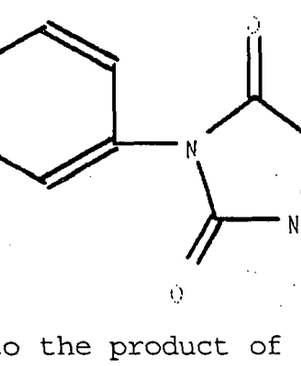


or N-bromosuccinimide in dimethylformamide, or the compound of formula (III) as defined above, in order to obtain the product of formula (A_2):



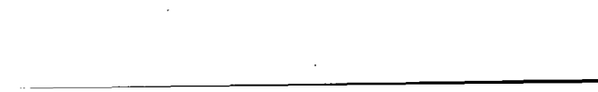
(A_2)

in which *Hal* represents a bromine atom or another halogen atom, which can be reacted with a compound of formula (IV):



(IV)

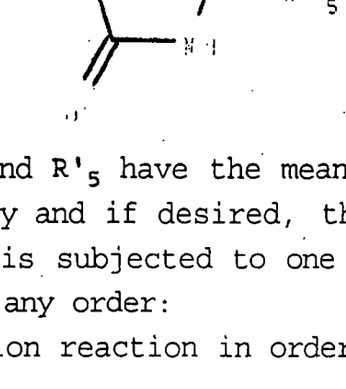
in which R'_4 and R'_5 have the meanings indicated above, in order to obtain the product of formula (A_3):



(A_3)

corresponding to the product of formula (A) in which W

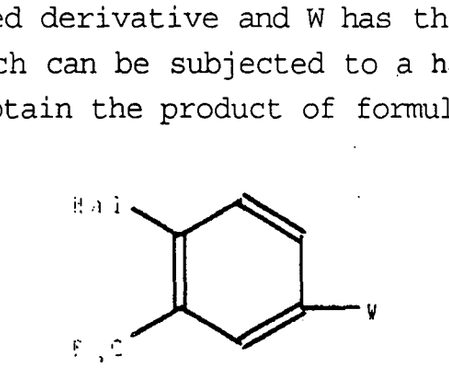
represents the radical:



in which R'_4 and R'_5 have the meanings indicated above,

b) if necessary and if desired, the product of formula (A) thus obtained is subjected to one or more of the following reactions, in any order:

i) a diazotation reaction in order to obtain the product of formula (V):



(V)

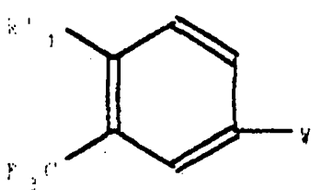
in which $A^{\ominus}$ represent an anion of a halogen atom or of ahalogenated derivative and W has the meaning indicated above, which can be subjected to a halogenation reaction in order to obtain the product of formula (F_1):

(F_1)

in which Hal and W have the meanings indicated above, which can be subjected to a substitution reaction on the halogen atom by a metallic derivative of formula (VI):

R'_1-M (VI)

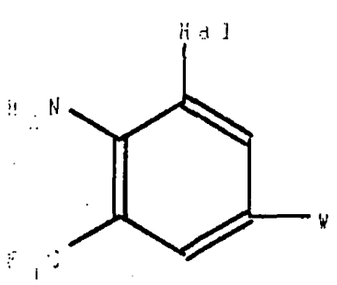
in which M represents a metal and R'_1 has the meaning indicated above for R_1, in which the optional reactive functions are optionally protected, in order to obtain the product of formula (F_2):



(F_2)

in which R'_1 and W have the meanings indicated above,

ii) a halogenation reaction in order to obtain the product of formula (F_3):



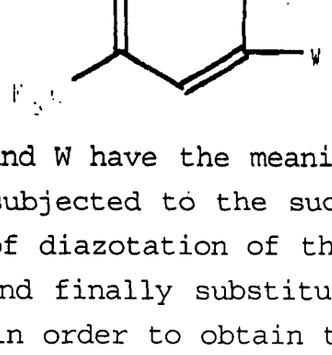
(F_3)

in which Hal represents a halogen atom and W has the meaning indicated above, which can:

either be subjected to a substitution reaction on the halogen atom, by a metallic derivative of formula (VII):

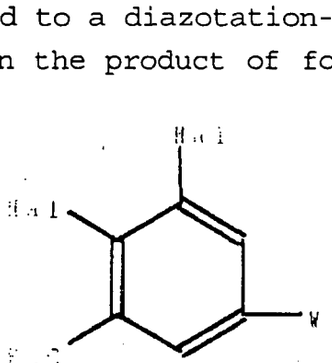
$$R'_2\text{-}M \qquad \text{(VII)}$$

in which M represents a metal and R'_2 has the meaning indicated above for R_2 in which the optional reactive functions are optionally protected, in order to obtain the product of formula (F_4):



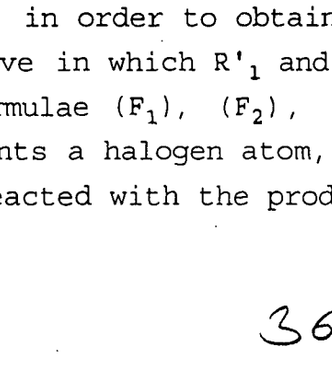
(F_4)

in which R'_2 and W have the meanings indicated above, which can be subjected to the successive reactions, defined above in i), of diazotation of the amino radical, then halogenation and finally substitution by the compound of formula (VI) in order to obtain the product of formula (F_5):



(F_5)

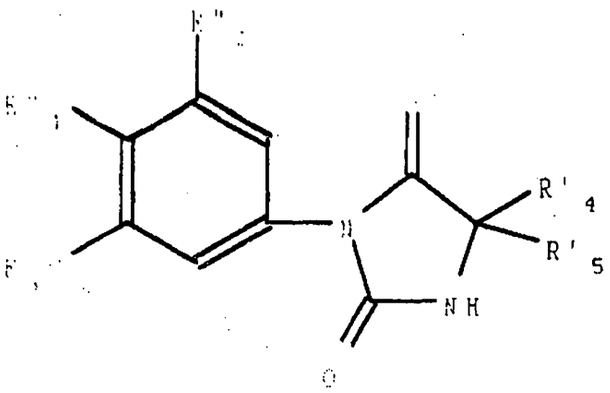
in which R'_1, R'_2 and W have the meanings indicated above, or is subjected to a diazotation-halogenation reaction in order to obtain the product of formula (F_6):



(F_6)

in which the two halogen atoms represented by Hal are identical or different and W has the meaning indicated above, which can be subjected to a substitution reaction on the halogen atoms by the compound of formula (VI) or (VII) as defined above, in order to obtain the product of formula (F_5) as defined above in which R'_1 and R'_2 are identical, which products of formulae (F_1), (F_2), (F_3), (F_4), (F_5) and (F_6) when W represents a halogen atom, can, if necessary and if desired, be reacted with the product of formula (IV), as

defined above, in order to obtain the product of formula (I'):



(I')

in which R''_1 and R''_2 are such that:
either R''_2 represents a hydrogen atom
and R''_1 represents a halogen atom or R'_1 as defined above,
or R''_2 represents a halogen atom
and R''_1 represents an amino radical or a halogen atom,
or R''_2 represents R'_2 as defined above
and R''_1 represents an amino radical or R'_1 as defined above,
which products of formulae (A_1), (A_3) and (I'), if appropriate and if necessary, or if desired, are subjected to any one or more of the following reactions, in any order:
a) an elimination reaction of the optional protective groups which can be carried by R''_1, R''_2, R'_4 and R'_5,
b) a conversion reaction of the >C=O into the >C=S group,
c) the action of a reagent of formula Hal-R'_3 in which R'_3 has the values of R_3 as defined in claim *I*, with the exception of the hydrogen value and in which the optional reactive functions are optionally protected and Hal represents a halogen atom, in order to obtain products of formula (I) as defined in claim 1, then, if desired, the action on these products of an agent for eliminating the optional protective groups which can be carried by R'_3 or if appropriate, the action of an esterification, amidification or salification agent,
d) a conversion reaction of the amino radical into a nitro radical.

For the definition of the substituents indicated above

and in what follows, the definitions used can have the following values:

By **halogen**, is meant of course, fluorine, chlorine, bromine or iodine atoms.

The term **alkyl** designates a linear or branched alkyl radical having at most 12 carbon atoms, such as for example the following radicals: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, **sec-butyl**, **tert-butyl**, pentyl, isopentyl, **sec-pentyl**, **tert-pentyl**, **neo-pentyl**, **hexyl**, **isohexyl**, **sec-hexyl**, tert-hexyl, **heptyl**, octyl, **decyl**, undecyl, **dodecyl**.

The alkyl radicals having at most 6 carbon atoms are preferred and in particular the methyl, **ethyl**, propyl, isopropyl, pentyl or hexyl radicals.

The term alkenyl designates a linear or branched alkenyl radical having at most 12 carbon atoms such as for example the vinyl, allyl, 1-propenyl, butenyl, pentenyl, hexenyl radicals.

Among the alkenyl radicals, those with 6 carbon atoms are preferred such as the allyl, propenyl, butenyl, pentenyl or hexenyl radicals.

The term alkynyl designates a linear or branched alkynyl radical having at most 12 carbon atoms, such as for example the ethynyl, **propargyl**, butynyl, pentynyl or **hexynyl** radicals.

Among the alkynyl radicals, those with 4 carbon atoms are preferred such as the propargyl radical.

The term **alkoxy** designates a linear or branched radical containing at most 12 carbon atoms and preferably 6 such as preferably **methoxy**, **ethoxy**, **propoxy** or **isopropoxy** radicals, but also linear, secondary or tertiary **butoxy**, **pentyloxy** or **hexyloxy**.

- the term **alkenyloxy** radical designates a linear or branched radical containing at most 12 carbon atoms and preferably 6, such as for example an allyloxy, 1-**butenyloxy** or **pentenyloxy** radical,
- the term **alkynyloxy** radical designates a linear or branched radical containing at most 12 carbon atoms and preferably at most 5, such as for example a propargyloxy, **butynyloxy** or

pentynyloxy radical.

By acyl radical is preferably meant a radical having at most 7 carbon atoms such as the formyl, acetyl, propionyl, butyryl or benzoyl radical, but also the valeryl, hexanoyl, acryloyl, crotonoyl or carbamoyl radical.

By monoalkylamino radical is preferably meant the radicals in which the alkyl contains at most 4 carbon atoms. The methylamino, ethylamino, propylamino or butyl (linear or branched) amino radicals can be mentioned.

Similarly, by dialkylamino radical is preferably meant the radicals in which the alkyl contains at most 4 carbon atoms. For example the dimethylamino, diethylamino, methylethylamino radicals can be mentioned.

The carboxy radical or radicals of the products of formula (I) can be salified, amidified or esterified by the various groups known to a man skilled in the art.

By esterified carboxy is meant for example the alkyloxycarbonyl radicals such as for example methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, n-butyl, tert-butyloxycarbonyl, or also benzyloxycarbonyl radicals, these alkyl radicals being able to be substituted by one or more radicals chosen for example from halogen atoms, hydroxyl, alkoxy, acyl, alcyloxy, alkylthio, amino or aryl radicals such as, for example, in the chloromethyl, hydroxypropyl, propionyloxymethyl, methylthiomethyl, dimethylaminoethyl, benzyl or phenethyl groups.

There can be mentioned the radicals formed with the remainders of easily cleavable esters such as methoxymethyl, ethoxymethyl radicals; acyloxyalkyl radicals such as pivaloyloxymethyl, pivaloyloxyethyl, acetoxymethyl or acetoxyethyl; alkyloxycarbonyloxy alkyl radicals such as the methoxycarbonyloxy methyl or ethyl radicals, isopropyloxy-carbonyloxy methyl or ethyl radicals.

A list of such ester radicals can be found for example in the European Patent EP 0,034,536.

By amidified carboxy is meant the groups of $-CON(R_6)(R_7)$ type in which the identical or different R_6 and R_7 radicals represent a hydrogen atom or an alkyl radical having 1 to 4

carbon atoms such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl radicals.

In the groups defined above, $-N(R_6)(R_7)$ therefore represents the amino radical, or a monoalkylamino or diethylamino radical as defined above, but can also represent a heterocycle formed by R_6 and R_7 with the nitrogen atom to which they are attached which may or may not contain an additional heteroatom. The pyrrolyl, imidazolyl, indolyl, piperidino, morpholino, piperazinyl radicals can be mentioned. There are preferred the piperidino, morpholino radicals or piperazinyl radicals optionally substituted on the second nitrogen atom, such as for example in methylpiperazinyl, fluoro-methylpiperazinyl, ethyl-piperazinyl, propylpiperazinyl, phenylpiperazinyl or benzylpiperazinyl: in these last two radicals, the phenyl and benzyl radicals can be substituted, such as for example in chlorophenyl or trifluorophenyl.

By salified carboxy is meant the salts formed for example with equivalent of sodium, potassium, lithium, calcium, magnesium or ammonium. The salts formed with organic bases such as methylamine, propylamine, trimethylamine, diethylamine, triethylamine, N,N-dimethylethanolamine, tris (hydroxymethyl) amino methane, ethanolamine, pyridine, picoline, dicyclohexylamine, morpholine, benzylamine, procaine, lysine, arginine, histidine, N-methylglucamine can also be mentioned.

The sodium salt is preferred.

By aryl is meant the carbocyclic aryl radicals such as phenyl or naphthyl or the monocyclic heterocyclic aryl radicals with 5 or 6 members or constituted by condensed rings, containing one or more heteroatoms preferably chosen from oxygen, sulphur and nitrogen. Among the heterocyclic aryls with 5 members the furyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, thiadiazolyl, pyrazolyl, isoxazolyl, tetrazolyl radicals can be mentioned.

Among the heterocyclic aryls with 6 members, the pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl radicals can be mentioned.

Among the condensed aryl radicals, the indolyl, benzofuranyl, benzothienyl, quinoleinyl radicals can be mentioned.

The phenyl, tetrazolyl and pyridyl radicals are preferred.

By arylalkyl is meant the radicals resulting from the combination of the alkyl radicals and the aryl radicals mentioned above.

The benzyl, phenylethyl, pyridylmethyl, pyridylethyl or tetrazolylmethyl radicals are preferred.

By esterified, etherified or protected hydroxyl radical, is meant the

$-O-\overset{\overset{O}{\|}}{C}-alpha_1$, $alpha_2-O-alpha_3$ or $-O-P$ radicals respectively,

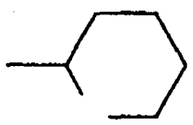
formed from an -OH hydroxyl radical, according to the usual methods known to a man skilled in the art and in which P represents a protective group and $alpha_1$, $alpha_2$ and $alpha_3$ represent in particular an alkyl, alkenyl, alkynyl, aryl or arylalkyl radical having at most 12 carbon atoms and optionally substituted as defined above.

Examples of protective group P, as well as the formation of the protected hydroxyl radical, are given in particular in the usual book known to a man skilled in the art: Protective Groups in Organic Synthesis, Theodora W. Greene, Harvard University, published in 1981 by Wiley-Interscience Publishers, John Wiley & Sons.

The protective group of the hydroxyl radical which can be represented by P, can be chosen for example from the following list: formyl, acetyl, chloroacetyl, bromoacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, benzoylformyl, p-nitrobenzoyl. The following groups can also be mentioned: ethoxycarbonyl, methoxycarbonyl, propoxycarbonyl, fiSS-trichloroethoxycarbonyl, benzyloxycarbonyl, tert-butoxycarbonyl, 1-cyclo propylethoxycarbonyl, tetra-hydropyrannyl, tetrahydrothiopyranyl, methoxytetra-hydropyranyl, trityl, benzyl, 4-methoxybenzyl, benzhydryl, trichloroethyl, 1-methyl 1-methoxyethyl, phthaloyl,

propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl and pivaloyl, phenylacetyl, phenylpropionyl, mesyl, chlorobenzoyl, para-nitrobenzoyl, para-tert-butylbenzoyl, caprylyl, acryloyl, methylcarbamoyl, phenylcarbamoyl, naphthylcarbamoyl.

P can in particular represent the



radical

or also a derivative of silicon such as trimethylsilyl.

By acyloxy radical is meant the radicals in which the acyl radicals have the meaning indicated above and for example the formyloxy, acetoxy, propionyloxy, butyryloxy or benzoyloxy radicals.

- the term arylthio radical preferably designates the radicals in which the aryl radical represents the radicals as defined above such as, for example, in phenylthio, pyridylthio, pyrimidylthio, imidazolylthio or N-methyl-imidazolylthio,
- the term alkylthio radical preferably designates the radicals in which the alkyl radical is as defined above such as, for example, in methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, isopentylthio or isohexylthio; the alkylthio radical is optionally substituted such as, for example, in hydroxy-methylthio, aminoethylthio, haloalkylthio such as preferably bromoethylthio, trifluoromethylthio, trifluoroethylthio or also pentafluoroethylthio, arylalkylthio such as, for example, benzylthio or phenethylthio.

By cyclic radical containing 3 to 6 members is meant a carbocyclic or heterocyclic radical optionally containing one or more heteroatoms chosen from sulphur, oxygen or nitrogen atoms.

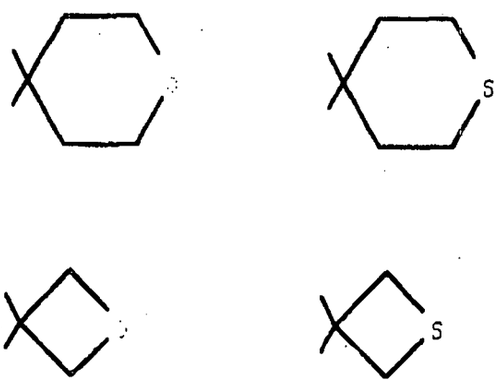
By carbocyclic radical is meant in particular the cycloalkyl radical which preferably designates the cyclopropyl, cyclobutyl radicals and quite particularly the cyclopentyl, cyclohexyl and cycloheptyl radicals.

By heterocyclic radical containing one or more heteroatoms is preferably meant the saturated, heterocyclic, monocyclic radicals such as for example the following radicals: oxirannyl, oxolannyl, dioxolannyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl or morpholinyl.

By alkyl, alkenyl or alkynyl radicals optionally interrupted by a heteroatom chosen from sulphur, oxygen or nitrogen atoms is meant the radicals containing one or more of these atoms identical or different in their structure, these heteroatoms obviously not being able to be situated at the end of the radical. There can be mentioned, for example, the alkoxyalkyl radicals such as methoxymethyl, methoxyethyl or propyloxypropyl, the alkoxyalkoxyalkyl radicals such as methoxyethoxymethyl or also the alkylthioalkyl radicals such as for example propylthiopropyl, propylthioethyl, methylthiomethyl or also N-methyl N-propylaminopropyl.

In all these radicals, the sulphur atoms can be non-oxidized as in the alkylthio, arylthio radicals or on the contrary be oxidized to produce the alkylsulphinyl, arylsulphinyl, alkylsulphonyl, or arylsulphonyl radicals: alkylsulphinyl and alkylsulphonyl designate radicals in which the alkyl radical is chosen for example from the values indicated above for the alkyl radical such as for example methylsulphinyl, ethylsulphinyl, methylsulphonyl or ethylsulphonyl radicals,
arylsulphinyl and arylsulphonyl designate arylthio radicals, in which the aryl radical is chosen, for example, from the values indicated above for the aryl radical such as for example the following radicals: phenyl-sulphinyl or -sulphonyl, pyridyl-sulphinyl or -sulphonyl, pyrimidyl-sulphinyl or -sulphonyl, imidazolyl-sulphinyl or -sulphonyl or N-methylimidazolyl-sulphinyl or -sulphonyl.

R_4 and R_5 can in particular form together the following heterocycles:



As particular examples of alkyl radicals substitutedby one or more halogens or haloalkyl, there can be mentioned the monofluoro, chloro, bromo or iodomethyl or -ethyl, difluoro, dichloro or dibromomethyl, trifluoromethyl or pentafluoroethyl radicals.

As particular examples of alkoxy radicals substitutedby one or more halogens or haloalkoxy, there can be mentioned the bromoethoxy, trifluoromethoxy, trifluoroethoxy or also pentafluoroethoxy radicals.

As particular examples of substituted aryl or aralkyl radicals, there can be mentioned those in which the phenyl radical is substituted by one or more radicals chosen from iodine, chlorine or bromine atoms, methoxy, trifluoromethyl, cyano or amino radicals.

When the products of formula (I) as defined above contain an amino radical salifiable by an acid it is understood that these acid salts also form part of the invention.

The addition salts with mineral or organic acids of the products of formula (I) can be, for example, the salts formed with the following acids: hydrochloric, hydrobromic, hydroiodic, nitric, sulphuric, phosphoric, propionic, acetic, formic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic, ascorbic, alkylmonosulphonic such as for example methanesulphonic, ethanesulphonic, propanesulphonic, alkyldisulphonics such as for example methanedisulphonic, alpha, beta-ethanedisulphonic, arylmonosulphonics such as benzenesulphonic and

aryldisulphonic.

More particularly there can be mentioned the salts formed with hydrochloric or methanesulphonic acids for example.

A particular subject of the present invention is the preparation process as defined above for the products of formula (I) as defined above in which:

R_1 and R_2, identical or different, are chosen from the hydrogen atom, halogen atoms and alkyl, alkenyl, alkynyl, cyano, trifluoromethyl, amino, monoalkylamino and dialkylamino radicals,

R_3 represents a hydrogen atom, an alkyl radical, optionally interrupted by one or more oxygen or sulphur atoms, a phenyl or pyridyl radical, these radicals being optionally substituted by one or more radicals chosen from halogen atoms, the following radicals: phenyl, optionally esterified, etherified or protected ahydroxyl, alkoxy, cyano, trifluoromethyl, hydroxyalkyl, free, esterified, amidified or salified carboxy, amino, mono- or dialkylamino, the nitrogen atom of the pyridyl radical being optionally oxidized,

R_4 and R_5

either are identical or different and represent an alkyl radical, optionally substituted by one or more radicals chosen from optionally esterified, etherified or protected hydroxyl radicals, halogen atoms and alkylthio and phenylthio radicals themselves optionally substituted by one or more radicals chosen from halogen atoms and the hydroxyl radical, or together form the:

 radical

in which T represents an oxygen or sulphur atom, X and Y, identical or different, represent an oxygen or sulphur atom.

A more particular subject of the present invention is the preparation process as defined above for the products of formula (I) as defined above in which:

R_1 and R_2, identical or different, are such that one

represents a hydrogen atom or a cyano radical and the other is chosen from halogen atoms and cyano and amino radicals,
R_3 represents a hydrogen atom or an alkyl radical optionally substituted by an optionally esterified, etherified or protected hydroxyl radical,
R_4 and R_5, identical or different, represent a linear or branched alkyl radical containing at most 6 carbon atoms, optionally substituted by one or more radicals chosen from optionally esterified, etherified or protected hydroxyl radicals and halogen atoms and X and Y represent an oxygen atom.

An even more particular subject of the present invention is the preparation process as defined above for the following products

- 3-[4-amino-3-(trifluoromethyl) phenyl] 5,5-dimethyl 2,4-imidazolidine dione,
- 5,5-dimethyl-3-(4-iodo-3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione,
- 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl-2,5-dioxo-3-(4-hydroxybutyl)-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile,
- 4-(2,4-dioxo 1-(4-hydroxybutyl)-8-oxa-1,3-diazaspiro(4,5) decan-3-yl)-2-(trifluoromethyl) benzonitrile,
- 5,5-dimethyl-3-(4,5-dicyano-3-(trifluoromethyl) phenyl)-2,4-imidazolidinedione,

these products being in all possible racemic, enantiomeric or diastereoisomeric isomer forms, as well as their addition salts with the pharmaceutically acceptable mineral and organic acids or mineral and organic bases.

To implement the process indicated above, the operation is preferably carried out under the conditions indicated hereafter.

To obtain the product of formula (A_1), the operation is preferably carried out by using one half-mol of the compound of formula (III) per mol of the compound of formula (II), in dimethylformamide or preferably dimethylacetamide, at a temperature of approximately 0°C.

In a preferred manner, the compound of formula (III) is dimethyldibromohydantoin used in solution in dimethyl-acetamide and introduced into the orthotrifluorometylanilane of formula (II) itself in solution in dimethylacetamide while maintaining the temperature at approximately 0°C.

The compound of formula (A_2) which forms intermediately in situ, and which is not isolated, thus has a selective bromination which is situated in para position of the amino radical.

Then, in situ, a half-mol of compound B, i.e. dimethylhydantoin, is added, preferably in the presence of cuprous oxide at a temperature of approximately 155°C and in this way the product formula (A_1) is obtained with a remarkable yield.

To isolate the product of formula (A_2), the reaction of the compound of formula (II) with the compound of formula (III) can be carried out in dimethylacetamide, preferably at a temperature of 0°C.

The compound of formula (A_2) can also be obtained by selective bromination by N-bromosuccinimide in solid form or in solution, choosing dimethylformamide or dimethyl-acetamide as solvent, preferably using a solvent such as water, acetone or other polar solvents usually employed.

In an unexpected manner, a remarkable selectivity of the bromination position is in fact observed under these conditions.

Also the operation is preferably carried out under these conditions at a temperature of 0 to 20°C.

The product of formula (A_2) thus obtained can be subjected to a reaction with a derivative of hydantoin, i.e. the compound of formula (IV), in order to obtain the product of formula (A_3); the operation is carried out in a solvent such as the triglyme, dimethylsulphoxide, diphenyl oxide, dimethylformamide or also and preferably dimethylacetamide.

The operation is preferably carried out in the presence of a catalyst such as copper in the native state or in the form of cuprous or cupric oxide.

The operation is preferably carried out in dimethyl-

acetamide in the presence of cuprous oxide at a temperature of the order 165°C.

The product of formula (A) can then be subjected to a diazotation reaction such as for example by formation of the hydrochloride: in this way the diazonium salt ($N{=}N^{\oplus}$-, $Cl^{\ominus}$) is generated by reacting sodium nitrite in hydrochloric acid.

The diazonium salt thus obtained can be isolated if desired, in the form of the tetrafluoroborate ($BF_4^{\ominus}$) salt which is insoluble in water by treatment with sodium tetrafluoroborate ($NaBF_4$).

The diazonium salt i.e. the product of formula (V) obtained can then be subjected to a halogenation reaction in order to obtain the product of formula (F_1).

This halogenation can be a bromination by reaction, for example, of sodium or lithium bromide in a solvent such as for example a water/methylene chloride mixture or also, and preferably, an iodination by the action of sodium iodide in a water/methylene chloride mixture.

The product of formula (F_1) in which the halogen atom is a fluorine can also be obtained by heating the diazonium salt isolated above in the form of tetrafluoroborate at a temperature of the order of 60 to 80°C.

The product of formula (F_1) thus obtained can then be subjected to a substitution reaction on the halogen atom, which is preferably an iodine atom, to introduce the R'_1 radical and in this way to obtain the product of formula F_2. The operation is carried out in a solvent such as for example dimethylformamide. In the compounds of formulae (VI) and (VII), M represents a metal such as copper or nickel, or also palladium in particular to introduce an acetylenic. The compounds of formulae (VI) and (VII) can therefore in particular be copper cyanide or also trifluoro-methyl cuprate (CF_3Cu) obtained by the reaction of trimethyl-(trifluoromethyl) silane with potassium fluoride and copper iodide in dimethylformamide.

The halogenation reaction of the product of formula (A) to produce the product of formula (F_3) can be carried out under the usual conditions such as for example by bromination

by N-bromo succinimide, in a solvent such as for example dimethylformamide at a temperature of the order of 20 to 30°C: the halogen atom is thus introduced into the ortho position of the amino radical.

The product of formula (F_3) to produce the product of formula (F_4) can be subjected to a substitution reaction of the halogen atom by the R'_2 radical according to the usual conditions known to a man skilled in the art and in particular as defined above, to introduce the R'_1 radical onto the product of formula (F_1).

The amine of formula (F_4) thus obtained can be converted into the diazonium salt then halogenated and finally substituted on the halogen atom by the radical R'_1 under the same conditions as those described above, to thus produce the product of formula (F_5).

The halogenation reaction of the product of formula (F_3) into the product of formula (F_6) can be carried out according to the usual conditions in particular by formation of the diazonium salt on the amino radical then halogenation under the conditions defined above.

The product of formula (F_6) can in turn be substituted on the two halogen atoms in particular by the same cyano radical for example by the action of copper cyanide in dimethylformamide.

The products of formula (F_1), (F_2), (F_3), (F_4), (F_5) or (F_6) can be subjected to the action of the product of formula (IV) to produce the corresponding product of formula (I) under the conditions defined above for the reaction of the product of formula (A_2) with the product of formula (IV) to produce the product of formula (I').

The products of formulae (A_1), (A_3) and (I') thus obtained can then if necessary and if desired, be subjected to a substitution reaction by a halogenated derivative of formula R'_3-Hal in which R'_3 can in particular represent an acylated derivative such as in particular the ZO-alk-Hal compound in which alk represents an alkyl radical, Z an acyl radical such as in particular the acetyl radical or also a silyl radical and Hal represents a halogen atom such as

preferably a bromine, iodine or chlorine atom, preferably fluorine.

The operation is carried out in a solvent such as for example and in particular dimethylformamide or dimethylacetamide in the presence of a strong base such as soda, sodium or potassium hydride. The operation can be carried out by phase transfer reaction in the presence of quaternary ammonium salts such as tert-butyl ammonium.

In this way the products of formula (I) are in particular obtained in which R_3 represents an alkyl radical substituted by a free, esterified, etherified or protected hydroxyl radical such as an acylated or silylated radical.

The optional reactive functions which can be carried by or represented by R''_1, R''_2, R'_3, R'_4 or R'_5 and which are optionally protected, can be in particular the hydroxy or amino functions. The usual protective groups are used to protected these functions. For example the following protective groups of the amino radical can be mentioned: tert-butyl, tert-amyl, trichloroacetyl, chloroacetyl, benzhydryl, trityl, formyl, benzyloxycarbonyl.

As a protective group of the hydroxy radical the radicals such as formyl, chloroacetyl, tetrahydropyrannyl, trimethylsilyl, tert-butyl dimethylsilyl can be mentioned.

Of course the above list is not limitative and other protective groups, for example known in the chemistry of the peptides, can be used. A list of such protective groups is found for example in the French Patent BF 2,499,995 the content of which is incorporated here by reference.

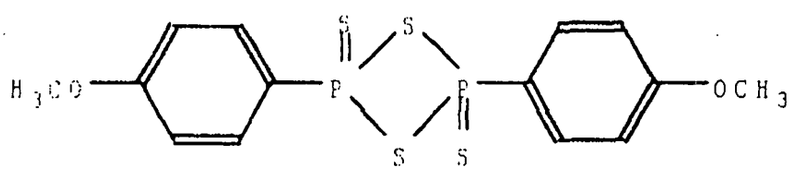
The optional elimination reactions of the protective groups are carried out as indicated in said Patent BF 2,499,995. The preferred method of elimination is acid hydrolysis using acids chosen from the following acids: hydrochloric, benzene sulphonic or paratoluene sulphonic, formic or trifluoroacetic. Hydrochloric acid is preferred.

- The optional esterification of products, in which R'_3 contains a free OH radical is carried out under standard conditions. For example an acid or a functional derivative can be used, for example an anhydride such as acetic

anhydride in the presence of a base such as pyridine.

The optional **esterification** or salification of the products in which R'_3 contains a COOH group is carried out under standard conditions known to a man skilled in the art. - The optional **amidification** of products, in which R'_3 contains a COOH radical is carried out under standard conditions. A primary or secondary **amine** can be used on a functional derivative of the acid for example a symmetrical or mixed anhydride.

The conversion reaction of the >C=O group or groups into a >C=S group is carried out using a so-called Lawesson reagent of formula:



which is a product commercially available for example from the firm **FLUKA** and the use of which is described for example in the publication: Bull. Soc. Chim. **Belg. Vol.** 87, No. 3, (1987) p. 229.

When it is desired to convert two >C=O **functions** into two >C=S functions the operation is carried out in the presence of an excess of Lawesson **reagent.** The same is true when one starts from a molecule containing a >C=S function and a >C=O function and it is desired to convert said >C=O function into a >C=S function.

On the other hand when one starts from a molecule containing two >C=O functions and it is desired to obtain a product containing only a single >C=S function. The operation is carried out in the presence a deficit of Lawesson **reagent.** Then in general a mixture of three products is obtained: each of the two products containing a >C=O function and a >C=S function and the product containing two >C=S functions. These products can then be separated by the usual methods such as **chromatography.**

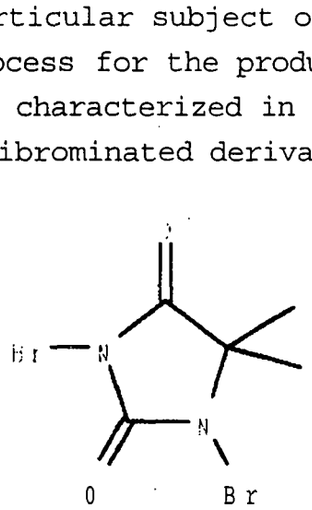
The conversion reaction of the amino radical into a nitro radical can be carried out under the usual conditions known to a man skilled in the art, such as in particular those described in the following references:

- Emmons W.D., J. Am. Chem. Soc. 1957, 79, 5528,
- Holmes R R and Bayer R p, J. Am. Chem. Soc. 1960, 82, 3454.

A preparation process for certain products of formula (I) as defined above is described in the French Patent No. 2,693,461.

A quite particular subject of the present invention is a preparation process for the products of formula *(I)* as defined above, characterized in that to obtain the product of formula (A_1) from the products of formulae (II), (III) and B, as defined above, the operation is carried out in a solvent chosen from dimethylsulphoxide, triglyme, dimethylacetamide or dimethylformamide and preferably dimethylacetamide.

A more particular subject of the present invention is a preparation process for the products of formula (I) as defined above, characterized in that the compound of formula (III) is the dibrominated derivative of formula:



and that a half-mol of this compound and a half-mol of the compound of formula (B) are used per mol of the compound of formula (II).

An even more particular subject of the present invention is a preparation process for the products of formula (I) as defined above, characterized in that the reaction is carried out at a temperature of 130°C to 160°C and preferably at 155°C.

The starting products of formulae (II), (III), (B), (IV), (VI) and (VII) on which the process, which is a subject

of the invention, is carried out in order to obtain the products of formula (I), are known and commercially available or can be prepared according to methods known to a man skilled in the art.

The products of formula (IV) which are derivatives of hydantoin are widely used and mentioned in the literature such as for example in the following articles:

- J. Pharm. Pharmacol., 67, Vol. 19 (4), p. 209-16 (1967)
- J. Chem. Soc., 74, (2), p. 219-21 (1972)
- Khim. Farm. Zh., 67, Vol. 1 (5) p. 51-2
- German Patent 2,217,914
- European Patent 0,091,596
- J. Chem. Soc. Perkin. Trans. 1, 74 (2) p. 48, p. 219-21.

A subject of the present invention is also as new industrial products, the following products:

- 3-[4-amino 3-(trifluoromethyl) phenyl]-5,5-dimethyl 2,4-imidazolidine dione,
- 5,5-dimethyl 3-(4-iodo 3-(trifluoromethyl) phenyl)-2,4-imidazolidinedione,
- 5,5-dimethyl 3-(4,5-dicyano 3-(trifluoromethyl) phenyl) 2,4- imidazolidinedione.

The examples given hereafter illustrate the invention without however limiting it.

EXAMPLE **1: 3-[4-amino 3-(trifluoromethyl) phenyl] 5,5-dimethyl 2,4-imidazolidine** dione

100 g of O-trifluoromethylaniline is introduced at 20°±2°C then 100 ml of dimethylacetamide is added while maintaining the same temperature. After cooling down under agitation at 0°C±2°C a solution of 88.8 g of dibromodimethylhydantoin and 100 ml of dimethylacetamide isthen added over about 30 minutes while maintaining the temperature at 0°C±2°C. The reaction medium is maintained under agitation for 30 minutes, then taken to 20°C±2°C and 40 g of dimethylhydantoin then 50 g copper oxide are added. The whole is heated under reflux for approximately 18 hours then cooled down to 20°C±2°C, agitation is carried out for 30 minutes followed by filtering, separating and washing with 4 x 25 ml of dimethylacetamide. The resultant product is then

poured into 300 ml of pure 22°Bé ammonium hydroxide and 300 ml of demineralized water under agitation over 1 hour at 20°C±2°C, agitation is continued for 1 hour at 20°C±2°C then the whole is cooled down to 0°C±5°C and is maintained under agitation for another hour, followed by separating, washing at 20°C±2°C, with 100 ml of pure 22°Bé ammonium hydroxide then with 4 x 100 ml of demineralized water and drying. In this way 155.8 g of expected product is obtained.

Analyses: IR $CHCl_3$ (cm^{-1})

NH/NH_2	$=C-NH_2$	3510
	=C-NH	3449
	$=C-NH_2$	3429

$\rangle$=O 1781-1719

Aromatics + NH_2 def. 1637-1585-1516-1511

EXAMPLE 2: **5,5-dimethyl-3-(4-iodo 3-(trifluoromethyl) phenyl)-2,4-imidazolidine** dione

140 g of the product of Example 1 and 210 ml of demineralized water are introduced at 20°±2°C, agitation is carried out and 210 ml of pure 22°Bé hydrochloric acid is added over about 5 minutes. The reaction medium is maintained at 35°-40°C for 30 minutes under agitation then cooled down to 0°±5°C under agitation. Then 28 ml of methylene chloride is added, a solution of 43.7 g of sodium nitrite in 70 ml of demineralized water is then added over about 30 minutes, at 0°±5°C. The reaction medium is maintained for another hour under agitation at 0°±5°C, a solution of 87.7 g of sodium iodide in 140 ml of demineralized water is added over 45 minutes. The reaction medium is maintained under agitation for another hour and 700 ml of methylene chloride is added. Agitation is carried out for 15 minutes at 0°±5°C, 28 g of sodium metabisulphite is added in one go and agitation is carried out for another 30 minutes while leaving the temperature to return to 20°C. After pouring, the organic phase is decanted, the aqueous phase is reextracted with 280 ml of methylene chloride, then

the organic phases are washed with 3 x 140 ml of a saturated aqueous solution of NaCl. The joint chloromethylenic phases are dried, followed by filtering and washing with 3 x 70 ml of methylene chloride and 184.5 g of expected product (white crystals) is obtained, M.p. = 164-165°C.

EXAMPLE 3: 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile

184 g of the product of Example 2 is introduced at 20°±2°C and 66.15 g of copper cyanide and 420 ml of dimethylformamide are added under agitation the whole is heated while distilling the methylene chloride until a temperature of 130°C is obtained in the reaction medium and then it is maintained for 5 hours under agitation at this temperature. The medium is cooled down to 20°±2°C under agitation, maintained for 1 hour under these conditions followed by separation and washing with 3 x 0.3 vol of dimethylformamide. Then 700 ml of pure 22°Bé ammonium hydroxide and 700 ml of demineralized water are added to the mixture agitated at 20°±2°C. Agitation is carried out for 1 hour at 20°±2°C then the whole is cooled down to 0°±5°C, maintained for 1 hour under agitation at 0°±5°C, followed by separating and washing with 2 x 140 ml of pure 22°Bé ammonium hydroxide at 20°±2°C then with 4 x 140 ml of demineralized water then drying. Purification is carried out by adding 1105 ml of ethyl acetate then taking to reflux under agitation and then 12.3 g of acticarbon black CX is added. The reaction medium is maintained under agitation under reflux for 30 minutes, then filtered, followed by washing with 3 x 61 ml of boiling ethyl acetate, concentration under agitation, cooling down under agitation to 0°±2°C and maintaining under these conditions for 2 hours. Separation, washing with 3 x 37 ml of ethyl acetate at 0°±2°C and drying are carried out. In this way 103.7 g of expected product (clear beige powder) is obtained.

M.p.° = 210°C

Analyses: IR nujol (cm^{-1})

OH/NH region	max	3340
-ON		2245

>=O 1789-1720

Aromatics 1612-1575-1505

EXAMPLE 4: 4-(4,4-dimethyl-2,5-dioxo-3-(4-hydroxybutyl) 1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile

300 ml of dimethylformamide and 100 g of the product of Example 3 are introduced at 20°/22°C and the reaction medium is maintained under agitation at this temperature for approximately 5 minutes then 98.5 g of 4-bromobutyl acetate then 20 g of soda are added and the whole is maintained under agitation and under a nitrogen atmosphere at +20°/+22°C for approximately 22 hours. While maintaining agitation, at this temperature, 20 g of soda is added then over approximately 5 minutes 400 ml of methanol is added and the whole is maintained in this way for 1 hour. While leaving the temperature to rise, 500 ml of demineralized water at +20°C is introduced under agitation, then the reaction medium is placed under agitation, 500 ml of demineralized water is added at +20°C and the whole is maintained under agitation for 1 hour at 25°/30°C, then cooled down under agitation to +0°/+5°C, and maintained for 2 hours, followed by separating, washing with 4 x 100 ml of demineralized water and drying. Purification is carried out by adding 696 ml of methylene chloride at 20°/22°C and washing with 3 x 232 ml of demineralized water then drying, 5.8 g of supra black is added, the medium is maintained under agitation at 20°±2°C for 2 hours followed by filtering and rinsing with 2 x 116 ml of methylene chloride. After concentrating under agitation, 116 ml of denat. ethanol toluene is added at 20°C then 174 ml of demineralized water is added. The reaction medium is cooled down under agitation to 20°/22°C, maintained under agiatation for 2 hours at this temperature then cooled down to 0°±2°C and maintained for 1 hour under these conditions, followed by separating, washing with 2 x 58 ml of ethanol with 50% water at 0°/+2°C and drying. In this way 111.5 g of expected product (white powder) is obtained. M.p. = 102°C.

EXAMPLE 5: 4-(4,4-dimethyl 2,5-dioxo 1-imidazolidinyl) 2-

(trifluoromethyl) benzonitrile

Stage *I*: para-bromo ortho-trifluoromethyl aniline

1st method:

100 g of ortho trifluoromethylaniline and 200 ml of dimethylacetamide are introduced and the reaction medium is cooled down to 0°±2°C. 88.8 g of dibromo-dimethyl hydantoin is added over 30 minutes at 0°±2°C, the temperature is maintained at 0°±2°C and agitation is carried out at 0°±2°C for 15 minutes. Then the temperature is allowed to rise to 20°C and the whole is poured into 200 ml of demineralized water at 20°±2°C. Agitation is carried out for 15 minutes, 400 ml of isopropyl ether is added, the aqueous phase is decanted and the organic phase is washed with 2 x 100 ml of demineralized water, the aqueous phases are reextracted with 100 ml of isopropyl ether and the combined organic phases are dried, filtered and washed with 2 x 20 ml of isopropyl ether. Concentration is carried out a temperature of 30-40°C and in this way 149 g of expected product (orangy-brown oil) is obtained.

2nd method:

100 g of ortho trifluoromethylaniline and 200 ml of dimethylacetamide are introduced and 107.3 g of N-bromo succinimide in powder form is added over about 30 minutes at 20°±2°C. The temperature is maintained at 20°±2°C and agitation is carried out under a nitrogen atmosphere at 20°±2°C for 15 minutes, then the whole is poured into 200 ml of demineralized water at 20°±2°C, agitation is carried out for 15 minutes and 400 ml of isopropyl ether is added. The aqueous phase is decanted, the organic phase is washed with 2 x 100 ml of demineralized water, the aqueous phases are reextracted with 100 ml of isopropyl ether and the combined organic phases are dried, followed by filtering, washing with 2 x 20 ml of isopropyl ether, concentrating and in this way 149 g of expected product is obtained.

Analyses: IR on $CHCl_3$ (cm^{-1})

$=C-NH_2$	3520-3430
NH_2 def. + aromatics	1634-1610-1581-1492

Stage 2: p-bromo o-trifluoromethyl diazonium fluoroborate

120 g of the product obtained in Stage 1 above and 240 ml of demineralized water are introduced at 20°C, then 375 ml of 22°Bé concentrated hydrochloric acid is introduced over about 15 minutes, while leaving the temperature to rise to 35-40°C. Agitation is carried out for 30 minutes while leaving the temperature to drop to 20°C, followed by cooling down to 0°C±2°C, and a solution of 240 ml of demineralized water and 72.5 g of sodium nitrite is introduced over about 30 minutes, while maintaining the temperature at 0°C±2°C, followed by agitation for 1 hour while maintaining the temperature at 0°C±2°C. 140 g of sodium tetrafluoroborate is added at this temperature and agitation is carried out while maintaining the temperature at 0°C±2°C for 1 hour, followed by filtering, rinsing with 2 x 50 ml of ice-cooled demineralized water and in this way 194.14 g of expected product is obtained.

Stage 3: p-bromo o-trifluoromethyl benzonitrile

13.5 g of copper cyanide and 400 ml of demineralized water are introduced at 20°C, the temperature is maintained at +20°C±2°C, a solution of 41.6 g of sodium cyanide and 100 ml of demineralized water is added over 5 minutes, followed by cooling down to 0°C±2°C and 194 g of the diazonium salt obtained in Stage 2 above is introduced while maintaining this temperature over about 10 minutes. The reaction medium is maintained under agitation at 0°C±2°C for 1 hour then the temperature is allowed to rise to 20°C and 50 ml of concentrated ammonium hydroxide and 1 litre of methylene chloride are added, followed by decanting, washing, drying, concentrating, taking up in 160 ml of heptane, filtering, drying and purifying by chromatographing on silica eluting with heptane-ethyl acetate (9-1) and in this way 86 g of expected product (white crystals) is obtained.

M.p. = 30°C.

Analyses: IR $CHCl_3$ (cm^{-1})

-ON	~ 2240
Aromatics	1598-1570-1488

Stage 4: 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile

110 g of the product obtained in Stage 3 above and 275

ml of dimethyl acetamide are introduced at 20°C. 31.7 g of copper oxide Cu_2O and 67.7 g of dimethyl hydantoin are added at 20°C under agitation. The reaction medium is heated for about 5 hours at 165°C, left to cool down to 20°C, then filtered and rinsed with 3 x 55 ml of dimethyl acetamide. A solution of 550 ml of 22°Bé concentrated ammonium hydroxide and 550 ml of ice-cooled water is prepared and it is introduced over about 15 minutes at 0°C and the reaction medium is left for about 1 hour at 0°C, followed by separating, washing with 110 ml of a 50% aqueous solution of ammonium hydroxide then with 4 x 110 ml of demineralized water. After drying, purification is carried out by adding 125 ml of toluene and 125 ml of acetonitrile then heating to 80°C for 1 hour and leaving to cool down. Agitation is then carried out for 1 hour at 0°C, followed by filtering, separating and washing with 2 x 25 ml of an ice-cooled solution (acetonitrile/toluene (1:1)). After drying, 104.4 g of expected product is obtained in this way. M.p. = 210°C.

EXAMPLE 6: **4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile**

Stage 1: 3-(trifluoromethyl)-4-cyano chloro benzene

100 g of 2-trifluoromethyl-4-chloro iodobenzene, 200 ml of dimethylformamide and 58.7 g of copper cyanide are introduced at 20°C, the reaction medium is heated for 3 hours at 140°C, left to cool down to 20°C, then poured into 600 ml of ice-cooled demineralized water. After filtering, rinsing with 3 x 200 ml of isopropyl ether, the aqueous phase is decanted and reextracted with 3 x 200 ml of isopropyl ether. The organic phases are combined and washed with 200 ml of demineralized water and dried. In this way 66.64 g of expected product is obtained.

Analyses: IR on $CHCl_3$ (cm^{-1})

C=N	- 2238
Aromatics	1601-1570

Stage 2: 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile

4.47 g of the product obtained in Stage 1 above, 11.2 ml of triglyme, 2.78 g of 5,5-dimethyl hydantoin and 1.34 g of

cuprous oxide are introduced then the suspension is agitated and taken to 215°C for 4 hours. Then it is returned to ambient temperature, followed by filtering, washing with 4.5 ml of triglyme and agitating without exceeding 25°C, 4.5 ml of 22°Bé concentrated ammonium hydroxide, 26 ml of water and 4.5 ml of toluene. Agitation is carried out for 15 minutes at 20°C then the reaction medium is cooled down to -10°C, agitation is carried out for 1 hour, followed by separating, washing with 2.2 ml of toluene then 4.5 ml of water and drying. In this way 1.98 g of expected product (brown crystals) is obtained. M.p. = 210°C.

Analyses: IR nujol (cm^{-1})

OH/NH absorption	~ 3340
C≡N	- 2240
	1788-1721
Aromatics	1610-1572-1504

EXAMPLE 7: **5,5-dimethyl-3-(4,5-dicyano-3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione**

Stage 1: 3-(5,5-dimethyl-2,4-imidazolidine)-2-amino 3-(trifluoromethyl) bromo benzene

20 g of the product of Example 1 and 40 ml of dimethylacetamide are introduced at 20±2°C, followed by cooling down to +10°C±2°C and 12.5 g of N-bromo succinimide in powder form is added over about 30 minutes at 10°C±2°C and under agitation and under a nitrogen atmosphere. The temperature is maintained at 10°C±2°C, agitation is carried out for 15 minutes, the temperature is allowed to rise to 20°C then agitation is carried out for 1 hour. The reaction medium is poured into 200 ml of methylene chloride, 100 ml of demineralized water is introduced at 20°C±2°C, followed by decanting, washing the organic phase with 2 x 50 ml of demineralized water at 20°C±2°C, drying and concentrating. In this way 22 g of expected product is obtained.

Stage 2: 4-(5,5-dimethyl-2,4-imidazolidinedione)-2-bromo 5-(trifluoromethyl) iodo benzene

20 g of the product obtained in Stage 1 above and 30 ml

of demineralized water are introduced at 20°C and 30 ml of 22°Bé concentrated hydrochloric acid is introduced over 15 minutes, while allowing the temperature to rise to 35-40°C. Agitation is carried out for 30 minutes while allowing the temperature to drop to 20°C, followed by cooling down to 0°C±2°C and a solution of 12 ml of demineralized water and 4.9 g of sodium nitrite is introduced over 30 minutes while maintaining this temperature. Agitation is carried out for 1 hour while maintaining this temperature and under agitation 100 ml of methylene chloride is added then a solution of 9.83 g of sodium iodide and 10 ml of demineralized water is added over 30 minutes and the reaction medium is maintained under agitation for 1 hour at 0°C±2°C, then the temperature is allowed to rise to 10°C. Then 4 g of sodium metabisulphite is added, followed by decanting, the chloromethylenic phase is washed with water, dried and concentrated. In this way 18.5 g of expected product is obtained.

Analyses: $CHCl_3$ (cm^{-1})

=C-NH	3446
	1790-1730
Aromatics	1597-1560

Stage 3: 5,5-dimethyl-3-(4,5-dicyano 3-(trifluoromethyl) phenyl)-2,4-imidazolidinedione

13 g of the product obtained in Stage 2 above, 26 ml of dimethylformamide, 2.7 g of copper cyanide and 1.47 g of sodium cyanide are introduced at 20°C and the reaction medium is heated for 20 hours at 150°C. Then it is left to cool down to 20°C, poured into a mixture of 50 ml of demineralized water and 50 ml of 22° pure ammonium hydroxide, followed by filtering, rinsing with 3 x 50 ml of methylene chloride, the aqueous phase is decanted and reextracted with 3 x 50 ml of methylene chloride. The organic phases are combined and washed with 50 ml of demineralized water and dried. The chloromethylenic phase is agitated for one hour at 20°C with 1.5 g of acticarbon black and the methylene chloride is evaporated off and replaced with 30 ml of isopropyl ether.

Separation is carried out at 20°C, followed by washing with 3 x 10 ml of isopropyl ether and drying. Purification is carried out by chromatography on silica eluting with methylene chloride-ethyl acetate (95-5), then by dissolution in isopropanol under reflux, filtering, rinsing with isopropanol, concentrating, ice-cooling for 1 hour, separating and drying. In this way 3.1 g of expected product (white crystals) is obtained. M.p. = 159-160°C.

Analyses: IR

OH/NH	3403-3388
ON	2236
>=O	1776-1738-1729
Aromatics	1606-1575-1502.

EXAMPLE 8: 4-(2,4-dioxo 8-oxa 1,3-diaza spiro[4,5]decan 3-yl) 2-trifluoromethyl) aminobenzyl

A mixture of 7 g of para-bromo-orthotrifluoromethyl-aniline obtained in Stage 1 of Example 5, 15 ml of dimethylacetamide, 2.33 g of cuprous oxide and 6 g of 5[spiro(4-pyran)] 2,4-imidazolidine dione (the preparation of which is given hereafter) is agitated for 18 hours at 150°-155°C. The reaction medium is cooled down to 20-22°C, filtered, washed with 2 times 7 ml of dimethylacetamide and poured into 200 ml of water. Agitation is carried out for 1 hour at ambient temperature, followed by separating and washing with a mixture of water and 20% ammonium hydroxide (50/50) then with water. After drying at 40°C, 9.1 g of the desired product is collected.

PREPARATION OF; 5[spiro(4-pyran)] 2,4-imidazolidine dioneused at the start of Example 8.

5 g of tetrahydro-4h-pyran-4-one, 25 ml of demineralized water, 25 ml of ethanol, 7.2 g of potassium cyanide and 57 g of ammonium carbonate are heated for 4 hours at 45-50°C. Concentration under reduced pressure is carried out to dryness. The dry extract is taken up in 50 ml of water, separated, washed and dried at 40°C. 7.2 g of expected product is obtained.

NMR spectrum (DMSO)

1.47-1.84: the CH_2-C's; 3.59-3.81: the CH_2O's; 8.57-10.67: the NH-C=O's.

EXAMPLE 9: 4-(2,4-dioxo 8-oxa 1,3-diaza spiro[4,5]decan 3-yl) 2-trifluoromethyl) iodobenzyl

The operation is carried out as in Example 2, starting with 8 g of the product obtained in Example 8 using 10 ml of 22°Bé hydrochloric acid, 2.18 g of sodium nitrite and 5.5 g of sodium iodide. In this way 8.9 g of the desired product is collected.

EXAMPLE 10: 4-(2,4-dioxo 8-oxa 1,3-diaza spiro[4,5]decan 3-yl) 2-trifluoromethyl) benzonitrile

The operation is carried out as in Example 3, using 3.2 g of copper cyanide. After recrystallization from isopropanol, 1.8 g of the desired product is collected.

NMR spectrum: $CDCl_3$

1.78 (m), 2.55 (m): C-CH_2; 3.70 (m), 4.13 (m): CHO; 6.21 (s): CONH; 7.95 (m), 8.11 (m): aromatic H's.

EXAMPLE 11; 4-(2,4-dioxo 1-(4-hydroxybutyl) 8-oxa 1,3-diaza spiro[4,5]decan 3-yl) 2-trifluoromethyl) benzonitrile

55 g of sodium hydride at 50% in oil is introduced and 340 mg of the product obtained in Example 10 in solution in 25 ml of dimethylformamide is added over 25 minutes, 20 minutes after the release of hydrogen has finished, 0.41 g of 4-iodobutoxy trimethylsilane is added and agitation is carried out for 18 hours at ambient temperature. The reaction medium is poured into 10 ml of water, followed by extraction with ethyl ether, washing with water then with salt water and drying, 10 ml of methanol and 1 ml of 2N hydrochloric acid are added, agitation is carried out 30 minutes and the whole is poured into 20 ml of water saturated with NaCl, extracted with chloroform, the extracts are dried, evaporated to dryness and the residue is chromatographed on silica eluting with a methylene chloride-acetone (8-2) mixture. 369 mg of the desired product is obtained.

I.R. Spectrum ($CHCl_3$) cm^{-1}

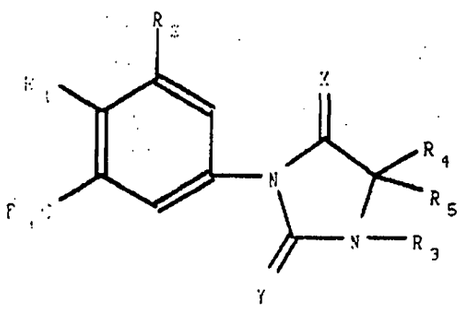
OH	3626-3485
ON	2235

C=O	1775-1721
aromatics	1615-1602-1575-1505.

We claim

~~CLAIMS~~

1) Preparation process for the products of formula (I):



(I)

in which:

R_1 and R_2, identical or different, are chosen from the hydrogen atom, halogen atoms and the following radicals **alkyl**, alkenyl, alkynyl, **alkyloxy**, **alkenyloxy**, **alkynyloxy**, **phenyl**, **phenoxy**, nitro, **trifluoro-methyl**, **acyl**, cyano, **amino**, monoalkylamino, **dialkylamino**, free, **esterified**, **amidified** or salified **carboxy**,

R_3 is chosen from the hydrogen atom and alkyl, alkenyl, alkynyl, **aryl** and arylalkyl radicals, all these radicals being optionally substituted by one or more **substituents** chosen from halogen atoms, the following radicals: optionally esterified, etherified or protected **hydroxyl**, **alkoxy**, alkenyloxy, alkynyloxy, **trifluoromethyl**, mercapto, cyano, acyl, **acyloxy**, free, esterified, amidified or salified carboxy, amino, mono- and **dialkylamino**, **arylthio** and cyclic radicals containing 3 to 6 members, the alkyl, alkenyl or alkynyl radicals being moreover optionally interrupted by one or more oxygen, nitrogen or sulphur atoms,

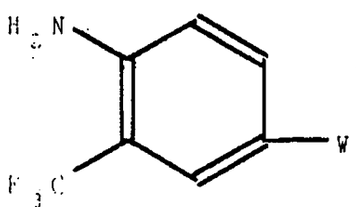
all the sulphur atoms being optionally oxidized in the form of the sulphoxide or **sulphone**,

the aryl and aralkyl radicals being moreover optionally substituted by an alkyl, alkenyl or alkynyl radical,

R_4 and R_5 :

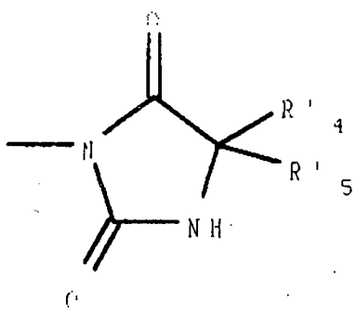
either are identical or different and represent a hydrogen atom or an alkyl radical, optionally substituted by one or more substituents chosen from halogen **atoms**, the optionally esterified, etherified or protected hydroxyl radical and

phenylthio and alkylthio radicals, in which the sulphur atom can be oxidized into the sulphoxide or sulphone and being optionally substituted by one or more radicals chosen from halogen atoms and optionally esterified, etherified or protected hydroxyl radicals, free, esterified, amidified or salified carboxy radicals, amino, mono- and dialkylamino radicals,
or form together a heterocyclic radical with 4 to 6 members containing an oxygen or sulphur atom,
X and Y, identical or different, represent an oxygen or sulphur atom,
said products of formula (I) being in all possible racemic, enantiomeric or diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or mineral and organic bases of said products of formula (I),
characterized in that:
a) a product of formula (A):

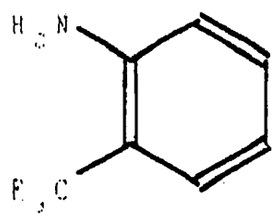


(A)

is prepared, in which W represents a halogen atom or a hydantoin derivative of formula:

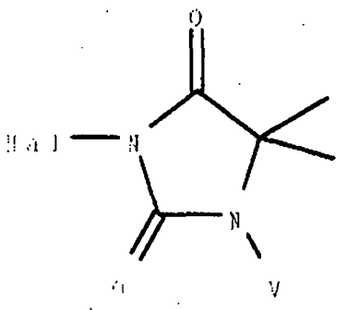


in which R'_4 and R'_5 have the meanings indicated above for R_4 and R_5 in which the optional reactive functions are optionally protected,
by reacting on the compound of formula (II):



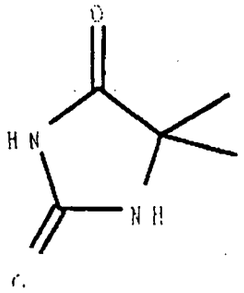
(II)

either first of all, a compound of formula (III):



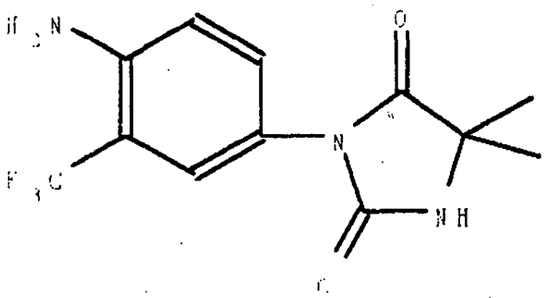
(III)

in which Hal represents a halogen atom and V represents a hydrogen atom or a halogen atom, then the compound of formula (B):



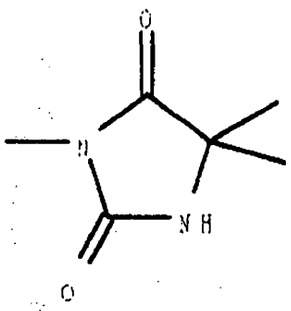
(B)

in order to obtain the product of formula (A_1):

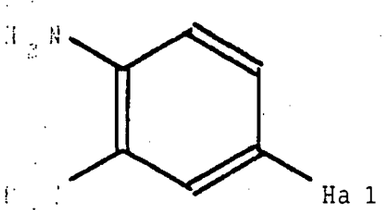


(A_1)

corresponding to the product of formula (A) in which W represents the dimethylhydantoin radical:

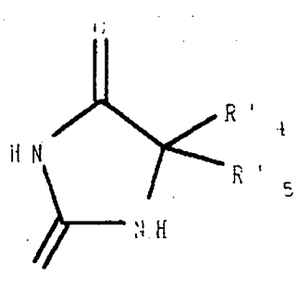


or N-bromosuccinimide in dimethylformamide, or the compound of formula (III) as defined above, in order to obtain the product of formula (A_2):



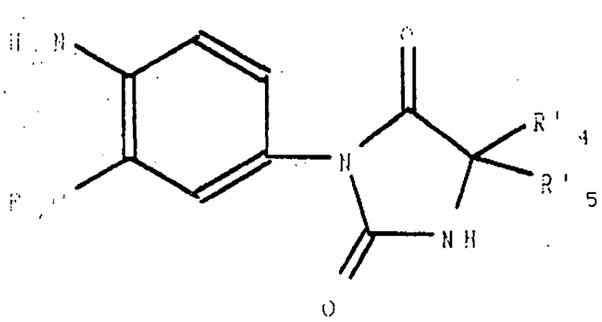
(A_2)

in which Hal represents a bromine atom or another halogen atom, which can be reacted with a compound of formula (IV):



(IV)

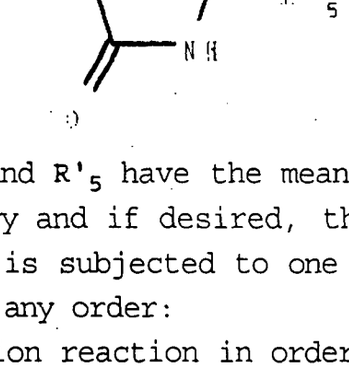
in which R'_4 and R'_5 have the meanings indicated above, in order to obtain the product of formula (A_3):



(A_3)

corresponding to the product of formula (A) in which W

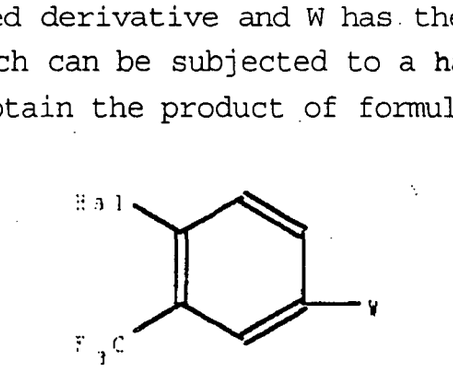
represents the radical:



in which R'_4 and R'_5 have the meanings indicated above,

b) if necessary and if desired, the product of formula (A) thus obtained is subjected to one or more of the following reactions, in any order:

i) a diazotation reaction in order to obtain the product of formula (V):



(V)

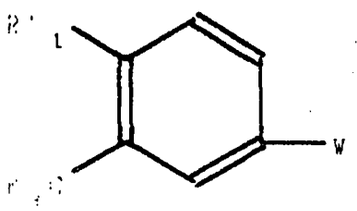
in which $A^{\ominus}$ represents an anion of a halogen atom or of ahalogenated derivative and W has the meaning indicated above, which can be subjected to a **halogenation** reaction in order to obtain the product of formula (F_1):

(F_1)

in which Hal and W have the meanings indicated above, which can be subjected to a substitution reaction on the halogen atom by a metallic derivative of formula (VI):

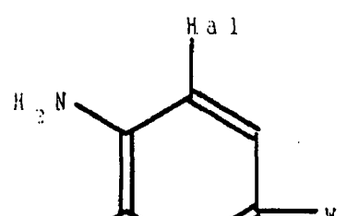
$$R'_1\text{-}M \qquad \text{(VI)}$$

in which M represents a metal and R'_1 has the meaning indicated above for R_1, in which the optional reactive functions are optionally protected, in order to obtain the product of formula (F_2):



(F_2)

in which R'_1 and W have the meanings indicated above,
ii) a halogenation reaction in order to obtain the product of formula (F_3):

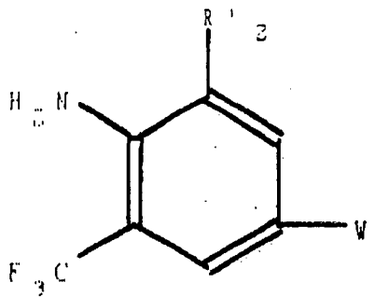


(F_3)

in which Hal represents a halogen atom and W has the meaning indicated above, which can:
either be subjected to a substitution reaction on the halogen atom, by a metallic derivative of formula (VII):

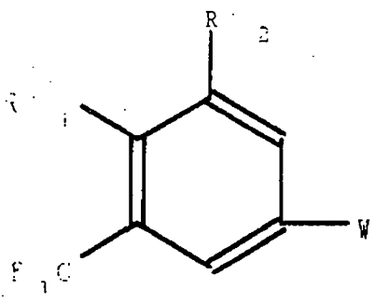
$$R'_2\text{-}M \qquad \text{(VII)}$$

in which M represents a metal and R'_2 has the meaning indicated above for R_2 in which the optional reactive functions are optionally protected, in order to obtain the product of formula (F_4):



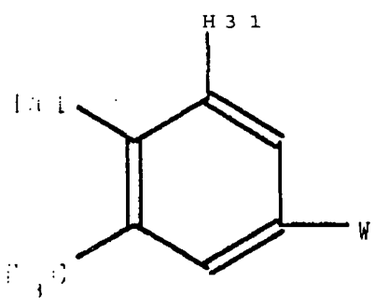
(F_4)

in which R'_2 and W have the meanings indicated above, which can be subjected to the successive reactions, defined above in i), of diazotation of the amino radical, then halogenation and finally substitution by the compound of formula (VI) in order to obtain the product of formula (F_5):



(F_5)

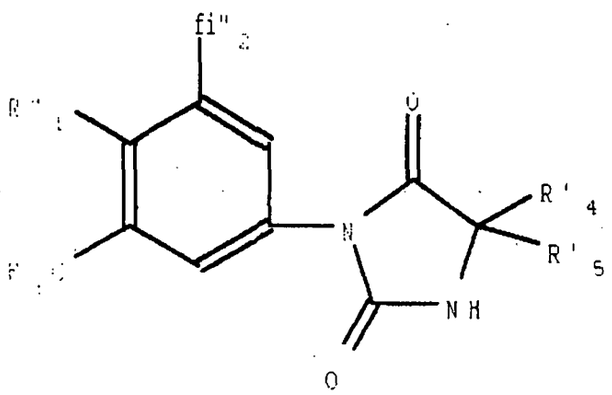
in which R'_1, R'_2 and W have the meanings indicated above, or is subjected to a diazotation-halogenation reaction in order to obtain the product of formula (F_6):



(F_6)

in which the two halogen atoms represented by Hal are identical or different and W has the meaning indicated above, which can be subjected to a substitution reaction on the halogen atoms by the compound of formula (VI) or (VII) as defined above, in order to obtain the product of formula (F_5) as defined above in which R'_1 and R'_2 are identical, which

products of formulae (F_1), (F_2), (F_3), (F_4), (F_5) and (F_6) when W represents a halogen atom, can, if necessary and if desired, be reacted with the product of formula (IV), as defined above in order to obtain the product of formula (I'):



(I')

in which $R"_1$ and $R"_2$ are such that:
either $R"_2$ represents a hydrogen atom
and $R"_1$ represents a halogen atom or R'_1 as defined above,
or $R"_2$ represents a halogen atom
and $R"_1$ represents an amino radical or a halogen atom,
or $R"_2$ represents R'_2 as defined above
and $R"_1$ represents an amino radical or R'_1 as defined above,
which products of formulae (A_1), (A_3) and (I'), if appropriate and if necessary, or if desired, are subjected to any one or more of the following reactions, in any order:
a) an elimination reaction of the optional protective groups which can be carried by $R"_1$, $R"_2$, R'_4 and R'_5,
b) a conversion reaction of the >C=O into the >C=S group,
c) the action of a reagent of formula Hal-R'_3 in which R'_3 has the values of R_3 as defined in claim 1, with the exception of the hydrogen value and in which the optional reactive functions are optionally protected and Hal represents a halogen atom, in order to obtain products of formula (I) as defined in claim 1, then, if desired, the action on these products of an agent for eliminating the optional protective groups which can be carried by R'_3 or if appropriate, the action of an esterification, amidification or salification agent,
d) a conversion reaction of the amino radical into a nitro

radical.

2) Preparation process as defined in claim 1, for the products of formula (I), as defined in claim 1, in which R_1 and R_2, identical or different, are chosen from the hydrogen atom, halogen atoms and alkyl, alkenyl, alkynyl, cyano, trifluoromethyl, amino, monoalkylamino and dialkylamino radicals,

R_3 represents a hydrogen atom, an alkyl radical, optionally interrupted by one or more oxygen or sulphur atoms, a phenyl or pyridyl radical, these radicals being optionally substituted by one or more radicals chosen from halogen atoms, the following radicals: phenyl, optionally esterified, etherified or protected hydroxyl, alkoxy, cyano, trifluoromethyl, hydroxyalkyl, free, esterified, amidified or salified carboxy, amino, mono- or dialkylamino, the nitrogen atom of the pyridyl radical being optionally oxidized,

R_4 and R_5

either are identical or different and represent an alkyl radical, optionally substituted by one or more radicals chosen from optionally esterified, etherified or protected hydroxyl radicals, halogen atoms and alkylthio and phenylthio radicals themselves optionally substituted by one or more radicals chosen from halogen atoms and the hydroxyl radical, or together form the:

radical

in which T represents an oxygen or sulphur atom,

X and Y, identical or different, represent an oxygen or sulphur atom.

3) Preparation process as defined in claim 1, for the products of formula (I) as defined in claims 1 and 2 in which R_1 and R_2, identical or different, are such that one represents a hydrogen atom or a cyano radical and the other is chosen from halogen atoms and cyano and amino radicals,

R_3 represents a hydrogen atom or an alkyl radical optionally substituted by an optionally esterified, etherified or

protected hydroxyl radical,
R_4 and R_5, identical or different, represent a linear or branched alkyl radical containing at most 6 carbon atoms, optionally substituted by one or more radicals chosen from optionally esterified, etherified or protected hydroxyl radicals and halogen atoms and X and Y represent an oxygen atom.

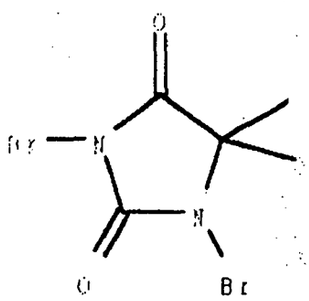
4) Preparation process as defined in claim 1 for the following products:

- 3-[4-amino-3-(trifluoromethyl) phenyl] 5,5-dimethyl 2,4-imidazolidine dione,
- 5,5-dimethyl-3-(4-iodo-3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione,
- 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl) benzonitrile,
- 4-(4,4-dimethyl-2,5-dioxo-3-(4-hydroxybutyl)-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile,
- 4-(2,4-dioxo 1-(4-hydroxybutyl)-8-oxa-1,3-diazaspiro(4,5) decan-3-yl)-2-(trifluoromethyl) benzonitrile,
- 5,5-dimethyl-3-(4,5-dicyano-3-(trifluoromethyl) phenyl)-2,4-imidazolidinedione,

these products being in all possible racemic, enantiomeric or diastereoisomeric isomer forms, as well as their addition salts with pharmaceutically acceptable mineral and organic acids or mineral and organic bases.

5) Preparation process for the products of formula (I) as defined in claims 1 to 4, characterized in that in order to obtain the product of formula (A_1) from the products of formulae (II), (III) and B, as defined in claim 1, the operation is carried out in a solvent chosen from dimethylsulphoxide, triglyme, dimethylacetamide or dimethylformamide and preferably dimethylacetamide.

6) Preparation process for the products of formula (I) as defined in claim 5, characterized in that the compound of formula (III) is the dibrominated derivative of formula:



and that a half-mol of this compound and a half-mol of the compound of formula (B) is used per one mol of the compound of formula (II).

7) Preparation process for the products of formula (I) as defined in claims 5 and 6, characterized in that the reaction is carried out at a temperature of 130°C to 160°C and preferably at 155°C.

8) As new industrial products, the following products:

- 3-[4-amino 3-(trifluoromethyl) phenyl] -5,5-dimethyl 2,4-imidazolidine dione,
- 5,5-dimethyl 3-(4-iodo 3-(trifluoromethyl) phenyl)-2,4-imidazolidinedione,
- 5,5-dimethyl 3-(4,5-dicyano 3-(trifluoromethyl) phenyl) 2,4-imidazolidinedione.

9. Preparation process for the products of formula (I) substantially as herein described with reference to the foregoing examples.

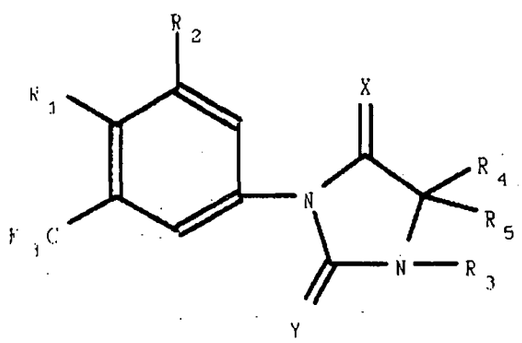
10. New industrial products substantially as hereinbefore described with reference to the foregoing examples.

Dated this 6th day of November, 1996

(B. KOMBI)
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

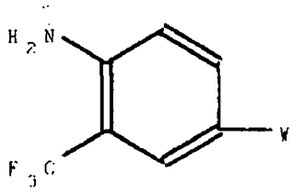
A B S T R A C T

A subject of the invention is a preparation process for the products of formula (I):



(I)

in which R_1 and R_2 represent in particular hydrogen, cyano, halogen or amino, R_3 represents in particular hydrogen or hydroxyl alkyl,
R_4 and R_5 represent in particular optionally substituted alkyl,
X and y represent oxygen or sulphur,
characterized in that a product of formula (A):



(A)

is prepared in which W represents a halogen atom or a hydantoin derivative,
which is subjected to various reactions in order to obtain the products of formula (I), all their isomers and their salts.

Annexure VI

US005627201A

United States Patent [19]

Gaillard-Kelly et al.

[11] Patent Number: 5,627,201

[45] Date of Patent: May 6, 1997

[54] **PHENYLIMIDAZOLIDINES HAVING ANTIANDROGENIC ACTIVITY**

[75] Inventors: **Martine Gaillard-Kelly**; **Francois Goubet**, both of Paris; **Daniel Phillbert**, La Verenne Saint Hilaire; **Jean-Georges Teutsch**, Pantin, all of France

[73] Assignee: **Roussel Uclaf**, France

[21] Appl. No.: **372,648**

[22] Filed: **Jan. 13, 1995**

Related U.S. Application Data

[60] Division of Ser. No. 64,257, May 18, 1993, Pat. No. 5,411, 981, which is a continuation-in-part of Ser. No. 819,910, Jan. 9, 1992, abandoned.

[30] **Foreign Application Priority Data**

Jan. 9, 1991 [FR] France 91 00185
Jul. 8, 1992 [FR] France 92 08431

[51] **Int. Cl.**[6] **A61K 31/415**; C07D 233/72

[52] **U.S. Cl.** **514/386**; 514/342; 514/391; 548/311.1; 548/317.1; 548/318.5; 548/320.1; 548/320.5; 548/321.1

[58] **Field of Search** 548/317.1, 320.5; 514/386, 391, 342

[56] **References Cited**

U.S. PATENT DOCUMENTS

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Primary Examiner—Floyd D. Higel
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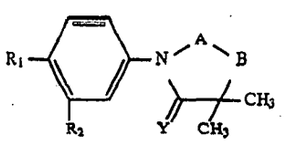
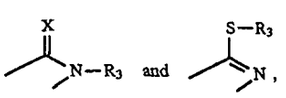
[57] **ABSTRACT**

A compound of the formula

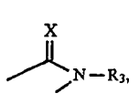


I

wherein R_1 is selected from the group consisting of —CN, —NO_2 and halogen, R_2 is —CF_3 or halogen, —A—B— is selected from the group consisting of



X is —O— or —S—, R_3 is selected from the group consisting of hydrogen, alkyl, alkenyl and alkynyl of up to 12 carbon atoms, aryl and aralkyl of up to 12 carbon atoms. all optionally substituted with at least one member of the group consisting of —OH, halogen, —SH, —CN, acyl and acyloxy of up to 7 carbon atoms, —aryl, —O—aryl, —O—aralkyl —S— aryl of up to 12 carbon atoms the aryl and aralkyl being optionally substituted with a member of the group consisting of halogen, —CF_3, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl and alkynyloxy with the sulfur being optionally oxidized to sulfone or sulfoxide, free, esterified, amidified or salified carboxy, —NH_2, mono and dialkylamino and heterocyclic of 3 to 6 ring members and containing at least one heteroatom selected from the group consisting of oxygen, sulfur and nitrogen, the alkyl, alkenyl and alkynyl being optionally interrupted with at least one member of the group consisting of oxygen, nitrogen and sulfur optionally oxidized to sulfoxide or sulfone, trialkylsilyl with the alkyl having 1 to 6 carbon atoms and acyl and acyloxy of an organic carboxylic acid of 1 to 7 carbon atoms and Y is —O—, —S— or —NH—, except the compounds wherein —A—B— is



X is oxygen, R_3 is hydrogen and Y is oxygen or —NH—, R_2 is —CF_3 or halogen and R_1 is —NO_2 or halogen and their non-toxic, pharmaceutically acceptable acid addition salts.

19 Claims, No Drawings

PHENYLIMIDAZOLIDINES HAVING ANTIANDROGENIC ACTIVITY

PRIOR APPLICATION

This application is a division of U.S. patent application Ser. No. 064,257 filed May 18, 1993, now U.S. Pat. No. 5,411,981 which is a continuation-in-part of U.S. patent application Ser. No. 819,910, filed Jan. 9, 1992, now abandoned.

STATE OF THE ART

Japanese application No. J 48087030 describes 3-phenyl-2-thiohydantoins useful for inhibiting the germination of certain plants. U.S. Pat. No. 4,097,578 describes imidazolidines different from formula I having antiandrogenic activity. Other pertinent art includes U.S. Pat. Nos. 3,823,240; 4,873,256; 4,407,814; 4,482,739 and 4,234,736.

OBJECTS OF THE INVENTION

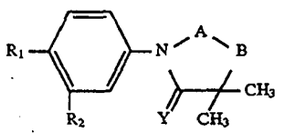
It is an object of the invention to provide the novel compounds of formula I and a novel process and novel intermediates for their preparation.

It another object of the invention to provide novel anti-androgenic compositions and a novel method of inducing anti-androgenic activity in warm-blooded animals.

These and other objects and advantages of the invention will become obvious from the following detailed description.

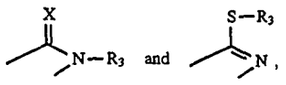
THE INVENTION

The novel phenylimidazolidines of the invention have the formula

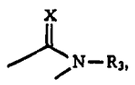


I

wherein R_1 is selected from the group consisting of —CN, $—NO_2$ and halogen, R_2 is $—CF_3$ or halogen, —A—B— is selected from the group consisting of



X is —O— or —S—, R_3 is selected from the group consisting of hydrogen, alkyl, alkenyl and alkynyl of up to 12 carbon atoms, aryl and aralkyl of up to 12 carbon atoms, all optionally substituted with at least one member of the group consisting of —OH, halogen, —SH, —CN, acyl and acyloxy of up to 7 carbon atoms, —aryl, —O—aryl, —O—aralkyl —S— aryl of up to 12 carbon atoms, the aryl and aralkyl being optionally substituted with a member of the group consisting of halogen, $—CF_3$, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl and alkynyloxy with the sulfur being optionally oxidized to sulfone or sulfoxide, free, esterified, amidified or salified carboxy, $—NH_2$, mono and dialkylamino and heterocyclic of 3 to 6 ring members and containing at least one heteroatom selected from the group consisting of oxygen, sulfur and nitrogen, the alkyl, alkenyl and alkynyl being optionally interrupted with at least one member of the group consisting of oxygen, nitrogen and sulfur optionally oxidized to sulfoxide or sulfone, trialkylsilyl with the alkyl having 1 to 6 carbon atoms and acyl and acyloxy of an organic carboxylic acid of 1 to 7 carbon atoms, and Y is —O—, —S— or —NH—, except the compounds wherein —A—B— is



X is oxygen, R_3 is hydrogen and Y is oxygen or —NH—, R_2 is $—CF_3$ or halogen and R_1 is $—NO_2$ or halogen and their non-toxic, pharmaceutically acceptable acid addition salts.

The following examples are given for the values of R_3. Alkyl of up to 12 carbon atoms includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, sec.-pentyl, tert.-pentyl, neopentyl, hexyl, isohexyl, sec.-hexyl, tert.-hexyl, heptyl, octyl, decyl, undecyl and dodecyl, branched or linear. Preferred are alkyl of 1 to 6 carbon atoms, especially methyl, ethyl, propyl and isopropyl, n-butyl, isobutyl, tert-butyl and branched or linear pentyl and hexyl.

Examples of alkenyl of up to 12 carbon atoms are vinyl, allyl, 1-propenyl, butenyl, pentenyl and hexenyl and preferably alkenyl of 2 to 4 carbon atoms and especially vinyl, allyl or butenyl. Examples of alkynyl of up to 12 carbon atoms are ethynyl, propargyl, butynyl, pentynyl and hexynyl and preferably 2 to 4 carbon atoms such as ethynyl and propargyl.

Examples of aryl are carbocyclic aryl such as phenyl and naphthyl, heterocyclic aryl of 5 to 6 ring members containing at least one heteroatom selected from the group consisting of oxygen, sulfur and nitrogen. Examples of 5 ring heteroaryls are furyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, thiadiazolyl, pyrazolyl and isoxazolyl. Examples of 6 ring heteroaryl are pyridyl, pyrimidinyl, pyridazinyl and pyrazinyl. Examples of condensed aryls are indolyl, benzofurannyl, benzothienyl and quinoleinyl. The preferred aryl is phenyl.

Examples of aralkyl include the alkyl recited above substituted with the aryl cited above. The preferred aralkyl are triphenylmethyl, phenethyl and benzyl. Examples of halogen are fluorine, chlorine, bromine and iodine but preferred are fluorine, chlorine and bromine. Examples of alkyl substituted with at least one halogen are fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, dichloromethyl, dibromomethyl and trifluoromethyl.

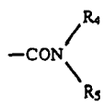
Examples of substituents for aryl and aralkyl are phenyl substituted by fluorine, $—OCH_3$ or $—CF_3$ in the p-position.

Examples of acyl are preferably those of up to 7 carbon atoms such as acetyl, propionyl, butyryl and benzoyl as well as valeryl, hexanoyl, acryloyl, crotonoyl, carbamoyl or formyl. The acyloxy may be derived for the same acids, especially acetyloxy and propionyloxy.

The esterified carboxy may be alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert. -butoxycarbonyl, cyclobutyloxy carbonyl, cyclopentyloxy carbonyl and cyclohexyloxy carbonyl.

Examples of easily cleavable esters includes methoxymethyl, ethoxymethyl; acyloxyalkyl such as pivaloyloxymethyl, pivaloyloxyethyl, acetoxymethyl and acetoxyethyl; alkoxycarbonyloxyalkyl such as methoxycarbonyloxymethyl, methoxycarbonyloxyethyl, isopropoxycarbonyloxymethyl and isopropoxycarbonyloxyethyl. Other esters are described in European Patent No. 0.034.536.

The amidified carboxy are of the type



wherein R_4 and R_5 are individually selected from the group consisting of hydrogen and alkyl of 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and tert.-butyl.

Examples of the mono and dialkylamino are methylamimo, ethylamino, dimethylamino, diethylamino and methylethylamino. The hetero-cyclic of 5 of 6 ring members optionally containing another heteroatom may be pyrrolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidyl, indolyl, piperidino, morpholino and piperazinyl, preferably piperidino or morpholino.

Examples of salts of salified carboxy are sodium, potassium, lithium, calcium, magnesium, ammonium and organic bases such as methylamine, propylamine, trimethylamine, diethylamine and triethylamine. Sodium salt is preferred.

The alkylamino and dialkylamino are preferably alkyl of 1 to 4 carbon atoms such as methylamino, ethylamino, propylamino, isopropylamino, dimethylamino, diethylamino and ethylmethylamino.

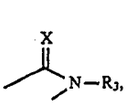
Examples of the heterocyclics containing at least one heteroatom are saturated monocyclics such as oxirannyl, oxolannyl, dioxolannyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl and morpholinyl.

The alkyl, alkenyl and alkynyl may be optionally interrupted by one or more sulfur, oxygen or nitrogen heteroatoms. Examples are alkoxyalkyl such as methoxymethyl, methoxyethyl, methoxypropyl or methoxybutyl or alkoxy alkoxyalkyl such as methoxyethoxymethyl.

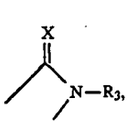
Examples of trialkylsilyl groups are trimethylsilyl, triethylsilyl and (1,1-dimethylethyl) dimethylsilyl.

When the products of formula I contain a salifiable amino group, the acid addition salts of non-toxic, pharmaceutically acceptable acids may be formed. Examples of said acids are inorganic acids such as nitric acid, hydrochloric acid, sulfuric acid and phosphoric acid and organic acids such as formic acid, acetic acid, propionic acid, benzoic acid and methane sulfonic acid.

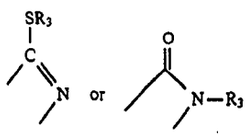
Among the preferred compounds of formula I are those wherein Y is oxygen except for the compounds wherein —A—B— is



X is oxygen, R_3 is hydrogen, R_2 is $—CF_3$ or halogen and R_1 is $—NO_2$ or halogen. Other preferred compounds of formula I are those wherein —A—B— is



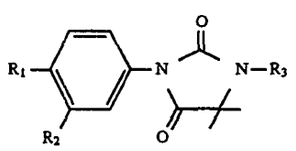
X is sulfur and R_3 has the above definition, those wherein R_3 is hydrogen or alkyl of 1 to 4 carbon atoms optionally substituted with —OH or methoxy, those wherein R_1 is cyano or halogen, preferably chlorine and those wherein —A—B is



and R_3 is optionally substituted alkyl or alkenyl or up to 6 carbon atoms and optionally interrupted by oxygen or optionally oxidized sulfur or optionally substituted aralkyl, acyl or trialkylsilyl.

Other preferred examples of the invention are those in which R_3 is alkyl of up to 6 carbon atoms optionally substituted by at least one member of the group consisting of halogen, free or esterified hydroxy or carboxy, heterocyle, O-aralkyl or S-aryl in which the aryl radical is optionally substituted by at least one halogen or alkoxy and the sulfur atom is optionally oxidized in the form of the sulfoxide or sulfone and quite particularly those in which R_3 is alkyl of 2 to 4 carbon atoms substituted by a member of the group consisting of chlorine, ethoxycarbonyl, terbutoxycarbonyl, cyclopentyl-oxycarbonyl, 4-fluorophenylthio optionally oxidized in the form of the sulfoxide or sulfone, morpholino, phenylmethoxy, triphenylmethoxy and methylsulfonyloxy.

Other preferred compounds of formula I are those wherein R_3 is acetyl or benzoyl or (1,1-dimethylethyl) dimethylsilyl, those wherein R_1 is nitro and R_3 is alkyl or alkenyl of up to 4 carbon atoms optionally substituted with esterified or salified or free carboxy and those of the formula

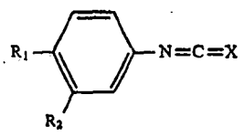


I

in which R_1, R_2 and R_3 have the above meaning with the exception of the products in which R_1 is nitro, R_2 is trifluoromethyl and R_3 is hydrogen.

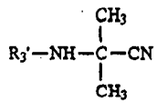
Examples of specific preferred compounds of formula I are 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-[4,4-dimethyl 3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl]-2-(trifluoromethyl)-benzonitrile, 3-(3,4-dichlorophenyl)-2-thioxo-1,5,5-trimethyl-4-imidazolidinone, 1-(4-nitro-3-(trifluoromethyl)phenyl)-3,4,4-trimethyl-2,5-imidazolidinedione, 4-[[4,5-dihydro-4,4-dimethyl-5-oxo-2-benzyl-thio]-1H-imidazo-1-yl]-2-(trifluoromethyl)-benzonitrile, 4-[4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile and 3-(4-cyano 3-(trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoic acid.

The process of the invention for the preparation of a compound of formula I comprises either reacting a compound of the formula



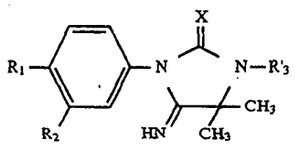
II

wherein R_1, R_2 and X have the above definitions with a compound of the formula



III

in the presence of a tertiary base wherein R'_3 has the definition of R_3 with reactive group optionally protected and if R_1 is $—NO_2$ or halogen, R_2 is halogen or $—CF_3$ and X is oxygen, R'_3 is not hydrogen to obtain a compound of the formula



IV

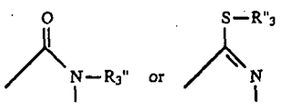
wherein R_1, R_2, X and R'_3 have the above definitions and optionally subjecting the latter to one or more of the following reactions in any order:

a) reaction to eliminate the optional protective groups of R'_3

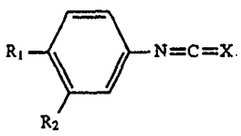
b) reaction of hydrolysis of C=NH to a ketone function or transformation of >C=S to >C=O

c) transformation reaction of >C=O to >C=S

d) and reacting the products of formula IV wherein R'_3 is hydrogen and after hydrolysis of >C=NH to a ketone with a compound of the formula $R"_3$—Hal where Hal is a halogen and $R"_3$ is R'_3 except hydrogen to obtain a compound of formula I wherein —A—B— is

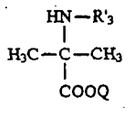


and optionally reacting the latter to eliminate the protective group of $R"_3$ or reacting the same with an esterification, salification or amidification agent or reacting a compound of the formula



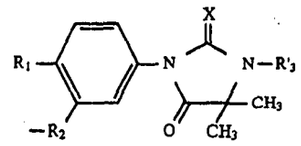
II

in which R_1, R_2 and X have the above meaning in the presence of a tertiary base with a product of the formula



III

in which R'_3 has the above meaning and Q is either an alkali metal for example sodium or alkyl of 1 to 6 carbon atoms to obtain a product of the formula



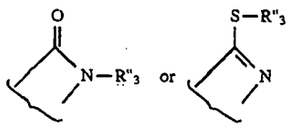
IVa

in which X, R_1, R_2 and R'_3 have the above meaning which if desired is subjected to any one or more of the following reactions in any order:

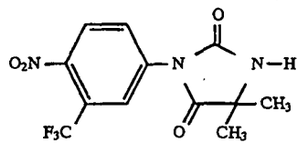
a) elimination reaction of the optional protective groups that can be carried by R'_3;

b) conversion reaction of the >C=O group or groups into the >C=S or if appropriate of >C=S into >C=O;

c) the action on the products of formula IVa in which R'_3 is hydrogen of a reagent of formula Hal—$R"_3$ in which $R"_3$ has the values of R'_3 with the exception of hydrogen and Hal is halogen to obtain the products of formula I in which —A—B— is

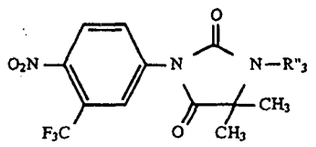


in which R"3 has the above meaning, then, if desired, the action of these products of an elimination agent of the optional protective groups that can be carried by $R"_3$ or if appropriate, the action of an esterification, amidification or salification agent, or reacting a reagent of the formula $R"_3$—Hal as defined above with a compound of the formula



IV'

to obtain a compound of the formula



IV"

and optionally subjecting the latter to one or more of the following reactions:

a) elimination reaction of optional protective groups of $R"_3$ and then to reaction with an esterification, salification or amidification reagent

b) reaction of transformation of >C=O to >C=S.

The reaction of the products of formula II with the products of formula III is preferably effected in an organic solvent such as tetrahydrofuran or dichloroethane or ethyl ether or isopropyl ether in the presence of a tertiary base such as pyridine or methylethyl pyridine.

The optional reactive functional groups of R_3 which are optionally protected in compounds of formula III, IVa or IV" are —OH or amino which are protected by the usual protective groups. Examples of such protective groups for $—NH_2$ are tert.-butyl, tert.-amyl, trichloroacetyl, chloroacetyl, benzhydryl, trityl, formyl and benzyloxycarbonyl. Examples of hydroxy protective groups are formyl, chloroacetyl, tetrahydropyrannyl, trimethylsilyl and tert.-butyldimethylsilyl.

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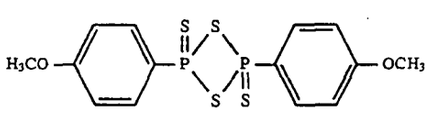
The above list of protective groups is not intended to be exhaustive and any protective group known, for example, in peptide chemistry may be used. Other known protective groups are described in French Patent No. 2.499.995 which is incorporated herein by reference. The optional reactions to eliminate groups are indicated in the said patent and the preferred method of elimination is acid hydrolysis with hydrochloric acid, benzene sulfonic acid, p-toluene sulfonic acid, formic acid or trifluoroacetic acid, preferably hydrochloric acid.

The optional reaction of hydrolysis of >C=NH to >C=O is preferably effected with an acid such as refluxing aqueous hydrochloric acid. When the hydrolysis of >C=NH into a >C=O is effected with a molecule also containing >C=S, the latter may be transformed in >C=O group. The free hydroxy optionally contained in R_3 may also be transformed into —SH.

The transformation of the group >C=O into >C=S is effected with a Lawesson reagent of the formula



which is a commercial product sold by Fluka for example and is described in Bull. Soc. Chim. Belg., Vol. 87 No. 3 (1987), p. 229 When two >C=O groups are to be changed to >C=S, the reaction is effected in an excess of the Lawesson reagent. The same is used also when the molecule contains both >C=S and C=O and it is desired to change the >C=O to >C=S.

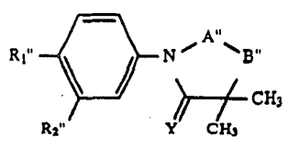
On the contrary, when part of the molecule contain two >C=O and it is desired to obtain a product with only one >C=S, a deficiency of the Lawesson reagent is used to obtain a mixture of 3 products, each of two products with a >C=O and >C=S and one containing two >C=S. The said products can be separated by known methods such as chromatography.

The reaction of the compounds of formulae IV, IVA or IV' with a compound of the formula $R"_3$-Hal is effected in the presence of a strong base such as sodium hydride or potassium hydride in a phase transfer reaction in the presence of quaternary ammonium salts such as tert.-butyl ammonium. The protective groups of $R"_3$ may be those discussed above for R_3. The reaction to eliminate the protective groups are as discussed above. For example, a tert-butyl dimethylsilyl group may be removed by hydrochloric acid as described in the examples infra.

The optional esterification of the compounds of formula I wherein $R"_3$ is free —OH is effected under the classical conditions using for example an acid or a functional derivative thereof such as its anhydride like acetic acid anhydride in the presence of a base such as pyridine. The optional esterification or salification of the compounds of formula I wherein $R"_3$ is —COOH may be effected by known methods.

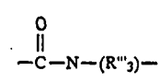
The optional amidification of the compounds of formula I wherein $R"_3$ is —COOH is effected also under classical conditions with primary or secondary amine with a functional derivative of —COOH such as symetrical or mixed anhydride thereof.

The process of the invention to prepare compounds of the formula

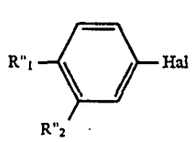


I"

wherein $R"_1$, $R"_2$ and —A"—B"— have the definitions of R_1, R_2 and —A—B— except when —A"—B"— is

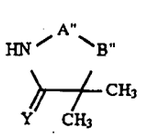


and $R"'_3$, is hydrogen or alkyl of 1 to 7 carbon atoms and Y is oxygen, $R"_1$ is —CN comprises reacting a compound of the formula



V

wherein $R"_1$ and $R"_2$ have the above definitions and Hal is halogen with a compound of the formula



VI

wherein —A"—B"— and Y have the above definitions in the presence of a catalyst and optionally a solvent. In the compounds of formula V, the halogen is preferably chlorine but may be iodine or bromine.

The role of the catalyst is obviously to trap the hydrogen halide as it forms and to facilitate the condensation reaction of the compounds of formulae V and VI to form the desired product. The catalyst is preferably a metal in its native form or its oxide or salt form or it may be a base. When the catalyst is a metal, it is preferably copper or nickel and the metallic salts are preferably the chloride or acetate. When the catalyst is a base, it is preferably sodium hydroxide or potassium hydroxide and dimethylsulfoxide may be added to the reaction medium.

The catalyst of the process may be selected from cuprous oxide, cupric oxide, metallic copper or a base such as sodium hydroxide or potassium hydroxide, preferably cuprous oxide in powdered form. The solvent used preferably is a high boiling point ether such as phenyl oxide, diglyme, triglyme and dimethylsulfoxide but also useful are high boiling point oils such as paraffin or vaseline. Preferably, the process is effected in an ether solvent such as phenyl oxide, diglyme, triglyme or dimethylsulfoxide, most preferably in phenyl oxide or triglyme.

The process may be effected at atmospheric pressure or under pressure at temperatures above 100° C., preferably above 150° C. for more than two hours. The reaction is preferably effected with cuprous oxide in triglyme at temperatures of 200° C. or higher for more than three hours.

The novel anti-androgenic compositions of the invention are comprised of an anti-androgenically effective amount of at least one compound of formula I and its non-toxic, pharmaceutically acceptable acid addition salts and an inert pharmaceutical carrier. The compositions may be in the form of tablets, dragees, capsules, syrups, suppositories, creams, pomades, lotions or injectable solutions prepared in the usual manner.

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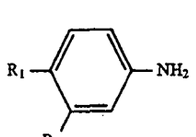
Examples of suitable excipients are aqueous or non-aqueous vehicles, arabic gum, lactose, starch, magnesium stearate, cocoa butter, fatty bodies of animal or vegetable origin, paraffinic derivatives, glycols, diverse wetting agents, dispersants or emulsifiers and preservatives.

The compositions inhibit the effect of androgens on peripherical receptors and have an anti-androgenic activity useful for therapy in adults without the certain effects of a chemical castration. The compositions are useful for the treatment of adenomas and neoplasies of the prostate as well as benign hypertrophia of the prostate as well as the treatment of benign or malignant tumors of cells containing androgen receptors. They are particularly useful for the treatment of breast, brain, skin and ovarian cancer and bladder, lymphatic system, liver and kidney cancers. They are equally useful for the treatment of hirsutism, acne, seborrhea, androgenic alopecia and hyperpilosity and in the veterinary field.

The compositions of the invention are useful in dermatology and can contain another ingredient such as an antibiotic such as derivatives of azelaic acid, fusidic acid, erythromycin or with a derivative of retinoids for the treatment of acne, or with a 5α-reductase inhibitor such as (5α, 17β)-1,1-dimethylethyl 3-oxo 4-aza-Δ^1-androstene-17 carboxamide (or Finasteride Merck, 11th ed.) or azelaic acid or a blocking agent of androgen receptors for the treatment of acne, alopecia or hirsutism, or with a product stimulating the growth of hair such as Minoxidil for the treatment of alopecia. The compositions can also be used in the veterinary domain and in the form of radioactive products, can also be used in diagnostics as specific labels for the androgen receptors. As radioactive products, the products labelled with tritium, with carbon 14 or also with iodine 125 can be used.

The novel method of the invention for inducing anti-androgenic activity in warm-blooded animals, including humans, comprises administering to warm-blooded animals an anti-androgenically effective amount of at least one compound of formula I and its non-toxic, pharmaceutically acceptable acid addition salts. The compounds may be administered parenterally, buccally, perlingually, rectally or topically and the usual daily dose is 0.133 to 6.66 mg/kg depending on the condition treated, the specific compound and the method of administration.

The starting compounds of formula II may be prepared by reacting phosgene when X is oxygen or thiophosgene when X is sulfur with an amine of the formula



A

A product of this type is described in French Patent No. 2,329,276. The amines of formula A are described in EP Patent No. 0,002,892 and French Patent No. 2,142,804.

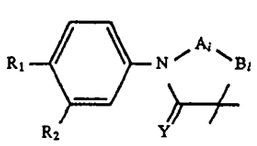
The products of formula III or III' are known or can be prepared from the corresponding cyanhydrin by the process of J. Am. Chem. Soc., Vol. 75 (1953), P. 4841. The compounds of formula III wherein R'_3 is other than hydrogen may be obtained by reacting a compound of the formula R''_3 Hal with 2-cyano-2-amino-propane under the conditions described above for reacting the said halide with the compounds of formula IV. An example is described by Jilek et al, Collect. Czech. Chem. Comm., Vol. 54(8) (1989), p. 2248. The products of formula IV' are described in French Patent No. 2,329,276.

The compounds of formulae V and VI are commercially available known compounds and can be prepared by known methods.

The preparation of the compounds of formula VI are described in the following publications: Zhur Preklad Khim., Vol. 28 (1955), p. 969–75 (CA, Vol. 50 (1956), p 4881a); Tetrahedron, Vol. 43 (1987), p. 1753; J. Org. Chem., Vol. 52 (1987), p. 2407; Zh. Org. Khim., Vol. 21 (1985), p. 2006; J. Fluor. Chem., Vol. 17 (1981), p. 345; German Patent No. 637,318, European Patent No. 0,130,875 and Japanese Patent No. 81-121,524.

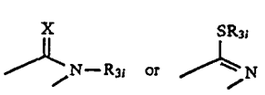
The product of formula VI which are derivatives of hydantoin are largely used and are known in the literature such as J. Pharm. Pharmacal., 67, Vol. 19(4) (1967), p. 209–16; J. Chem. Soc., Vol. 74(2) (1972), p. 219–221; Khim. Farm. Zh., Vol. 67(1) (5), p. 51–2; German Patent No. 2,217,914; European Patent No. 0,091,596 and J. Chem. Soc. Perkin. Trans. 1, Vol. 74(2), p. 48 and 219–221.

The novel intermediates of the invention are the compounds of the formula



IVi

wherein R_1, R_2 and Y have the above definitions and —Ai—Bi— is



wherein X is oxygen or sulfur and R_{3i} is R_3 with the reactive groups protected among which are —OH or —NH_2 protected as above for R_3.

In the following examples, there are described several preferred embodiments to illustrate the invention. However, it should be understood that the invention is not intended to be limited to the specific embodiments.

EXAMPLE 1

1-(4-nitro-3-trifluoromethyl-phenyl)-3,4,4-trimethyl-2,5-imidazolidinedione

A solution of 3.17 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl-imidazoline-2,5-dione (French Patent No. 2,329,276) and 32 ml of dimethylformamide were added at 23° C. to 26° C. to a 50% suspension of 492 mg of sodium hydride in oil and 3 ml of dimethylformamide and after stirring for 15 minutes, a solution of 0.7 ml of methyl iodide in 2 ml of dimethylformamide was added. The mixture was stirred for 25 minutes at 24° C. to 28° C. and was then poured into 200 g of a 1-1 water-ice mixture. The mixture was extracted with ether and the organic phase was washed with saturated aqueous sodium chloride, dried, filtered and evaporated to dryness under reduced pressure to obtain 3.6 g of the desired product melting at 116° C. An analytical sample was crystallized from isopropyl alcohol to obtain 2.73 g of the product melting at 116° C.

Analysis: $C_{13}H_{12}F_3N_3O_4$; molecular weight=331.25 Calculated: %C 47.14 %H 3.65 %F 17.20 %N 12.68 Found: 47.0 3.5 17.1 12.5

IR Spectrum ($CHCl_3$): C=O 1780, 1727 cm^{-1} aromatics 1615, 1596, 1497 cm^{-1} NO_2 1545, 1357 cm^{-1}

EXAMPLE 2

5,5-dimethyl-1-ethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl-imidazoline-2,5-dione prepared as in French Patent No. 2,329,276 was reacted

with 0.37 ml of ethyl iodide and a 50% suspension of 166 mg of sodium hydride in oil to obtain 1.19 g of the desired product melting at 110° C. to 111° C. which was crystallized from isopropanol to obtain 934 mg of the product melting at 110° C. to 111° C.

Analysis: $C_{14}H_{14}F_3N_3O_4$; molecular weight=245.28 Calculated: %C 48.70 %H 4.09 %F 16.51 %N 12.17 Found: 48.6 4.0 16.8 12.1

IR Spectrum ($CHCl_3$): C=O 1777, 1724 cm^{-1} NO_2 1545, 1356 cm^{-1} aromatics 1614, 1596, 1497 cm^{-1}

EXAMPLE 3

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-propyl-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl-imidazoline-2,5-dione was reacted with 0.35 ml of 1-iodopropane and a 50% suspension of 155 mg of sodium hydride in oil to obtain after chromatography on silica with an eluant of acetone-methylene chloride (1–99), 1.087 g of raw product melting at 102° C. The product was crystallized from isopropanol to obtain 945 mg of the desired product melting at 102° C.

Analysis: $C_{15}H_{16}F_3N_3O_4$; molecular weight=359.31 Calculated: %C 50.14 %H 4.49 %F 15.86 %N 11.69 Found: 50.1 4.4 15.9 11.5

IR Spectrum ($CHCl_3$): C=O 1778, 1724 cm^{-1} NO_2 1544, 1358 cm^{-1} aromatics 1615, 1596, 1497 cm^{-1}

EXAMPLE 4

5,5-dimethyl-1-isopropyl-3-(4-nitro-3-trifluoromethyl-phenyl)-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl-imidazoline-2,5-dione was reacted with 0.4 ml of 2-iodopropane and a 50% suspension of 166 mg of sodium hydride in oil for 18 hours at 50° C. to obtain after chromatography over silica (eluant methylene chloride-acetone 99-1), 685 mg of product melting at 130° C. which after crystallization from isopropanol yielded 661 of the desired product melting at 130° C.

Analysis: $C_{15}H_{16}N_3F_3O_4$; molecular weight=359.31 Calculated: %C 50.14 %H 4.49 %F 15.86 %N 11.69 Found: 50.1 4.4 16.2 11.6

IR Spectrum ($CHCl_3$): C=O 1779, 1771, 1723 cm^{-1} NO_2 1544, 1361 cm^{-1} aromatics 1615, 1596, 1497 cm^{-1}

EXAMPLE 5

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-(2-propenyl)-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl-imidazoline-2,5-dione was reacted with 0.35 ml of allyl bromide and a 50% suspension of 166 mg of sodiumhydride in oil to obtain after chromatography over silica (eluant-methylene chloride-acetone (99-1)) 1.19 g of product which after crystallization from isopropanol yielded 1.01 g of the desired product melting at 105° C.

Analysis: $C_{15}H_{14}F_3N_3O_4$; molecular weight=357.29 Calculated: %C 50.42 %H 3.95 %F 15.95 %N 11.76 Found: 50.4 3.8 15.8 11.7

IR Spectrum ($CHCl_3$): C=O 1779, 1724 cm^{-1} NO_2 1545, 1358 cm^{-1} aromatics 1615, 1596, 1497 cm^{-1} CH=CH_2 1643, 930 cm^{-1}

EXAMPLE 6

5,5-dimethyl-3-(3-trifluoromethyl-4-nitro-phenyl)-1-benzyl-2,4-imidazolidinedione

Using the procedure of Example 1, 2 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl-imidazolidine-2,5-dione was reacted with 0.71 ml of benzyl bromide and a 50% suspension of 332 mg of sodium hydride in oil to obtain after chromatography on silica and elution with 99-1 methylene chloride-acetone 2.375 g of the desired product which was crystallized from isopropanol to obtain 2.165 g of product melting at 99° C.

Analysis: $C_{19}H_{16}N_3F_3O_4$; molecular weight=407.3 Calculated: %C 56.02 %H 3.96 %F 10.31 %N 14.00 Found: 56.1 3.8 10.2 13.9

IR Spectrum ($CHCl_3$): C=O 1799, 1723 cm^{-1} aromatics 1608 cm^{-1} +1594 cm^{-1} (m) NO_2 1545 cm^{-1} (F) 1497 cm^{-1}

EXAMPLE 7

4-(4,4-dimethyl-5-imino-2-oxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

A solution of 10 g of 4-cyano-3-trifluoromethyl-aniline (described in European Patent No. 0.002,892) in 30 ml of ethyl acetate was added at 0° to 5° C. to 33.6 ml of a toluene solution of 1.93M/l of phosgene and after stirring at 0° to 5° C. for 30 minutes, the temperature was raised to 25° C. The mixture was distilled while introducing fresh toluene maintaining to constant level for compensate the distilled volume of toluene until a temperature of about 110° C. was reached. The mixture was held at reflux until the disengagement of hydrogen chloride ceased (4½ hours). The temperature returned to room temperature and the white solid was dried over sodium sulfate and was rinsed with toluene 3 times. The organic phase was evaporated to dryness under reduced pressure, heated at 60° C. for one hour and then cooled under argon to obtain 11.6 g of 4-isocyanate of 2-trifluoromethyl-benzonitrile.

IR Spectrum: —NC=O 2268 cm^{-1} —CN 2233 cm^{-1}

A solution of 6.6 g of 4-isocyanate of 2-trifluoromethyl-benzonitrile in 10 ml of dichloroethane was added at 5° C. to a solution of 2.63 g of 2-amino-2-cyano-propane and 36 ml of dichloroethane and 0.9 ml of triethylamine and after stirring 16 hours at room temperature, the mixture was evaporated to dryness. The 7.7 g of residue were chromatographed on silica and eluted with a 85-15 methylene chloride-acetone mixture to obtain 3.54 g of the desired product melting at 228° C. An analytical sample was prepared by crystallizing 300 mg from isopropanol to obtain 267 mg of the product melting at 228° C.

Analysis: $C_{13}H_{11}F_3N_4O$; molecular weight=296.25 Calculated: %C 52.71 %H 3.74 %F 19.24 %N 18.91 Found: 52.7 3.6 19.1 18.6

IR Spectrum (Nujol): NH/OH 3340, 3290 cm^{-1} CN 2240 cm^{-1} C=O 1760 cm^{-1} C=N 1655 cm^{-1} aromatics 1606, 1570, 1502 cm^{-1}

EXAMPLE 8

4(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

A solution of 2.76 g of the product of Example 7 and 60 ml of 0.5 hydrochloric acid was refluxed for 35 minutes and was poured into 100 g of water and ice. The mixture was extracted with ethyl acetate and the organic phase was washed with water, dried and evaporated to dryness under reduced pressure to obtain 2.70 g of the desired product melting at 210° C. An analytical sample was obtained by crystallizing 440 mg of product from isopropanol to obtain 383 mg of product melting at 210° to 211° C.

Analysis: $C_{13}H_{10}F_3N_3O_2$; molecular weight=297.24 Calculated: %C 52.53 %H 3.39 %F 19.17 %N 14.14 Found: 52.4 3.2 19.4 13.9

IR Spectrum ($CHCl_3$): CN 2245 cm^{-1} C=O 1788, 1722 cm^{-1} aromatics 1610, 1572, 1502 cm^{-1} NH (max) 3340 cm^{-1}

EXAMPLE 9

3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2,4-dioxo-1-imidazolidine acetic acid

A solution of 600 mg of the product of Example 8 in 6 ml of dimethylformamide was added with stirring over 15 minutes to a suspension of a 50% suspension of 210 mg of sodium hydride in oil in 3 ml of dimethylformamide and after the addition of 290 mg of bromoacetic acid, the mixture was stirred for 16 hours at room temperature. After another 105 mg of sodium hydride were added, 145 mg of bromoacetic acid were added to the mixture which was stirred for 30 minutes and then poured into a mixture of 50 ml of water and 5 ml of 2N hydrochloric acid. The mixture was extracted with ether and the organic phase was washed with saturated aqueous sodium chloride, dried, filtered and evaporated to dryness under reduced pressure. The 1.22 g of residue were chromatographed on silica and eluted with a 90-10-0.5 methylene chloride-methanolacetic acid mixture to obtain 367 mg of the desired product.

IR Spectrum: CN 2238 cm^{-1} C=O hydantoin & acid 1784, 1725, 1710 cm^{-1} aromatic 1616, 1580, 1508 cm^{-1}

Ultra-violet Spectrum:

ETOH - 0.1N HCl	max	258 nm	ϵ = 13,300
	inflex	277 nm	ϵ = 5,000
	inflex	285 nm	ϵ = 2,600
ETOH 0.1N NaOH	max	287 nm	ϵ = 19,100
	max	342 nm	ϵ = 1,900

EXAMPLE 10

Ethyl3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2,4-dioxo-1-imidazolidine-acetate

A solution of 600 mg of the product of Example 8 in 6 ml of dimethylformamide was added to a 50% suspension of 100 mg of sodium hydride in oil and 3 ml of dimethylformamide and after stirring for 15 minutes, 0.25 ml of ethyl bromoacetate was slowly added at less than 30° C. The mixture was stirred for 30 minutes and then was poured into 50 g of a 1-1 ice-water mixture. 0.5 g of monopotassium phosphate was added and the mixture was extracted with ether. The organic phase was washed with water, dried and evaporated to dryness to obtain 1.1 g of residue which was chromatographed on silica and eluted with 97-3 methylene chloride-acetone to obtain 709 mg of the desired product melting at 152° C. An analytical sample was prepared by crystallization from isopropanol to obtain 667 mg of the desired product melting at 152° C.

Analysis: $C_{17}H_{16}N_3F_3O_4$; molecular weight =383.33 Calculated; %C 53.21 %H 4.21 %F 14.83 %N 10.96 Found: 53.3 4.0 14.9 10.8

IR Spectrum ($CHCl_3$); CN 2225 cm^{-1} imidazolidine 1786, 1729 cm^{-1} COOEt 1751 cm^{-1} aromatics 1616, 1572, 1505 cm^{-1}

EXAMPLE 11

4-(5-imino-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

2.23 g of 1-trifluoromethyl-4-amino-benzonitrile (described in European Patent No. 0,002,892) were slowly added to a solution of 22 ml of distilled water and 1 ml of thiophosgene and after stirring for one hour, the mixture was extracted with chloroform. The organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness under reduced pressure to obtain 3 g of isocyanate product which was used as is.

A mixture of the 3 g of product, 1.33 ml of 2-methylamino-2-cyano-propane, 23 ml of tetrahydrofuran and 0.23 ml of triethylamine was refluxed for 40 minutes and was evaporated to dryness. The 3.07 g of residue were chromatographed on silica and eluted with a 1-1 cyclohexane-ethyl acetate mixture and then a 95-5 methylene chloride-acetone mixture to obtain 2.83 g of product which was crystallized from isopropanol to obtain 2.63 g of the desired product melting at 173° C. to 174° C.

Analysis: $C_{14}H_{13}F_3N_4S$; molecular weight=326.35 Calculated: %C 51.53 %H 4.01 %F 17.17 %N 17.46 %S 9.82 Found: 51.7 3.9 17.2 17.2 9.9

IR Spectrum C=NH 3308, 1679 cm^{-1} C=S+aromatics 1608, 1575, 1505, 1488 cm^{-1} CN 2230 cm^{-1} CF_3 1185 cm^{-1}

EXAMPLE 12

4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

A mixture of 2.21 g of the product of Example 11 and 44 ml of 0.5N hydrochloric acid was refluxed with stirring for one hour and was then poured into 200 g of an ice-water (1-1) mixture. The mixture was extracted with methylene chloride and the organic phase was washed with saturated aqueous sodium chloride, dried and evaporated to dryness. The residue was chromatographed on silica and eluted with a 1-1 cyclohexane-ethyl acetate mixture to obtain 2.1 g of product melting at 171° C. which was crystallized from isopropanol to obtain 1.99 g of the desired product melting at 171° C.

Analysis: $C_{14}H_{12}F_3N_3OS$; molecular weight=327.33 Calculated: %C 51.37 %H 3.69 %F 12.84 %N 17.41 %S 9.79 Found: 51.4 3.5 12.7 17.6 10.79

IR Spectrum ($CHCl_3$): C=O 1761, 1756 cm^{-1} aromatics 1610, 1578, 1505 cm^{-1} CN 2230 cm^{-1} CF_3 1178 cm^{-1}

EXAMPLE 13

4-(2,5-(dithioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

A mixture of 839 mg of the product of Example 12, 518 mg of Lawesson reagent and 4.7 ml of toluene was refluxed for 24 hours and was then evaporated to dryness under reduced pressure. The 1.36 g of residue were chromatographed on silica and eluted with a 99-1 methylene chloride-ethyl acetate mixture and then an 85-15 cyclohexane-ethyl acetate mixture to obtain 783 mg of product which was crystallized from isopropanol to obtain 690 mg of the desired product melting at 211° C. to 212° C.

Analysis: $C_{14}H_{12}F_3N_3S_2$; molecular weight=343.40 Calculated: %C 48.97 %H 3.52 %F 16.60 %N 12.24 %S 18.67 Found: 49.0 3.4 16.6 12.2 18.6

IR Spectrum ($CHCl_3$): CN 2230 cm^{-1} aromatics+conjugated system 1612, 1582, 1508 cm^{-1} CF_3 1178 cm^{-1}

EXAMPLE 14

4-(4,4-dimethyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

1 g of 2-amino-2-cyano-propane and 1 ml of tetrahydrofuran were added with stirring to a mixture of 2.54 g of the isocyanate product of Example 11, 20 ml of tetrahydrofuran and 0.2 ml of triethylamine at room temperature and was then evaporated to dryness. The 3.5 g of residue were chromatographed on silica and eluted with a 7-3 ethyl acetate-cyclohexane mixture and then a 1-1 ethyl acetate-cyclohexane mixture to obtain 940 mg of the desired product. 300 g were crystallized from isopropanol to obtain 263 mg of product melting at 296° C.

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Analysis: $C_{13}H_{11}F_3N_4S$; molecular weight=312.32 Calculated: %C 50.00 %H 3.55 %F 18.25 %N 17.94 %S 10.27 Found: 49.9 3.4 18.3 17.6 10.4

IR Spectrum (Nujol): OH/NH 3260 cm^{-1} CN 2230 cm^{-1} C=S 1764 cm^{-1} aromatic+C=C 1612, 1575, 1530, 1501 cm^{-1}

A new preparation was effected using 1,2-dichloroethane in place of tetrahydrofuran to obtain the product in a 60% yield.

EXAMPLE 15

4-(4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl)-1-trifluoromethyl-benzonitrile

A mixture of 635 mg of the product of Example 14 and 14 ml of 0.5N hydrochloric acid was stirred for one hour at reflux and after cooling, 100 ml of water were added. The mixture was extracted with ethyl acetate and the organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness. The 600 mg of residue were chromatographed and eluted with a 95-5 methylene chloride-acetone mixture to obtain 590 mg of product melting at 190° C. to 191° C. The latter was crystallized from isopropanol to obtain 490 mg of product melting to 190° C. to 191° C.

Analysis: $C_{13}H_{10}F_3N_3OS$; molecular weight=313.30 Calculated: %C 49.84 %H 3.22 %F 18.19 %N 13.41 %S 10.23 Found: 49.6 3.1 18.4 13.2 10.0

IR Spectrum ($CHCl_3$): =C—NH 3430 cm^{-1} CN 2230 cm^{-1} C=O 1766 cm^{-1} aromatics and conjugated system 1612, 1578, 1505 cm^{-1}

EXAMPLE 16

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-pentyl-2,4-imidazolidine

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl-imidazolidine-2,5-dione was reacted with 170 mg of sodium hydride and 0.47 ml of 1-bromopentane to obtain after chromatography on silica and elution with an 8-2 methylene chloride-cyclohexane mixture 1.23 g of product which was crystallized from isopropanol to obtain 995 mg of the desired product melting at 84° C.

Analysis: $C_{17}H_{20}O_4F_3N_3$; molecular weight=387.35 Calculated: %C 52.71 %H 5.20 %F 14.71 %N 10.85 Found: 52.8 5.1 14.8 10.7

IR Spectrum ($CHCl_3$): C=O 1778, 1723 cm^{-1} NO_2 1544, 1360 cm^{-1}

EXAMPLE 17

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-nonyl-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl-imidazolidine-2,5-dione was reacted with a 50% suspension of 170 mg of sodium hydride in oil and 0.7 ml of 1-bromo-nonane to obtain after chromatography on silica 1.08 g of the desired product melting at 63° C.

Analysis: $C_{21}H_{28}O_4F_3N_3$; molecular weight=443.46 Calculated: %C 56.87 %H 6.36 %F 12.85 %N 9.48 Found: 57.0 6.5 12.8 9.5

IR Spectrum ($CHCl_3$): C=O 1788, 1723 cm^{-1} NO_2 1544, 1359 cm^{-1}

IR Spectrum ($CHCl_3$): C=O 1778, 1723 cm^{-1} NO_2 1544, 1360 cm^{-1}

EXAMPLE 17

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-nonyl-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl-imidazolidine-2,5-dione prepared from a 50% suspension of 170 mg of sodium hydride in oil and 0.7 ml of 1-bromo-nonane were reacted to obtain after chromatography on silica 1.08 g of the desired product melting at 63° C.

Analysis: $C_{21}H_{28}O_4F_3N_3$; molecular weight=443.46 Calculated: %C 56.87 %H 6.36 %F 12.85 %N 9.48 Found: 57.0 6.5 12.8 9.5

IR Spectrum ($CHCl_3$): C=O 1788, 1723 cm^{-1} NO_2 1544, 1359 cm^{-1}

EXAMPLE 18

4-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 1, 300 mg of the product of Example 8 were reacted to obtain 275 mg of the desired product melting at 158° C.

IR Spectrum ($CHCl_3$): C=O 1780, 1727 cm^{-1} aromatics 1615, 1574, 1505 cm^{-1} CN 2238 cm^{-1}

EXAMPLE 19

4-(5-thioxo-2-oxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (product A), 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (product B) and 4-(2,5-dithioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (product C)

A suspension of 230 mg of the product of Example 18, 1.4 ml of toluene and 78 mg of Lawesson reagent was refluxed for 9 hours and then returned to room temperature and evaporated to dryness. The 330 mg of residue was chromatographed on silica and eluted with a 99-1 methylene chloride-acetone mixture to obtain in the following order of elution 46 mg of product C with a melting point of 210° C. to 211° C. and a Rf=0.63 (identical to the product of Example 13), 26 mg of product B with a melting point of 170° C. to 171° C. and a Rf=0.49 (identical to the product of Example 12) and 42 mg of product A with a melting point of 194° C. and a Rf=0.34.

Analysis for Product A

IR Spectrum ($CHCl_3$): C=O 1760 cm^{-1} CN 2235 cm^{-1} aromatics 1615, 1580, 1508 cm^{-1}

UV Spectrum (ethanol):

max	228 nm	ε = 19,400
	256 nm	ε = 12,100
	298 nm	ε = 8,600
	390 nm	ε = 70

EXAMPLE 20

4-(4,5-dihydro-4,4-dimethyl-2-methylthio-5-oxo-1H-imidazolidin-1-yl)-2-trifluoromethyl-benzonitrile

A solution of 626 mg of the product of Example 15 in 6 ml of dimethylformamide was added to a 50% suspension of 108 mg of sodium hydride in oil and 1.8 ml of dimethylformamide and after rinsing with 0.3 ml of dimethylformamide, the mixture was stirred for 10 minutes after cessation of hydrogen evolution. A mixture of 0.19 ml of methyl iodide in 1 ml of dimethylformamide was added dropwise and after 45 minutes of reaction, the mixture was poured into 50 g of an ice-water mixture containing 0.5 g of monosodium phosphate. The mixture was extracted 4 times with ether and the combined organic phases were washed with aqueous sodium chloride, dried over magnesium sulfate and evaporated to dryness. The 668 mg of residue were chromatographed on silica and eluted with a 95-5 dichloromethane-ethyl acetate mixture to obtain 640 mg of the desired product which chromatographed again on silica.

Elution with a 7-3 cyclohexane-ethyl acetate mixture yielded after taking up in ether 507 mg of the desired product melting at 62° C.

IR Spectrum: C=O 1747 cm^{-1} C=N and aromatics 1614, 1581, 1563, 1503 cm^{-1}

UV Spectrum (ethanol):

max	209 nm	ε = 26,000
inflex.	236 nm	ε = 11,500
inflex.	264 nm	ε = 8,700

EXAMPLE 21

4-(4,5-dihydro-4,4-dimethyl-5-oxo-2-benzylthio)-1H-imidazol-1-yl)-2-trifluoromethyl-benzonitrile

A solution of 313 mg of 4-(4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile in 3 ml of dimethylformamide were added to a suspension of 53 mg of sodium hydride in oil and 0.5 ml of dimethylformamide and after stirring for 10 minutes, 0.1 ml of benzyl bromide were added. The mixture was stirred for 30 minutes and then poured into an ice-water mixture containing 500 mg of monosodium phosphate. The mixture was extracted with ether and the organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness. The 450 mg of residue were chromatographed on silica and eluted with a 97.5-2.5 methylene chloride-ethyl acetate mixture to obtain 316 mg of the desired product with a Rf=0.38.

Analysis: Calculated: %C 59.54 %H 4.0 %F 14.12 %N 10.41 Found: 59.6 4.0 14.1 10.2

IR Spectrum ($CHCl_3$): C=O 1746 cm^{-1} CN 2236 cm^{-1} aromatics and conjugated system 1614, 1580, 1570, 1503, 1499 cm^{-1}

EXAMPLE 22

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

8 ml of ethanoline were added dropwise at 20° C. to 30° C. to 12.3 ml of the cyanhydrin of acetone and after stirring for 18 hours, the mixture was distilled to obtain 2.3 g of a mixture of 2-(2-hydroxyethyl)-amino-2-methyl-propanenitrile and 2,2-dimethyloxazolidine which was used as is for the next step.

A mixture of 1.18 g of the said mixture, 2.11 g of the isothiocyanate of Example 11 and 20 ml of tetrahydrofuran and 0.5 ml of triethylamine was refluxed for 30 minutes and then evaporated to dryness. The residue was chromatographed on silica and eluted with a 95-5 methylene chloride-acetone mixture to obtain 1.26 g of the desired product and 686 mg of N-(4-cyano-2-trifluoromethyl-phenyl)-2,2-dimethyl-3-oxazolidine-carbothioamide. The 686 mg were dissolved in 10 ml of ethyl acetate and after the addition of 30 ml of cyclohexane, the mixture was concentrated to 4 ml and vacuum filtered and dried to obtain another 518 mg of product. The raw product was dissolved in 20 ml of isopropanol and the solution was concentrated to 5 ml, vacuum filtered and dried to obtain 1.04 g of the desired product melting at 181° C.

Analysis: Calculated: %C 50.55 %H 4.24 %F 16.00 %N 15.72 %S 9.00 Found: 50.4 4.1 15.9 15.6 9.0

IR Spectrum ($CHCl_3$): OH 3630 cm^{-1} =NH 3314, 1677 cm^{-1} CN 2230 cm^{-1} aromatics 1611, 1576, 1504 cm^{-1}

EXAMPLE 23

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (Product A) and 4-(4,4-dimethyl-2,5-dioxo-3-(2-mercaptoethyl)-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (Product B)

A mixture of 680 mg of the product of Example 22, 7 ml of water and 7 ml of hydrochloric acid was refluxed for 10 minutes and after cooling to room temperature, the mixture was extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness. The residue was chromatographed on silica and eluted with a 1-1 cyclohexane-ethyl acetate mixture to obtain 119 mg of product B with a Rf-0.35 and 569 mg of product A with a Rf-0.14 and a melting point of ≈130° C.

Analysis: $C_{15}H_{14}F_3N_3O_2S$; molecular weight=357.36 Calculated: %C 50.42 %H 3.95 %F 15.95 %N 11.76 %S 8.97 Product A Found: 50.7 4.0 15.7 11.5 9.1 Product B Found: 50.6 3.8 15.9 11.6 9.1

IR Spectrum ($CHCl_3$): Product A: OH 3626 cm^{-1} CN 2236 cm^{-1} C=O 1763 cm^{-1} aromatics 1615, 1578, 1504 cm^{-1} Product B: Absence of OH CN 2228 cm^{-1} C=O 1780, 1726 cm^{-1} aromatics 1615, 1578, 1505 cm^{-1}

Using 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile of Example 8 and the appropriate reactants, the following products were prepared.

EXAMPLE 24

4-(4,4-dimethyl-2,5-dioxo-3-ethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile with a melting point of 100° C. to 101° C.

Analysis: $C_{15}H_{14}F_3N_3O_2$; molecular weight=325.29 Calculated: %C 55.39 %H 4.34 %F 17.52 %N 12.92 Found: 55.7 4.3 17.6 12.8

IR Spectrum ($CHCl_3$): CN 2238 cm^{-1} C=O 1777, 1724 cm^{-1} aromatics 1617, 1575, 1505 cm^{-1}

EXAMPLE 25

4-(4,4-dimethyl-2,5-dioxo-3-(2-propenyl)-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 109° C. to 110° C.

Analysis: $C_{16}H_{14}F_3N_3O_2$; molecular weight=337.35 Calculated: %C 56.97 %H 4.18 %F 16.90 %N 12.46 Found: 57.0 4.1 16.2 12.3

IR Spectrum ($CHCl_3$): CN 2238 cm^{-1} C=O 1728, 1725 cm^{-1} $HC=CH_2$ 1645 cm^{-1} aromatics 1616, 1575, 1505 cm^{-1}

EXAMPLE 26

4-(4,4-dimethyl-2,5-dioxo-3-benzyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 98° C. to 99° C.

Analysis: $C_{20}H_{16}F_3N_3O_2$; molecular weight=387.36 Calculated: %C 62.01 %H 4.16 %F 14.71 %N 10.85 Found: 62.0 4.1 14.7 10.8

IR Spectrum ($CHCl_3$): C—NH: 3430 cm^{-1} CN 2238 cm^{-1} C=O 1779, 1724 cm^{-1} aromatics 1615, 1605, 1575, 1504, 1497 cm^{-1}

EXAMPLE 27

4-(4,4-dimethyl-2,5-dioxo-o-(4-fluorobenzyl)-1-imidazolidinyl-2-trifluoromethyl-benzonitrile melting at 101° C. to 102° C.

Analysis: $C_{20}H_{15}F_4N_3O_2$; molecular weight=405.35 Calculated: %C 59.26 %H 3.73 %F 18.75 %N 10.37 Found: 59.1 3.5 18.9 10.3

IR Spectrum ($CHCl_3$): CN 2238 cm^{-1} C=O 1780, 1724 cm^{-1} aromatics 1615, 1612, 1505 cm^{-1}

EXAMPLE 28

4-(4,4-dimethyl-2,5-dioxo-3-(4-methoxybenzyl)-1-imidazolidinyl-benzonitrile melting at 95° C. to 96° C.

Analysis: $C_{21}H_{18}F_3N_3O_3$; molecular weight=417.39 Calculated: %C 60.43 %H 4.35 %F 13.65 %N 10.07 Found: 59.1 3.5 18.9 10.3

IR Spectrum ($CHCl_3$): CN 2238 cm^{-1} C=O 1778, 1723 cm^{-1} aromatics 1615, 1584, 1514, 1505 cm^{-1}

EXAMPLE 29

4-(4,4-dimethyl-2,5-dioxo-3-(4-trifluoromethyl-benzyl)-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at ≈89° C. to 90° C.

Analysis: $C_{21}H_{15}F_6N_3O_2$; molecular weight=313.30 Calculated: %C 55.39 %H 3.32 %F 25.03 %N 9.23 Found: 55.2 3.2 25.3 9.2

IR Spectrum ($CHCl_3$): CN 2238 cm^{-1} C=O 1615, 1505 cm^{-1} aromatics 1615, 1505 cm^{-1}

EXAMPLE 30

4-(4,4-dimethyl-2,5-dioxo-3-(2-epoxymethyl)-1-imidazolidinyl-2-trifluoromethyl-benzonitrile melting at 112° C. to 113° C.

Analysis: $C_{16}H_{14}F_3N_3O_3$; molecular weight=353.30 Calculated: %C 54.39 %H 3.99 %F 16.13 %N 11.89 Found: 54.7 4.0 16.1 11.8

IR Spectrum ($CHCl_3$): CN 2235 cm^{-1} C=O 1781, 1725 cm^{-1} aromatics 1615, 1576, 1505 cm^{-1}

EXAMPLE 31

4-(4,4-dimethyl-2,5-dioxo-3-propyl-1H-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 113° C. to 114° C.

Analysis: $C_{16}H_{16}F_3N_3O_2$; molecular weight=339.32 Calculated: %C 56.64 %H 4.75 %F 16.80 %N 12.38 Found: 56.7 4.7 16.7 12.2

IR Spectrum ($CHCl_3$): CN 2236 cm^{-1} C=O 1778, 1725 cm^{-1} aromatics 1616, 1505 cm^{-1}

EXAMPLE 32

4-(4,4-dimethyl-2,5-dioxo-3-isopropyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 138° C. to 139° C.

Analysis: $C_{16}H_{16}F_3N_3O_2$; molecular weight=339.32 Calculated: %C 56.64 %H 4.75 %F 16.80 %N 12.38 Found: 56.5 4.7 17.1 12.3

IR Spectrum ($CHCl_3$): CN 2236 cm^{-1} C=O 1778, 1724 cm^{-1} aromatics 1616, 1575, 1505 cm^{-1}

Using 4-(4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile of Example 15 and the appropriate reactants, the following compounds were prepared:

EXAMPLE 33

4-(4,5-dihydro-4,4-dimethyl-2-nonylthio-5-oxo-1H-imidazol-1-yl)-2-trifluoromethyl-benzonitrile with a Rf=0.35 (97.5-2.5 methylene chloride-ethyl acetate eluant).

EXAMPLE 34

4-(4,5-dihydro-4,4-dimethyl-2-(3-hydroxypropylthio)-5-oxo-1H-imidazol-1-yl)-2-trifluoromethyl-benzonitrile with a Rf=0.17 (8-2 methylene chloride-ethyl acetate eluant).

EXAMPLE 35

Ethyl [1-(4-cyano-3-trifluoromethyl-phenyl)-4,5-dihydro-4,4-dimethyl-5-oxo-1H-imidazol-2-yl)-thio]-acetate with a Rf=0.20 (65-35 cyclohexane-ethyl acetate eluant).

Using the isocyanate of Example 11 and the appropriate reactants, the following compounds were prepared.

EXAMPLE 36

4-(4,4-dimethyl-3-ethyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile with a Rf=0.16 (95-5 methylene chloride-acetone eluant).

EXAMPLE 37

4-(4,4-dimethyl-5-imino-3-pentyl-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile with a Rf=0.35 (8-2 ethyl acetate-cyclohexane eluant)

Using the 4-(4,4-dimethyl-3-ethyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile of Example 36 and the 4-(4,4-dimethyl-5-imino-3-pentyl-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile of Example 37 and 0.5N hydrochloric acid, the following compounds were prepared.

EXAMPLE 38

4-(4,4-dimethyl-3-ethyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile with a Rf=0.38 (1-1 ethyl acetate-cyclohexane eluant).

EXAMPLE 39

4-(4,4-dimethyl-5-oxo-3-pentyl-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile with a melting point of 78° C. and a Rf=0.66 (8-2 ethyl acetate-cyclohexane eluant)

Using 4-(4,5-dihydro-4,4-dimethyl-2-methylthio-5-oxo-1H-imidazol-1-yl)-2-trifluoromethyl-benzonitrile of Example 20 and 4-(4,5-dihydro-4,4-dimethyl-5-oxo-2-benzylthio-1H-imidazol-1-yl)-2-trifluoromethyl-benzonitrile of Example 21 and the Lawesson reagent, the following compounds were prepared.

EXAMPLE 40

4-(4,5-dihydro-4,4-dimethyl-2-methylthio-5-thioxo-1H-imidazol-1-yl)-2-trifluoromethyl-benzonitrile with a Rf=0.36 (97.5-2.5 methylene chloride-ethyl acetate eluant).

EXAMPLE 41

4-(4,5-dihydro-4,4-dimethyl-2-benzylthio-5-thioxo-1H-imidazol-1-yl)-2-trifluoromethyl-benzonitrile with a Rf=0.62 (98-2 methylene chloride-ethyl acetate eluant).

EXAMPLE 42

3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2,4-dioxo-N-methyl-N-isopropyl-1-imidazolidine-acetamide

0.1 ml of N-methyl-morpholine was added to a suspension of 3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2,4-dioxo-1-acetic acid in 4 ml of methylene chloride and after cooling the solution to −10° C., 0.1 ml of isobutyl chloroformate was added dropwise. After stirring for 25 minutes at −10° C., 0.15 ml of N-methyl-N-isopropylamine was added and the mixture was allowed to return to room temperature over 40 minutes. 5 ml of an aqueous saturated sodium bicarbonate solution were added and after stirring for 30 minutes, the mixture was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The residue was chromatographed on silica and eluted with a 96-4 methylene chloride-acetone mixture to obtain 147 mg of the desired product.

IR Spectrum ($CHCl_3$): CN 2236 cm^{-1} hydantoïin C=O 1783, 1728 cm^{-1} amide C=O 1661 cm^{-1} aromatics 1615, 1575, 1505 cm^{-1}

EXAMPLE 43

4-(4,4-dimethyl-2,5-dioxo-3-(2-hydroxyethyl)-1-imidazolidinyl) -2-trifluoromethyl-benzonitrile

Using the procedure of Example 9, 900 mg of the product of Example 8 and 1.91 g of 2-bromoethane tert.-butyldimethylsilyl ether were reacted to obtain 1 g of the silyloxy

ether derivative melting at 86° C. to 87° C. after chromatography on silica and elution with a 7 e cyclohexane-ethyl acetate mixture.

1 ml of 2N hydrochloric acid was added to a mixture of 380 mg of the silyloxy ether, 4 ml of methanol and 1 ml of methylene chloride and after stirring for 40 minutes at room temperature, the mixture was poured into 15 ml of water and was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness and the residue was chromatographed on silica. Elution with a 7-3 methylene chloride-ethyl acetate mixture yielded the desired product which after crystallization from isopropanol melted at 109° C. to 110° C. and had Rf=0.9.

Analysis: Calculated: %C 52.79 %H 4.23 %F 16.70 %N 12.31 Found: 52.5 4.2 16.7 12.1

EXAMPLE 44

Using the procedure of Example 43, 2-bromopropanol tert.-butyldimethylsilyl ether was reacted to obtain 4-(4,4-dimethyl-2,5-dioxo-3-(3-hydroxypropyl)-1-imidazolidinyl) -2-trifluoromethyl-benzonitrile melting at 131° C. to 132° C. and a Rf=0.13 (3-1 methylene chloride-ethyl acetate eluant).

EXAMPLE 45

4-[3-(2-acetyloxyethyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile

A mixture of 215 mg of the product of Example 43, 15 mg of 4-dimethylamino-pyridine, 1 ml of pyridine and 0.5 ml of acetic acid anhydride was stirred at room temperature for 30 minutes and was then poured into 20 ml of a saturated aqueous sodium bicarbonate solution. After stirring for 20 minutes, the mixture was extracted with ethyl acetate. The organic phase was washed with water and evaporated to dryness and the pyridine and residual acetic acid were distilled. The residue was chromatographed on silica and eluted with a 65-35 methylene chloride-ethyl acetate mixture. The residue with a Rf=0.35 was taken up in isopropanol, partially concentrated, iced and vacuum filtered to obtain after drying, 210 mg of the desired product melting at 99° C. to 100° C.

Analysis: Calculated: %C 53.27 %H 4.21 %F 14.87 %N 10.96 Found: 53.5 4.3 15.2 10.9

Using the above procedure, the following products were prepared.

EXAMPLE 46

4-(4,4-dimethyl-2,5-dioxo-3-(5-hydroxypentyl)-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 101° C. to 102° C.

EXAMPLE 47

4-(4,4-dimethyl-2,5-dioxo-3-(2-methoxyethyl)-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 68° C. to 69° C.

EXAMPLE 48

4-(4,4-dimethyl-2,5-dioxo-3-cyanomethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 186° C. to 187° C.

EXAMPLE 49

4-(4,4-dimethyl-2,5-dioxo-3-[(1,3-dioxolan-2-yl)-methyl]-1-imidazolinyl)-2-trifluoromethyl-benzonitrile melting at 135° C. to 136° C.

EXAMPLE 50

4-(4,4-dimethyl-2,5-dioxo-3-(2-chloroethyl)-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 120° C. to 121° C.

EXAMPLE 51

1-(3,4-dichlorophenyl)-5-imino-3,4,4-trimethyl-2-imidazolidine thione

A mixture of 2.4 g of the isocyanate of 3,4-dichlorophenyl, 1.3 ml of 2-methylamino-2-cyano-propane, 23 ml of tetrahydrofuran and 0.23 ml of triethylamine was refluxed for 16 hours and then evaporated to dryness under reduced pressure. The residue was chromatographed on silica and eluted with a 96-4 methylene chloride-acetone mixture to obtain after crystallization from ether, 2.54 g of the desired product melting at 133° C.

EXAMPLE 52

3-(3,4-dichlorophenyl)-2-thioxo-1,5,5-trimethyl-1-imidazolidinone

A suspension of 1.88 g of the product of Example 51 in 14 ml of 6N hydrochloric acid was refluxed for 45 minutes and after the addition of another 14 ml of 6N hydrochloric acid, the mixture was refluxed for 2 more hours. Another 4 ml of 6N hydrochloric acid were added and the mixture was refluxed for 90 minutes and then returned to room temperature. 100 g of ice were added and the mixture was extracted with ethyl acetate. The organic phase was washed with water, dried and evaporated to dryness. The residue was chromatographed on silica and eluted with a 1-1 cyclohexane-ethyl acetate mixture to obtain 1.84 g of the desired product melting at 129° C. after crystallization from isopropanol.

Analysis: $C_{12}H_{12}Cl_2N_2OS$; molecular weight=303.21 Calculated: %C 47.54 %H 3.99 %Cl 23.38 %N 9.24 %S 10.57 Found: 47.5 3.8 23.2 9.3 10.5

IR Spectrum ($CHCl_3$): C=O 1753 cm^{-1} C=S+aromatics 1595, 1570, 1496 cm^{-1}

Using the above procedures, the following compounds were prepared:

EXAMPLE 53

3-(3,4-dichlorophenyl)-3,5-dihydro-5,5-dimethyl-2-methylthio-4H-imidazol-4-one melting at 110° C.

EXAMPLE 54

1-(3,4-dichlorophenyl)-3,4-4-trimethyl-2,5-imidazolidinedithione melting at ≈146° C.

EXAMPLE 55

1-(4-chloro-3-trifluoromethyl-phenyl)-4,4-dimethyl-2-thioxo-5-imidazolidinone melting at 176° C.

EXAMPLE 56

1-(4-chloro-3-trifluoromethyl-phenyl)-4,4-dimethyl-5-imino-2-imidazolidinethione melting at 173° C. to 174° C.

EXAMPLE 57

3-(3,4-dichlorophenyl)-3,5-dihydro-5,5-dimethyl-2-benzylthio-4H-imidazol-4-one

IR Spectrum ($CHCl_3$): C=O 1736 cm^{-1} CN+aromatics 1578, 1496 cm^{-1}

EXAMPLE 58

4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxy butyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

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a) Condensation

600 mg of 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile obtained as in Example 8 in 5 ml of dimethylformamide were added to a suspension of 104 mg of sodium hydride in 0.8 ml of dimethylformamide, while maintaining the temperature below 20° C. After 10 minutes of stirring, 445 mg of 4-chloro-t-butyldimethylsilylether and 300 mg of sodium iodide were added. The mixture was heated for 16 hours at 50° C. and then, cooled to ambient temperature, 87 mg of sodium hydride were added followed by another 400 mg of the chlorinated ether and 267 mg of sodium hydride were added. The mixture was heated for another hour and then, returned to ambient temperature, and poured into 60 ml of water containing 6 mg of monopotassium phosphate. Extraction was carried out with ether and the organic phase was washed with water, dried and the solvent was evaporated. The residue was chromatographed on silica (eluant: methylene chloride-acetone (99-1)) to obtain 526 mg of product which was used as is for the stage following the cleavage.

The said product was mixed in 5 ml of methanol and 1.5 ml of 2N hydrochloric acid and the mixture was stirred for 40 minutes at ambient temperature. The mixture was poured into 30 ml of water and was extracted with methylene chloride. The organic phase was washed with water, dried and the solvent was evaporated. After chromatographing the residue on silica (eluant methylene chloride-acetone (9-1), the fractions with a Rf=0.15, were recovered, and after crystallization from isopropyl ether, 307 mg of the expected product melting at 102°–103° C. were obtained.

Analysis; $C_{17}H_{18}F_3N_3O_3$; molecular weight = 369.35

	C %	H %	F %	N %
Calculated	55.28	4.91	15.43	11.38
Found	55.2	4.9	15.3	11.1

IR Spectrum ($CHCl_3$); OH 3628 cm^{-1} C≡N 2236 cm^{-1} C=O 1778–1724 cm^{-1} Aromatics 1615-1575-1505 cm^{-1}

Preparation of the 4-chloro t-butyl dimethylsilylether used at the start of Example 58.

9.9 ml of 4-chloro-1-butanol and 24.3 g of imidazole in 50 ml of tetrahydrofuran were stirred and 2.82 g of terbutyldimethylsilyl chloride in 20 ml of tetrahydrofuran were added dropwise at a temperature of less than 20° C. The mixture was stirred for 18 hours at ambient temperature, followed by separating, rinsing with tetrahydrofuran and eliminating the solvent under reduced pressure. The residue was purified by chromatography on silica (eluant: cyclohexane-ethyl acetate (95-5)) to obtain 17.5 g of the expected product.

EXAMPLE 59

(1,1-methyl) ethyl 3-(4-cyano-trifluoro-methylphenyl)-5,5-dimethyl 2,4-dioxo-1-imidazolidine acetate

450 mg of the product of Example 8 in solution in 4 ml of dimethylformamide were added to a suspension of 78 mg of sodium hydride at 50% in oil and 0.5 ml of dimethylformamide. The mixture was stirred for 15 minutes and then without exceeding 30° C., 0.22 ml of terbutyl bromoacetate were slowly added. The mixture was stirred for 16 hours and then, was poured into 50 g of a water and ice mixture (1-1). 0.5 g of monopotassium phosphate were added and extraction was carried out with ether. The organic phase was washed with water, dried and evaporated to dryness. The 1.1 g of crude product was chromatographed on silica (eluant: methylene chloride-acetone (99-1)) to obtain 425 mg of the expected product melting at 122°–123° C. with a Rf=0.28 (eluant: methylene chloride-acetone (99-1))

IR Spectrum ($CHCl_3$); C=O 1788–1729 cm^{-1} (hydantoin) 1745 cm^{-1} (ester) C≡N 2235 cm^{-1} Aromatics 1616–1505 cm^{-1}

UV Spectrum (EtOH) Max. 258 nm=16100 Infl. 277 nm=6000 Infl. 285 nm=3000

EXAMPLE 60

cyclopentyl 3-(4-cyano-3-trifluoromethyl phenyl)-5,5-dimethyl 2,4-dioxo 1-imidazolidine acetate

A solution of 355 mg of the product of Example 9, 49 mg of 4-dimethylaminopyridine, 130 mg of cyclopentanol and 6.5 of methylene chloride was cooled to −10° C. and then 226 mg of dicyclohexylcarbodiimide in 2 ml of methylene chloride were added. The mixture was allowed to return to ambient temperature, stirred for 25 minutes, heated at reflux for 2 hours, returned to ambient temperature, filtered and the solvent was evaporated. The residue was chromatographed on silica (eluant: methylene chloride-acetone (99-1)) mg of the expecte product with a Rf=0.25 (eluant: methylene chloride-acetone (99-1))

IR Spectrum ($CHCl_3$); C=O 1786–1729 cm^{-1} (hydantoin) 1748 cm^{-1} (ester) C≡N 2235 cm^{-1} Aromatics 1615-1602-1576-1505 cm^{-1}

UV Spectrum (EtOH) Max. 258 nm=16800 Infl. 276 nm=5800 Infl. 286 nm=3000

EXAMPLE 61

ethyl 3-(4-cyano 3-(trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoate

Using the procedure of Example 59, the product of Example 8 and ethyl 4-bromobutyrate were reacted to obtain the expected product melting at 66°–67° C. with a Rf=0.16 (eluant: methylene chloride-acetone (99-1))

IR Spectrum ($CHCl_3$); C=O 1770–1726 cm^{-1} C≡N 2235 cm^{-1} Aromatics 1616-1576-1505 cm^{-1}

UV Spectrum (EtOH) Max. 260 nm=15500 Infl. 277 nm=7000 Infl. 286 nm=3600

EXAMPLE 62

3-(4-cyano 3-trifluoromethyl-phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidine butanoic acid

1 g of the product of Example 61 in 20 ml of methanol was stirred for 3 hours at ambient temperature in the presence of 3 ml of 2N sodium hydroxide and the mixture was poured into 20 ml of water and acidified to pH=1 using 7 ml of N hydrochloric acid. The mixture was extracted with ether and the extracts were washed with water and dried and the solvents were eliminated under reduced pressure to obtain 863 mg of crude product melting at 179°–180° C. which was purified by chromatography on silica (eluant: methylene chloride-methanol (92.5-7.5)). After crystallization from isopropanol, 614 mg of the expected product melting at 184°–185° C. and with a Rf=0.25 (eluant: methylene chloride-methanol (92.5-7.5)) were obtained.

IR Spectrum (nujol); C=O 1770-1753-1735-1712-1690-1645 cm^{-1} C≡N 2230 cm^{-1} Aromatics 1613-1587-1533-1502 cm^{-1}

EXAMPLE 63

(1,1-dimethyl) ethyl 3-(4-cyano 3-trifluoro-methyl-phenyl)-5,5-dimethyl 2,4-dioxo-1-imidazolidine-butanoate

By carrying out the esterification of the product of Example 62, with terbutanol in the presence of dicyclohexylcarbodiimide and 4-dimethylamino-pyridine as in Example

60, the expected product melting at 96°–97° C. with a Rf=0.32 (eluant: methylene chloride-acetone (98-2)) was obtained.

IR Spectrum ($CHCl_3$); C=O 1779–1725 cm^{-1} C≡N 2235 cm^{-1} Aromatics 1616-1576-1505 cm^{-1}

UV Spectrum (EtOH) Max. 261 nm=15600 Infl. 276 nm=7800 Infl. 286 nm=3700

EXAMPLE 64

cyclopentyl 3-(4-cyano 3-trifluoromethyl-phenyl) 5,5-dimethyl-2,4-dioxo-1-imidazolidine butanoate

Using the procedure of Example 63, cyclopentanol was reacted to obtain the expected product melting at 85°–86° C. with a Rf=0.33 (eluant: methylene chloride-acetone (98-2)).

IR Spectrum ($CHCl_3$) C=O 1779–1728 cm^{-1} C≡N 2236 cm^{-1} Aromatics 1616-1578-1505 cm^{-1}

UV Spectrum (EtOH) Max. 261 nm=16000 Infl. 277 nm=7600 Infl. 286 nm=3700

EXAMPLE 65

4-(4,4-dimethyl-2,5-dioxo 3-(2-(4-fluorophenylthio)ethyl)-1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile

a) Formation of the phenolate

0.16 ml of 4-fluorothiophenol in 1.6 ml of dimethylformamide were added at a temperature of less than 28° C. to a suspension of 80 mg of sodium hydride in 0.5 ml of dimethylformamide, and the solution was stirred for 10 minutes.

b) Substitution

548 mg of 4-[4,4-dimethyl-2,5-dioxo-3-(2-chloroethyl) 1-imidazolidinyl]-2-(trifluoromethyl) benzonitrile (Example 50 in solution in 4 ml of dimethylformamide were added to the solution of a) and the mixture was stirred for 2 hours, poured into 50 ml of water with 0.5 g of monopotassium phosphate. Extraction was carried out with ether and the organic phase was washed with water and dried and the solvent was evaporated. After chromatographing the residue on silica (eluant: cyclohexane-ethyl acetate (75-25)), 570 mg of the expected product melting at 93°–94° C. with a Rf=0.29 (eluant: cyclohexane-ethyl acetate (75-25)) were obtained.

IR Spectrum ($CHCl_3$) C=O 1780–1726 cm^{-1} C≡N 2238 cm^{-1} Aromatics 1616-1579-1506 cm^{-1} (fluorophenyl) thio 1591–1492 cm^{-1}

UV Spectrum (EtOH) Max. 254 nm=18600 Infl. 277 nm=7500 Infl. 286 nm=4200

EXAMPLE 66

4-(4,4-dimethyl-2.5-dioxo-3-(2-(4-fluorophenyl sulfonyl) ethyl)-1-imidazolidinyl-2-(trifluoromethyl) benzonitrile

1.21 g of metachloroperbenzoic acid in 24 ml of methylene chloride were added dropwise at a temperature of less than 29° C. to 222 mg of the product of Example 65 in 4.4 ml of methylene chloride. After 30 minutes of stirring, the mixture was poured into 30 ml of sodium thiosulfate (0.5 M/l). The mixture was stirred for 10 minutes, followed by decanting and extracting with methylene chloride. The organic phase was washed with a saturated aqueous solution of sodium bicarbonate, then with water, dried, and the solvent was evaporated. After chromatographing the residue on silica (eluant: cyclohexane-ethyl acetate (1-1)), 220 mg of product were obtained which was crystallized from isopropanol to obtain 196 mg of the expected product melting at 155°–156° C. with a Rf=0.22 (eluant: ethyl acetate-cyclohexane (1-1)).

IR Spectrum ($CHCl_3$); C=O 1783–1727 cm^{-1} C≡N 2236 cm^{-1} Aromatics 1615-1593-1505-1497 cm^{-1} SO_2 1314–1150 cm^{-1}

UV Spectrum (EtOH) Max. 258 nm=16700 Infl. 286 nm

EXAMPLE 67

4-(4,4-dimethyl 2,5-dioxo 3-(2-((4-fluorophenyl) sulfinyl) ethyl) 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile

222 mg of the product of Example 65 in 15 ml of methanol were stirred for 30 minutes at ambient temperature in the presence of 5 ml of an aqueous solution of sodium metaperiodate (0.1 M/l). The suspension was heated for one hour at 40° C. and 10 ml of methanol and 5 ml of oxidizing solution were added. The methanol was evaporated off and after 10 ml of a saturated solution of sodium chloride were added, extraction was carried out with ethyl acetate. The organic phase was washed with salt water, dried, and the solvent was evaporated. After chromatographing the residue on silica (eluant: methylene chloride-acetone (9-1)), 205 mg of product were obtained which was crystallized from isopropanol to obtain 180 mg of the expected product melting at 145°–146° C. with a Rf=0.10 (eluant: methylene chloride-acetone (9-1)).

IR Spectrum ($CHCl_3$); C=O 1782–1727 cm^{-1} C≡N 2236 cm^{-1} Aromatics 1615-1592-1505-1493 cm^{-1}

UV Spectrum (EtOH) Max. 258 nm ε=17600 Infl. 285 nm

Using the procedure of the preceding examples, 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl) benzonitrile of Example 8 and the appropriate reagents, the compounds of the following examples were obtained:

EXAMPLE 68

4-(4,4-dimethyl 2,5-dioxo 3-((3-methoxyphenyl) methyl) 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile melting at 88°–89° C. with a Rf=0.21 (eluant: cyclohexane-ethyl acetate (7-3))

IR Spectrum ($CHCl_3$) C=O 1779–1724 cm^{-1} C≡N 2238 cm^{-1} Aromatics 1614-1602-1588-1575-1504-1491

UV Spectrum (EtOH) Max. 260 nm ε=16800 Infl. 210 nm ε=28500 Infl. 280 nm ε=8900

EXAMPLE 69

4-(4,4-dimethyl 2,5-dioxo 3-(2-(4-morpholinyl) ethyl) 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile with a Rf=0.20 (eluant: methylene chloride-acetone (70-30))

IR Spectrum ($CHCl_3$) C=O 1779–1725 cm^{-1} C≡N 2235 cm^{-1} Aromatics 1616-1576-1505 cm^{-1} morpholinyl 1117 cm^{-1}

UV Spectrum (EtOH) Max. 261 nm ε=14000 Infl. 277 nm ε=6900 Infl. 286 nm ε=3600

EXAMPLE 70

4-(4,4-dimethyl 3-(2-hydroxyethyl) 5-imino 2-thioxo-1-imidazolidinyl)- 2-(trifluoromethyl)-benzonitrile

a) Preparation of the isothiocyanate

2.23 g of 1-trifluoromethyl-4-amino benzonitrile (prepared according to EP 0002892) were added slowly to a solution of 22 ml of distilled water and 1 ml of thiophosgene and the mixture was stirred for one hour and then extracted with chloroform. The extracts were washed with salt water, dried and evaporated to dryness under reduced pressure to obtain 3 g of product which was used as is for obtaining the imine.

b) Obtaining the imine

5 g of the said isothiocyanate were mixed with 37 ml of tetrahydrofuran in the presence of 1.5 ml of triethylamine and 2.8 g of 2-[(2-hydroxy ethyl) amino] 2-methyl propane nitrile (prepared in Example 22) in solution in 10 ml of

tetrahydrofuran were added all at once. The temperature spontaneously increased to 34° C. and the resultant mixture was allowed to return to ambient temperature while stirring for one hour. The solvent was evaporated off and the residue was chromatographed on silica (eluant: methylene chloride-methanol (7-3)) to obtain 5.87 g of the expected product melting at 181° C., after crystallization from isopropanol.

EXAMPLE 71

4-(4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

4.6 g of the product of Example 70 in 65 ml of methanol was refluxed for one hour in the presence of 10 ml of 2N hydrochloric acid. The mixture was cooled to ambient temperature and poured into 300 ml of ice-cooled water. Extraction was carried out with ethyl acetate and the organic phase was washed with salt water, dried, and the solvent was evaporated off. The residue was chromatographed on silica (ethyl acetate-cyclohexane (1-1)) and the fractions were collected with a Rf=0.14. After crystallization from methylene chloride and cyclohexane, 4.37 g of the expected product melting at 130° C. were obtained

Analysis: $C_{13}H_{14}F_3N_3O_2S$; molecular weight = 357.36

	C %	H %	F %	N %	S %
Calculated	50.42	3.95	15.95	11.76	8.97
Found	50.3	.9	15.9	11.6	8.9

IR Spectrum ($CHCl_3$); OH 3626 cm^{-1} C≡N 2236 cm^{-1} C=O 1763 cm^{-1} Aromatics 1615-1578-1504 cm^{-1}

EXAMPLE 72

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-imino-2-thioxo 1-imidazolidinyl)-2-(trifluoromethyl)-5-^{3}H-benzonitrile

a) Preparation of the tritiated benzonitrile

15 mg of 2-trifluoromethyl 4-amino 5-bromo benzonitrile were mixed with 200 µl of ethyl acetate in the presence of 6.5 µl of triethylamine and 2 mg of palladium on activated charcoal and then tritium (1.42 bar) was introduced. After filtering, rinsing with ethyl acetate and evaporating to dryness at ambient temperature, approximately 66.6 G.Bq (1.8 Ci) of product were obtained.

b) Preparation of the tritiated isothiocyanate

150 µl of a 10% solution of thiophosgene in chloroform were added to the above product, in 150 µl of water and the mixture was stirred for 45 minutes at ambient temperature. Dilution was carried out with 0.5 ml of water and 1 ml of chloroform, followed by extraction with chloroform. The solvent was evaporated off under reduced pressure and the residue was taken up in toluene to obtain 50.7 G.Bq (1.37 Ci) of the expected product which was kept at −80° C.

c) Preparation of the tritiated imine

Having eliminated the toluene from the above mixture under reduced pressure, 130 µl of tetrahydrofuran with 1% triethylamine were added and 13 µl of 2-[(2-hydroxyethyl) -amino] 2-methylpropanenitrile (Example 22) were added. Then, another 130 µl of tetrahydrofuran with 1% triethylamine were added and the mixture was stirred for 30 minutes at ambient temperature and the solvents were eliminated under reduced pressure.

Preparation of the 2-trifluoromethyl 4-amino 5-bromo benzonitrile used in Example 72.

A solution of 2 trifluoromethyl 4-amino benzonitrile (prepared according to EP 0002892) (5 moles) in 25 ml of methanol was cooled to 0° C. and bromine was added (5.2 moles). The mixture was allowed to return to ambient temperature, stirred for 3 hours, alkalinized with triethylamine and then an aqueous solution of sodium thiosulfate was added. The solvents were eliminated and extraction was carried out with chloroform. The organic phase was washed with water, dried, and the solvent was evaporated to obtain the product which was used as is for the following stage.

IR Spectrum ($CHCl_3$); NH_2 3612–3408 cm^{-1} C≡N 2230 cm^{-1} Aromatics 1621-1556-1506 cm^{-1}

EXAMPLE 73

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo 1-imidazolidinyl)-2-(trifluoromethyl) 5-^{3}H-benzonitrile

The product of Example 72 in 180 µl of water was heated to 100° C. and 60 µl of 2N hydrochloric acid was added. The mixture was stirred for 5 minutes at reflux and then approximately 600 mg of ice were added. Extraction is carried out with ethyl acetate and the extracts were washed with salt water and dried to obtain 34.7 G.Bq (937 mCi) of product. After chromatography on silica (eluant: cyclohexane-ethyl acetate (60-40)), 19 G.Bq (513 mCi) of the expected product were obtained.

EXAMPLE 74

4-(4,4-dimethyl-3-(3-hydroxypropyl) -5-imino-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile

Using the procedure of Example 22 2 g of the isothiocyanate of Example 70(a) and 1.2 g of the appropriate aminonitrile were reacted to obtain 1.70 g of the expected product with a Rf=0.25 (methylene chloride-acetone (65-35)).

IR Spectrum ($CHCl_3$); OH 3630 cm^{-1} =NH 3314–1676 cm^{-1} C≡N 2235 cm^{-1} Aromatics 1614-1578-1481 cm^{-1}

EXAMPLE 75

4-(4,4-dimethyl-3-(3-hydroxypropyl) 5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl) benzonitrile

Using the procedure of Example 71, 240 mg of the product of Example 74 were reacted to obtain 226 mg of the expected product melting at 149°–150° C. with a Rf=0.32 (eluant: methylene chloride-acetone (75-25)).

IR Spectrum ($CHCl_3$); OH 3626 cm^{-1} C=O 1763 cm^{-1} C≡N 2236 cm^{-1} Aromatics 1615-1580-1504-1483 cm^{-1}

EXAMPLE 76

4-(4,4-dimethyl 3-(4-hydroxybutyl)-5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 22, 2 g of isothio-cyanate and 1.38 g of the appropriate aminonitrile were reacted to obtain 2.08 g of the expected product with a Rf=0.25 (methylene chloride-acetone (65-35)).

IR Spectrum ($CHCl_3$); OH 3630 cm^{-1} =NH 3314–1675 cm^{-1} C≡N 2235 cm^{-1} Aromatics 1614-1577-1504 cm^{-1}

EXAMPLE 77

4-(4,4-dimethyl 3-(4-hydroxybutyl)-5-oxo 2-thioxo-1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 71, 300 mg of the product of Example 76 were reacted to obtain 236 mg of the expected product melting at 78°–79° C. with a Rf=0.31 (eluant: methylene chloride-acetone (75-25)).

IR Spectrum ($CHCl_3$); OH 3624 cm^{-1} C=O 1762 cm^{-1} C≡N 2237 cm^{-1} Aromatics 1615-1580-1504 cm^{-1}

UV Spectrum (EtOH)

Max. 232 nm	ε = 195000
Max. 254 nm	ε = 24000
Infl. 266 nm	

EXAMPLE 78

4-(4,4-dimethyl 3-(2-methoxyethyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 22, 2.5 g of isothiocyanate and 1.56 g of the appropriate aminonitrile were reacted to obtain 2.36 g of the expected product with a Rf=0.23 (methylene chloride-acetone (92.5-7.5)).

IR Spectrum ($CHCl_3$); =NH 3314 cm^{-1} C≡N 2236 cm^{-1} Aromatics 1614-1578-1504 cm^{-1} C=N 1675 cm^{-1}

EXAMPLE 79

4-(4,4-dimethyl 3-(2-methoxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 71, the product of Example 78 was reacted to obtain the expected product melting at 98°–99° C. with a Rf=0.32 (eluant: methylene chloride-acetone (99-1))

IR Spectrum ($CHCl_3$); C=O 1757 cm^{-1} C≡N 2236 cm^{-1} Aromatics 1615-1580-1504 cm^{-1}

UV Spectrum (EtOH)

Max. 232 nm	ε = 18200
Max. 254 nm	ε = 22400
Infl. 265 nm	

EXAMPLE 80

4-(4,4-dimethyl 3-(1-methylethyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 22, 2.5 g of the isothiocyanate and 1.32 g of the appropriate aminonitrile were reacted to obtain 880 mg of the expected product with a Rf=0.20 (eluant: methylene chloride-acetone (96-4)).

IR Spectrum ($CHCl_3$), =NH 3310–1675 cm^{-1} C≡N 2236 cm^{-1} Aromatics 1614–1580–1504 cm^{-1}

EXAMPLE 81

4-(4,4-dimethyl 3-(1-methylethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 71, 880 mg of the product of Example 80 and 35 ml of 6N hydrochloric acid were reacted to obtain after extraction with chloroform, 744 mg of the expected product melting at 203°–204° C. with a Rf=0.45 (eluant: cyclohexane-ethyl acetate (1-1)).

IR Spectrum ($CHCl_3$); OH 3626 cm^{-1} C=O 1753 cm^{-1} C≡N 2232 cm^{-1} Aromatics 1615–1580–1504 cm^{-1}

UV Spectrum (EtOH)

Max. 232 nm	ε = 18900
Max. 235 nm	ε = 22500
Infl. 273 nm	

EXAMPLE 82

3-(3,4-dichlorophenyl 5,5-dimethyl 1-(3-hydroxypropyl) 4-imino 2-imidazolidine thione

Using the procedure of Example 51, 2.4 g of 3,4-dichlorophenyl isocyanate and 1.6 g of the appropriate aminonitrile were reacted to obtain, after chromatography on silica (eluant: methylene chloride-acetone (6-4)), 2.16 g of expected product with a Rf=0.25

IR Spectrum ($CHCl_3$); OH 3630 cm^{-1}+associated C=NH 3294–1676 cm^{-1} (F) Aromatics 1595–1569–1482 cm^{-1}

EXAMPLE 83

3-(3,4-dichlorophenyl 5,5-dimethyl 1-(3-hydroxypropyl) 2-thioxo 4-imidazolidinone

Using the procedure of Example 52, 0.88 g of the product of Example 82 and 35 ml of 6N hydrochloric acid were reacted to obtain, after extraction with chloroform, 0.79 g of the expected product melting at 202°–203° C.

IR Spectrum ($CHCl_3$); C=O 1753 cm^{-1} C≡N 2232 cm^{-1} Aromatics 1615–1580–1504 cm^{-1}

UV Spectrum (EtOH)

Max. 232 nm	ε = 18900
Max. 235 nm	ε = 22500
Infl. 273 nm	

EXAMPLE 84

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

a) 4-amino 2-(trifluoromethyl) (5-^{3}H) benzonitrile

The following were cooled to −180° C. and mixed under an inert atmosphere: 16 mg of 2-trifluoromethyl 4-amino 5-bromo benzonitrile, 2 mg of palladium on activated charcoal, 200 µl of ethyl acetate and 6.5 µl of triethylamine. Then the mixture was left under a tritium atmosphere and taken to 20° C. and the pressure was then 1.68 bar. The mixture was stirred until absorption was complete (p=0.42 bar), followed by cooling to −180° C. The excess tritium was recovered, taken to 20° C. and then filtered. The filtrate was rinsed with ethyl acetate and concentrated at 40° C. under reduced pressure to obtain 68 G.Bq of the expected product.

b) 4-thioisocyanate 2-(trifluoromethyl) (5-^{3}H) benzonitrile

The following were mixed under an argon atmosphere: 34 G.Bq of the above tritiated amino derivative, 150 µl of demineralized water and 150 µl of 10% thiophosgene solution in chloroform. The mixture was stirred at 20° C. for 45 minutes, decanted and reextraction was carried out with chloroform. The extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The thioisocyanate obtained was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) (5-H) benzonitrile

The following were mixed under an argon atmosphere with the thioisocyanate of stage b): 350 µl of tetrahydrofuran with 1% triethylamine and 20 µl of propanonitrile prepared as indicated below. The mixture was stirred for 2 hours at 20° C., followed by concentration at 20° C. under reduced pressure. The imine was used as is for the following stage.

Preparation of the 2-(4-hydroxybutylamino) 2-methylpropano-nitrile used in stage c)

550 µl of acetone cyanohydrin and 500 µl of 4-amino 1-butanol were mixed together and the mixture was stirred for 16 hours at 20° C. to obtain the desired product which was used as is for the following stage.

EXAMPLE 85

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

200 µl of 2N hydrochloric acid were added to the imine of Example 84 and the mixture was refluxed for 5 minutes, then returned to 20° C. and diluted with 1 ml of water.

Extraction was carried out with ethyl acetate and the extracts were washed with water and concentrated under reduced pressure. The crude product was purified by chromatography on silica (eluant: cyclohexane-ethyl acetate (6-4)) to obtain 2.8 G.Bq of the expected product.

EXAMPLE 86

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

a) 4-amino 2-(trifluoromethyl) benzo (^{14}C) nitrile

377 mg of cuprous cyanide ^{14}C (9 G.Bq) and 1.0732 g of 4-bromo 3-(trifluoromethyl) benzenamine were mixed together under a nitrogen atmosphere in 8 ml of dimethylformamide and the mixture was refluxed for 4 hours, then cooled to 0° C. and diluted with 20 ml of acetone. The insoluble part was filtered off and the filtrate was concentrated at 70° C. under reduced pressure. The residue was taken up in methylene chloride, filtered and the filtrate was concentrated under reduced pressure. The benzonitrile (^{14}C) was purified by chromatography on silica (eluant: methylene chloride-cyclohexane (70-30)) to obtain 0.558 g (6.62 G.Bq) of the expected product.

b) 4-thioisocyanate 2-(trifluoromethyl) benzo (^{14}C) nitrile

The following were mixed under a nitrogen atmosphere: 189 mg of benzonitrile (^{14}C) of stage a), 2.7 ml of water and 85 µl of thiophosgene. The mixture was agitated vigorously stirred for 5 minutes, and after 30 µl of thiophosgene were added, stirring was continued for one hour at 20° C. Then extraction was carried out with chloroform and the extracts were washed with water, dried and concentrated under reduced pressure. The thioisocyanate obtained was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

2 ml of tetrahydrofuran, the propanonitrile prepared below in solution in 1.5 ml of methylene chloride and 150 µl of triethylamine were added under a nitrogen atmosphere to the thioisocyanate of stage b). The mixture was heated for 30 minutes under reflux and concentrated under reduced pressure to obtain the imine which was used as is for the following stage.

Preparation of the 2-(4-hydroxybutylamino) 2-methylpropano-nitrile of stage c

220 µl of acetone cyanohydrin and 200 µl of 4-amino 1-butanol were mixed together with stirring for 16 hours at 20° C. and then was diluted with 2 ml of methylene chloride, dried, filtered and the filtrate was concentrated under reduced pressure to obtain the propanonitrile which was used as is for the following stage.

EXAMPLE 87

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

6 ml of methanol and 1.6 ml of 2N hydrochloric acid were added to the imine of Example 86 and the mixture was refluxed for 45 minutes, cooled to 20° C. and diluted with 10 ml of water. Extraction was carried out with methylene chloride and the extracts were washed with water and concentrated under reduced pressure. The crude product was purified by chromatography on silica (eluant: ether-acetonitrile-cyclohexane (50-15-35)) to obtain 328 mg of the expected product.

EXAMPLE 88

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl), (5-^{3}H) benzonitrile

a) 4-amino 2-(trifluoromethyl) (5-^{3}H) benzonitrile

Using the procedure of stage a) of Example 84, 16 mg of 4-amino 5-bromo 2-trifluoromethyl benzonitrile, 2 mg of palladium on activated charcoal, 200 µl of ethyl acetate and 6.5 µl of triethylamine were reacted to obtain 68 G.Bq of the expected product.

b) 4-isocyanate 2-(trifluoromethyl) (5-^{3}H) benzonitrile

34 G.Bq of tritiated amino derivative of step a) and 100 µl of 20% phosgene in toluene were mixed together under an argon atmosphere and the mixture was taken to 80° C. for one hour. A further 100 µl of phosgene were added and the mixture heated for one hour at 80° C. This operation was repeated one more time, then concentration was carried out at 20° C. under reduced pressure to obtain the isocyanate which was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

The following were added under an argon atmosphere to the isocyanate of stage b): 200 µl of methylene chloride, 50 µl of the propanonitrile chloromethylene solution prepared as below and 20 µl of triethylamine and the mixture was stirred for 30 minutes. A further 50 µl of the propanonitrile solution were added and stirring was continued for 30 minutes followed by concentration at 20° C. under reduced pressure. The imine was used as is for the following stage.

Preparation of the 2-(4-hydroxybutylamino) 2-methyl propano-nitrile, of stage c)

220 µl of acetone cyanohydrin and 200 µl of 4-amino 1-butanol were mixed together and the mixture was stirred for 16 hours at 20° C., then diluted with 3 ml of methylene chloride and dried over magnesium sulfate. The decanted solution was used as is for the following stage.

EXAMPLE 89

4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

200 µl of methanol and 50 µl of 2N hydrochloric acid were added to the imine of Example 88 and the mixture was refluxed for 45 minutes, then returned to 20° C. and diluted with 1 ml of water. Extraction was carried out with methylene chloride and the extracts were washed with water and concentrated at 20° C. under reduced pressure. The crude product was purified by chromatography on silica (eluant: methylene chloride-ethyl acetate (7-3 then 5-5)) to obtain 16 G Bq of the expected product.

EXAMPLE 90

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

a) 4-amino 2-(trifluoromethyl) benzo (^{14}C) nitrile

Using the procedure of Example 86, stage a), 377 mg of cuprous cyanide ^{14}C, 1.0732 g of 4-bromo 3-trifluoromethyl benzenamine and 8 ml of dimethylformamide were reacted to obtain 0.558 g (6.62 G.Bq) of the expected product.

b) 4-isocyanato 2-(trifluoromethyl) benzo (^{14}C) nitrile

182.4 mg of benzonitrile (^{14}C) (0.97 mmole), 2 ml of dioxane and 1 ml of 20% phosgene in toluene were mixed together under a nitrogen atmosphere and the solution was heated at 60° C. for 22 hours, then concentrated at 60° C. under reduced pressure. The isocyanate was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

1.5 ml of methylene chloride (on siliporite NK 30), the propanonitrile of Example 88, in solution in 1.5 ml of methylene chloride, and 150 µl of triethylamine were added under a nitrogen atmosphere to the isocyanate of stage b). The mixture was stirred for one hour at 20° C. and concentrated under reduced pressure. The imine was used as is for the following stage.

EXAMPLE 91

4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

5 ml of methanol and 1.2 ml of 1N hydrochloric acid were added to the imine of Example 90 and the mixture was refluxed for 40 minutes, then returned to 20° C. and diluted with 10 ml of water. Extraction was carried out with methylene chloride and the extracts were washed with water and concentrated under reduced pressure. The crude product was purified by chromatography on silica (eluant: ether-acetonitrile-cyclohexane (50-15-35), to obtain 289 mg (1.26 G.Bq) of the expected product.

EXAMPLE 92

4-(2,5-dioxo 4,4-dimethyl 3-(4-triphenylmethoxy-butyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

370 mg of the product of Example 58, 307 mg of trityl chloride in the presence of 10 mg of 4-dimethylamino-pyridine, 0.25 ml of triethylamine and 4 ml of dimethylformamide were stirred at ambient temperature for 16 hours. The mixture was heated to 40° C. for 4 hours, poured into water and extraction was carried out with ether. The extracts were washed with water and dried and the solvent was eliminated under reduced pressure. The residue was chromatographed on silica (eluant: cyclohexane-ethyl acetate 75-25) to obtain 467 mg of the expected product with a Rf=0.25.

IR Spectrum ($CHCl_3$); C=O 1778, 1725 cm^{-1} (F) C≡N 2235 cm^{-1} Aromatics 1615, 1597, 1505, 1490 cm^{-1}

EXAMPLE 93

4-(2,5-dioxo 4,4-dimethyl 3-(4-phenylmethoxy-butyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

48 mg of sodium hydride were added in several lots to 370 mg of the product of Example 58 in solution in 4 ml of dimethylformamide and the mixture was stirred for 30 minutes. Then, 0.12 ml of benzyl bromide and 40 mg of tetrabutylammonium iodide were added and after 90 minutes of reaction, the same amount of each reagent was added. The mixture was stirred for one hour and the reaction medium was poured into an ice-cooled aqueous solution of monopotassium phosphate. Extraction was carried out with ether and the extracts were washed with water and dried. The solvent was eliminated under reduced pressure and the residue was chromatographed on silica (eluant: methylene chloride-acetone 99-1) to obtain 140 mg of the expected product melting at 75°–76° C.

IR Spectrum ($CHCl_3$); C=O 1779, 1725 cm^{-1} C≡N 2235 cm^{-1} Aromatics 1615, 1580, 1505, 1497 cm^{-1}

EXAMPLE 94

4-[4,4-dimethyl 2,5-dioxo 3-(4-methoxybutyl) 1-imidazolidinyl] 2-(trifluoromethyl)-benzonitrile

50 mg of sodium hydride were added in several lots to 370 mg of the product of Example 58 in solution in 3 ml of dimethylformamide and the mixture was stirred for 20 minutes. 0.06 ml of methyl iodide were added and the mixture was stirred for one hour. A further 50 mg of sodium hydride were added and then after 20 minutes, 0.06 ml of methyl iodide were added. The reaction medium was poured into water and extracted with ether. The extracts were washed with water, dried and the solvent was evaporated. The residue was chromatographed on silica (eluant: methylene chloride-acetone 98-2) to obtain 135 mg of the expected product melting at 80°–81° C.

IR Spectrum ($CHCl_3$); C=O 1779, 1725 cm^{-1} (F) C≡N 2234 cm^{-1} Aromatics 1616, 1576, 1505 cm^{-1} OCH_3 approx. 2830 cm^{-1}

EXAMPLE 95

4-[3-(4- chlorobutyl) 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 59, 600 mg of the product of Example 8 and 660 mg of 1-chloro 4-iodobutane in solution in 1 ml of dimethylformamide cooled down to +5° C. were reacted to obtain 604 mg of the expected product melting at 80°–81° C.

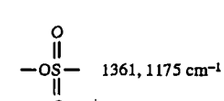
IR Spectrum ($CHCl_3$); C=O 1779, 1725 cm^{-1} (F) C≡N 2238 cm^{-1} Aromatics 1616, 1575, 1505 cm^{-1}

EXAMPLE 96

4-[3-[4-[(methylsulphonyl) oxy] butyl] 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrile

0.17 ml of methanesulfonyl chloride were added to 740 mg of the product of Example 58 in solution in 7.4 ml of pyridine and 24 mg of 4-dimethylamino-pyridine and the mixture was stirred for one hour. The mixture was poured into ice-cooled water and extraction was carried out with methylene chloride. The extracts were washed with water and the residual pyridine was eliminated by distillation. The residue was chromatographed on silica (eluant: methylene chloride-ethyl acetate 8-2) to obtain 771 mg of the expected product.

IR Spectrum ($CHCl_3$); C=O 1779, 1725 cm^{-1} C≡N 2235 cm^{-1} Aromatics 1615, 1575, 1505 cm^{-1}



1361, 1175 cm^{-1}

UV Spectrum (EtOH)

max. 261 nm infl. 279–297 nm	ε = 14900

EXAMPLE 97

4-(3-acetyl 4,4-dimethyl 2,5-dioxo 1-imidazo-lidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 59, 420 mg of the product of Example 8 and two lots of 0.1 ml of acetyl chloride were reacted to obtain after chromatography on silica (eluant: methylene chloride-ethyl acetate 98-2), 334 mg of the expected product melting at 129°–130° C.

IR Spectrum ($CHCl_3$); C=O 1800, 1740 1717 cm^{-1} C≡N 2240 cm^{-1} Aromatics 1616, 1505 cm^{-1}

UV Spectrum (EtOH)

max. 250 nm infl. 274–284 nm	ε = 12000

EXAMPLE 98

4-(3-benzoyl 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 59, 300 mg of the product of Example 8 and two lots of 0.12 ml of benzoyl chloride in solution in 0.5 ml of dimethylformamide were

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reacted to obtain after chromatography on silica (eluant: cyclohexane-ethyl acetate 8-2), 285 mg of the expected product melting at 179°180° C.

IR Spectrum ($CHCl_3$); C=O 1800, 1780, 1746, 1699 cm^{-1} C≡N 2235 cm^{-1} Aromatics 1617, 1600, 1580, 1504 cm^{-1}

UV Spectrum (EtOH)

max. 250 nm	ε = 28500
infl. 275 nm	ε = 6500
infl. 263 nm	ε = 3850

EXAMPLE 99

4-[3-dimethyl (1,1-dimethylethyl) silyl] 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrile

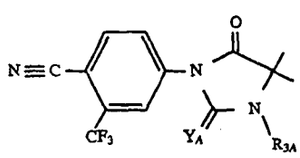
Using the procedure of Example 59, 450 mg of the product of Example 8 and 300 mg of dimethyl t-butylsilyl chloride in 2 ml of dimethylformamide were reacted to obtain after chromatography on silica (eluant: methylene chloride-acetone 99-1), 527 mg of the expected product melting at 147°–148° C.

IR Spectrum ($CHCl_3$); C≡N 2236 cm^{-1} Aromatics 1615, 1579, 1505 cm^{-1}

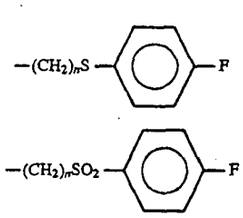
UV Spectrum (EtOH)

max. 258 nm	ε = 17000
infl. 275–285 nm	

In addition to the products described above, the following products are products which can be obtained within the scope of the present invention, namely the products of the formula:

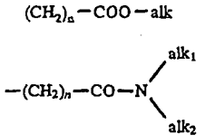


in which Y_A is oxygen or sulfur and R_{3A} has the following values:



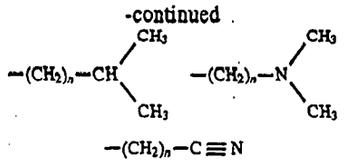
$-(CH_2)_n-OH$

$-(CH_2)_n-COO-alk$



$-(CH_2)_n-CO-alk$

-continued



$-(CH_2)_n-C\equiv N$

alk, alk_1 and alk_2 are alkyl of 1 to 4 carbon atoms and n is an integer between 1 and 4.

EXAMPLE 100

Tablets were prepared with a composition of 100 mg of 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolinyl)-2-trifluoromethyl-benzonitrile and sufficient excipient of lactose, starch, talc and magenisum stearate for a final tablet weight of 300 mg.

PHARMACOLOGICAL DATA

Study of the affinity of the products of the invention for the androgenic receptor.

1) Androgenic receptor

Male rats of the Sprague Dawley EOPS strain weighing 180 to 200 g, castrated 24 hours previously, were killed and the prostate was removed, weighed and homogenized at 0° C. with a potter glass in a buffered solution (Tris 10 mM, saccharose 0.25M, PMSF (phenyl methane sulfonyl fluoride) 0.1 mM, sodium molybdate 20 mM, HCl pH 7.4 into which was added extemporaneously 2M of DTT (DL dithiothreitol) at a rate of 1 g of tissue per 8 ml of buffer solution. The homogenate was then ultracentrifuged at 0° C. for 45 minutes at 105.000 g and the aliquots of supernatant (=cytosol) were incubated for 30 minutes and 24 hours with a concentration (T) of tritiated testosterone and in the presence of increasing concentrations (0 to $2{,}500.10^{-9}$M) of cold testosterone or the test products. The concentration of bound tritiated Testostrone (B) was then measured for each incubate by adsorption method of carbon-dextran. The relative affinity of bonding (RBA) was calculated.

The following two curves were graphed: the percentage of the bound tritiated hormone B/T as a logarithm function of the concentration of the cold hormone and B/T as a logarithm function of the concentration of the tested cold product. The line of the equation

$$I_{50} = \frac{(B/T\max + B/T\min)}{2}$$

was determined. B/T max=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T). B/T min=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T) in the presence of a large excess of cold hormone ($2{,}500\times 10^{-9}$M).

The intersections of the straight line I_{50} and the curves permit an evaluation of the concentrations of the cold reference hormones (CH) and the cold test product (CX) which inhibit by 50% the bonding of the tritiated hormone on the receptor. The RBA of the test product was determined by the equation

$$RBA=(CH)/(CX)$$

and the following results expressed in ARL were obtained with testosterone=100.

	Incubation 30 minutes	Incubation 24 hours
Product Example 1	27.5	3
Product Example 2	22	6.
Product Example 4	21	5
Product Example 11	28	8
Product Example 12	128	92
Product Example 13	31	39
Product Example 14	27	7
Product Example 15	69	24

2) Study of the affinity of the products of the invention for the androgen receptor.

Male rats of the Sprague Dawley EOPS strain weighing 180 to 200 g, castrated 24 hours previously, were killed and the prostate was removed, weighed and homogenized at 0° C. with a potter glass in a buffered solution (Tris 10 mM, saccharose 0.25M, PMSF (phenyl methane sulfonyl fluoride) 0.1 mM, sodium molybdate 20 mM, HCl pH 7.4 into which was added extemporaneously 2 mM of DTT (DL dithiothreitol) at a rate of 1 g of tissue per 8 ml of buffer solution. The homogenate was then ultracentrifuged at 0° C. for 30 minutes at 209,000 g and the aliquots of supernatant (=cytosol) were incubated for 30 minutes and 24 hours with a concentration (T) of tritiated testosterone and in the presence of increasing concentrations (0 to 2,500.10^{-9}M) of cold testosterone or the test products. The concentration of bound tritiated Testostrone (B) was then measured for each incubate by adsorption method of carbon-dextran. The relative affinity of bonding (RBA) was calculated.

The following two curves were graphed: the percentage of the bound tritiated hormone B/T as a logarithm function of the concentration of the cold hormone and B/T as a logarithm function of the concentration of the tested cold product. The line of the equation

$$I_{50} = \frac{(B/T\max + B/T\min)}{2}$$

was determined. B/T max=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T). B/T min=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T) in the presence of a large excess of cold hormone (2,500× 10^{-9}M).

The intersections of the straight line I_{50} and the curves permit an evaluation of the concentrations of the cold reference hormones (CH) and the cold test product (CX) which inhibit by 50% the bonding of the tritiated hormone on the receptor. The RBA of the test product was determined by the equation

RBA=100(CH)/(CX)

and the following results expressed in RBA were obtained with testosterone=100.

	Incubation 24 hours
Example 59	31
Example 71	163
Example 77	300
Example 79	81
Example 81	28

3) Determination of the androgen or anti-androgen activity by the dosage of ornithine carboxylase.

Six week old male Swiss mice castrated 24 hours received oral doses of the test products as a 0.5% suspension in methyl cellulose simultaneously with a sub-cutaneous injection of 3 mg/kg of testosterone propionate in solution in sesame oil containing 5% of benzyl alcohol to determine the anti-androgen activity. Active agonists were determined in the absence of testosterone propionate. The test compounds as well as testosterone were administered in a volume of 10 ml/kg. 16 hours after the treatments, the animals were killed, the kidneys were removed and then homogenized at 0° C. with a teflon-glass grinding apparatus in 10 volumes of buffer Tris-HCl 50 mM at a pH 7.4 containing 250 mM of pyridoxal phosphate, 0.1 mM EDTA and 5 mM of dithiothreitol. The homogenate was centrifuged at 105,000 g for 45 minutes.

At 37° C., renal ornithine decarboxylase transforms an isotropic mixture of cold ornithine and tritiated ornithine in cold putrescine and tritiated putrescine. The putrescine was then collected on selective ion-exchange papers, After drying, excess non-transformed cold and tritiated ornithine were eliminated by washing 3 times with 0.1M ammonium hydroxide. The papers were dried and the radioactivity was determined after addition of an Aqualite sample. The results expressed in fmoles (10^{-15}M) of tritiated putrescine formed per hour mg of protein are reported in the following Table

PRODUCT OF EXAMPLE	ANTAGONISM IN MG/KG		PERCENT
11		3	83
12		0.1	12
		0.3	36
		1	68
		3	94
		10	99
12	(Agonism)	10	0
14	Antagonism	3	87
15		0.3	4
		1	82

4) Determination of the androgen or anti-androgen activity by the dosage of ornithine carboxylase.

Swiss six week old male mice castrated 24 hours received oral or percutaneous doses of the test products as a 0.5% suspension in methyl cellulose or in ethanol simultaneously with a sub-cutaneous injection of 3 mg/kg of testosterone propionate in solution in corn oil to determine the anti-androgen activity. Active agonists were determined in the absence of testosterone propionate. The test compounds as well as testosterone were administered in a volume of 10 ml/kg. 20 hours after the treatments, the animals were killed, the kidneys were removed and then homogenized at 0° C. with a teflon-glass grinding appparatus in 10 volumes of buffer Tris-HCl 50 mM at a pH 7.4 containing 250 mM of pyridoxal phosphate, 0.1 mM EDTA and 5 mM of dithiothreitol. The homogenate was centrifuged at 209,000 g for 45 minutes.

Principle of dosage

At 37° C., renal ornithine decarboxylase transforms an isotopic mixture of cold ornithine and tritiated ornithine in cold putrescine and tritiated putrescine. The putrescine was then collected on selective ion-exchange papers, After drying, excess non-transformed cold and tritiated ornithine were eliminated by washing 3 times with 0.1M ammonium hydroxide. The papers were dried and the radioactivity was determined after addition of an Aqualite sample. The results expressed in fmoles (10^{-15}M) of tritiated putrescine formed per hour/mg of protein are reported in the following Table

The same test were repeated with the following changes:

Test A: the products were administered percutaneously at 1.5 mg/kg at a volume of 10 µl.

Test B: the products were administered orally at 1 mg/kg. The

Test C: the products are administered orally at 3 mg/kg. The results are in the following Table.

The results are expressed in % of inhibition of the OD the samples receiving only the testosterone propionate:

Products of example	ODL		
	Test A	Test B	Test C
58	40	36	
71	32		67
75	41		
78	78		
80	62		
81	35		
83	58		

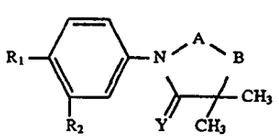
CONCLUSION

The tests show that the tested compounds of the invention possess a strong anti-androgen activity and do not have agonist activity.

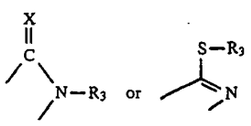
Various modifications of the compounds and method of the invention may be made without departing from the spirit or scope thereof and it is to be understood that the invention is intended to be limited only as defined in the appended claims.

We claim:

1. A compound selected from the group consisting of a compound of the formula



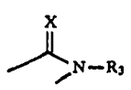
wherein R_1 is selected from the group consisting of —CN, $—NO_2$ and halogen, R_2 is $—CF_3$, or halogen, —A—B—is



X is —O— or —S—, R_3 is a) alkyl, alkenyl and alkynyl of up to 6 carbon atoms uninterrupted or interrupted with oxygen or unoxidized or oxidized sulfur, phenyl and phenylalkyl of 1 to 6 alkyl carbon atoms and all substituted with at least one member of the group consisting of —SH, acyloxy of an aliphatic carboxylic acid up to 7 carbon atoms, —phenyl, —O—phenyl, —O—phenalkyl, halo —S—phenyl, with the sulfur being unoxidized or oxidized to sulfone or sulfoxide, or heterocyclic of 3 to 6 ring members and containing at least one heteroatom selected from the group consisting of oxygen, sulfur and nitrogen, phenyl and phenalkyl being unsubstituted or substituted with a member of the group consisting of halogen, $—CF_3$, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl and alkynyloxy, b) trialkylsilyl with alkyl of 1 to 6 carbon atoms, c) acyl and acyloxy of an organic carboxylic acid of 1 to 7 carbon atoms, Y is selected from the group consisting of =O, =S and =NH and their non-toxic, pharmaceutically acceptable acid addition salts.

2. A compound of claim 1 wherein Y is oxygen.

3. A compound of claim 1 wherein —A—B— is



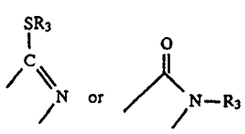
and X is sulfur.

4. A compound of claim 3 wherein R_3 is alkyl of 1 to 4 carbon atoms unsubstituted or substituted with a —OH or methoxy.

5. A compound of claim 1 wherein R_1 is —CN or halogen.

6. A compound of claim 1 wherein R_1 wherein R_1 is chlorine.

7. A compound of claim 1 wherein —A—B— is

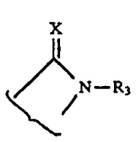


and R_3 is alkyl or alkenyl of up to 6 carbon atoms unsubstituted or substituted or optionally interrupted by oxygen or uninterrupted or oxidized sulfur or unoxidized or substituted or unsubstituted aralkyl.

8. A compound of claim 7 wherein R_3 is alkyl of 1 to 6 carbon atoms unsubstituted or substituted by at least one member of the group consisting of halogen, —OH, —O acyl, carboxy, carboxy esterified with alkyl, a heterocycle, O-aralkyl and unoxidized or oxidized S-aryl with the aryl unsubstituted or substituted with at least one member of the group consisting of halogen and alkoxy.

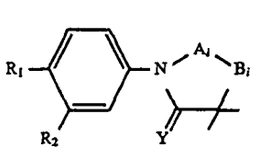
9. A compound of claim 8 wherein R_3 is alkyl of 2 to 4 carbon atoms substituted by a member selected from the group consisting of chlorine, ethoxycarbonyl, tert-butoxy carbonyl, cyclopentyloxycarbonyl, unoxidized or oxidized 4-fluorophenylthio, morpholino, phenylmethoxy, triphenylmethoxy and methylsulfonyloxy.

10. A compound of claim 1 wherein Y is —O— except the compounds wherein the —A—B— group is

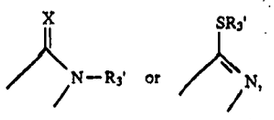


in which is oxygen and, R_2 is halogen or trifluoromethyl and R_1 is nitro or halogen.

11. A compound of the formula



wherein R_1, R_2 and Y have the definitions of claim 1, —A—$_i$ —B_i is



Y is oxygen or sulfur and R'$_3$ is R$_3$ with any reactive functions protected.

12. A compound of claim 1 selected from the group consisting of 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-(4,4-dimethyl-5-oxo-2-thioxo 1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-[4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile, 3-(3,4-dichlorophenyl)-2-thioxo-1,5,5-trimethyl-4-imidazolidinone, 1-(4-nitro-3-(trifluoromethyl)-phenyl-3,4,4-trimethyl-2,5-imidazolidinedione, 4-[[4,5-dihydro 4,4-dimethyl-5-oxo-2-(phenylmethyl)-thio]-1H-imidazol-1-yl]-2-(trifluoromethyl) benzonitrile, 4[4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl]2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile, 3-(4-cyano 3-trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoic acid and 4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile.

13. An anti-androgenic composition comprising an anti-androgenically effective amount of at least one compound of claim 1 and an inert pharmaceutical carrier.

14. A composition of claim 13 wherein the active compound is selected from the group consisting of 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-(4,4-dimethyl-5-oxo-2-thioxo 1-imidazolidinyl)-2-(trifluoromethyl)-benzoitrile, 4-[4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile, 3-(3,4-dichlorophenyl)-2-thioxo-1,5,5-trimethyl-4-imidazolidinone, 1-(4-nitro-3-(trifluoromethyl)-phenyl-3,4,4-trimethyl-2,5-imidazolidinedione, 4-[[4,5-dihydro 4,4-dimethyl-5-oxo-2-(phenylmethyl)-thio]-1H-imidazol-1-yl]-2-(trifluoromethyl) benzonitrile-4[4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl]2-(trifluoromethyl) benzonitrile, -4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile-3-(4-cyano 3-trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile.

15. A method of inducing anti-androgenic activity in warm-blooded animals comprising administering to warm-blooded animals an anti-androgenically effective amount of at least one compound of claim 1.

16. A method of claim 15 wherein Y is oxygen.

17. A method of claim 15 wherein R_1 is —CN or halogen.

18. A method of claim 15 wherein R_1 is chlorine.

19. A method of claim 13 wherein the active compound is selected from the group consisting of 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4(4,4-dimethyl-5-oxo-2-thioxo 1-imidazolidinyl)-2-(trifluoromethyl)-benzoitrile, 4-[4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile, 3-(3,4-dichlorophenyl)-2-thioxo-1,5,5-trimethyl-4-imidazolidinone, 1-(4-nitro-3-(trifluoromethyl)-phenyl-3,4,4-trimethyl-2,5-imidazolidinedione,4-[[4,5-dihydro 4,4-dimethyl-5-oxo-2-(phenylmethyl)-thio]-1H-imidaozl-1-yl]-2-(trifluoromethyl) benzonitrile-4[4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl]2-(trifluoromethyl) benzonitrile, -4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile-3-(4-cyano 3-trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoic and acid and 4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile.

* * * * *

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Annexure VII

US005434176A

United States Patent [19]

Claussner et al.

[11] Patent Number: 5,434,176

[45] Date of Patent: Jul. 18, 1995

[54] PHENYLIMIDAZOLIDINES

[75] Inventors: **André Claussner**, Villemomble; **Francois Goubet**, Paris; **Jean-Georges Teutsch**, Pantin, all of France

[73] Assignee: **Roussel UCLAF**, France

[21] Appl. No.: **68,736**

[22] Filed: **May 28, 1993**

[30] **Foreign Application Priority Data**

Jul. 8, 1992 [FR] France 92 08432

[51] **Int. Cl.**[6] **A61K 31/415**

[52] **U.S. Cl.** **514/391**; 548/301.4

[58] **Field of Search** 548/301.4; 514/391

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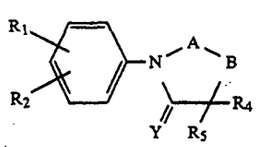
Primary Examiner—Joseph Paul Brust

Attorney, Agent, or Firm—Bierman and Muserlian

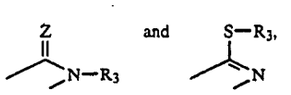
[57] **ABSTRACT**

A compound selected from the group consisting of compounds of the formula



I

wherein R_1 and R_2 are individually selected from the group consisting of —CN, —NO_2, halogen, —CF_3, free carboxy, salified carboxy, and carboxy esterified with lower alkyl; -A-B- is selected from the group consisting of



and X, R_3, R_4 and R_5 are defined as in the specification and their non-toxic, pharmaceutically acceptable acid addition salts having anti-androgenic activity.

8 Claims, No Drawings

PHENYLIMIDAZOLIDINES

STATE OF THE ART

Japanese application No. J 48087030 describes 3-phenyl-2-thiohydantoins useful for inhibiting the germination of certain plants. U.S. Pat. No. 4,907,518 describes imidazolidines different from Formula I having anti-androgenic activity. Other pertinent art includes U.S. Pat. Nos. 3,823,240; 4,873,256; 4,407,814; 4,482,739 and 4,234,736.

OBJECTS OF THE INVENTION

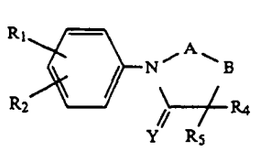
It is an object of the invention to provide novel compounds of Formula I and their non-toxic, pharmaceutically acceptable acid addition salts, novel intermediates, and a novel process for the preparation of the compounds.

It is another object of the invention to provide novel anti-androgenic compositions and a novel method of inducing anti-androgenic activity in warm-blooded animals.

These and other objects and advantages of the invention will become obvious from the following detailed description.

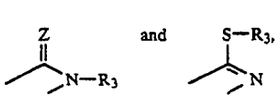
THE INVENTION

The novel phenylimidazolidines of the invention have the Formula

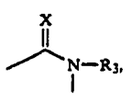


I

wherein R_1 and R_2 are individually selected from the group consisting of —CN, —NO_2, halogen, —CF_3, free carboxy, salified carboxy and carboxy esterified with lower alkyl, -A-B- is selected from the group consisting of



X, is —O— or —S—, R_3 is selected from the group consisting of hydrogen, alkyl, alkenyl and alkynyl all of up to 12 carbon atoms, aryl and aralkyl of up to 12 carbon atoms, all optionally substituted with at least one member of the group consisting of —OH, halogen, —SH, —CN, acyl of up to 7 carbon atoms, acyloxy of up to 7 carbon atoms, —S— aryl of up to 12 carbon atoms optionally substituted with a member of the group consisting of —CF_3, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl and alkynyloxy, with the sulfur being optionally oxidized to sulfone or sulfoxide, free, esterified, amidified or salified carboxy, —NH_2, mono and dialkylamino and heterocyclic of 3 to 6 ring members and containing at least one heteroatom selected from the group consisting of oxygen, sulfur, and nitrogen, the alkyl, alkenyl, and alkynyl being optionally interrupted with at least one member of the group consisting of oxygen, nitrogen, and sulfur optionally oxidized to sulfoxide or sulfone, Y is —O—, —S— or =NH, R_4 and R_5 are individually selected from the group consisting of hydrogen and alkyl of up to 12 carbon atoms optionally substituted with at least one halogen or, taken together with the carbon atom to which they are attached, form cycloalkyl of 3 to 7 carbon atoms except the compounds wherein R_4 and R_5 are both methyl or one is hydroxymethyl, Y is —O— or =NH—, -A-B- is



X is is oxygen, R_3 is hydrogen, R_1 is 4-NO_2 and R_2 is 3—CF_3; and their non-toxic, pharmaceutically acceptable acid addition salts.

The following examples of Alkyl of up to 12 carbon atoms includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, sec.-pentyl, tert.-pentyl, neopentyl, hexyl, isohexyl, sec.-hexyl, tert.-hexyl, heptyl, octyl, decyl, undecyl, and dodecyl, whether branched or linear. Preferred are alkyl of 1 to 4 carbon atoms, especially methyl, ethyl, propyl, isopropyl.

Examples of alkenyl of up to 12 carbon atoms are vinyl, allyl, 1-propenyl, butenyl, pentenyl, hexenyl, preferably alkenyl of 2 to 4 carbon atoms, and especially butenyl or allyl. Examples of alkynyl of up to 12 carbon atoms are ethynyl, propargyl, butynyl, pentynyl and hexynyl, preferably 2 to 4 carbon atoms such as propargyl. Examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Examples of aryl are carbocyclic aryl such as phenyl and naphthyl, heterocyclic aryl of 5 to 6 ring members containing at least one heteroatom selected from the group consisting of oxygen, sulfur, and nitrogen. Examples of 5 membered ring heteroaryls are furyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, thiadiazolyl, pyrazolyl, and isoxazolyl. Examples of 6 membered ring heteroaryl are pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl. Examples of condensed aryls are indolyl, benzofuranyl, benzothienyl and quinoleinyl. The preferred aryl is phenyl.

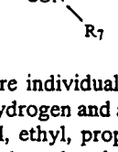
Examples of aralkyl include the alkyls recited above substituted with the aryls cited above. The preferred aralkyls are phenethyl and benzyl. Examples of halogen are fluorine, chlorine, bromine, and iodine, but preferred are fluorine, chlorine, and bromine. Examples of alkyl substituted with at least one halogen are fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, dichloromethyl, dibromomethyl, and trifluoromethyl.

Examples of substituents for aryl and aralkyl are phenyl substituted by fluorine, —OCH_3, or —CF_3 in the p-position. Examples of acyl are preferably those of up to 7 carbon atoms, such as acetyl, propionyl, butyryl, and benzoyl, as well as valeryl, hexanoyl, acryloyl, crotonoyl, carbamoyl, and formyl. The acyloxy may be derived from the same acids, especially acetyloxy and propionyloxy.

The esterified carboxy may be alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert.-butoxycarbonyl, cyclobutyloxy carbonyl, cyclopentyloxy carbonyl and cyclohexyloxy carbonyl.

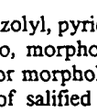
Examples of easily cleavable esters include methoxymethyl, ethoxymethyl, acyloxyalkyl such as pivaloyloxymethyl, pivaloyloxyethyl, acetoxymethyl, and acetoxyethyl; alkoxycarbonyloxyalkyl such as methoxycarbonyloxymethyl, methoxycarbonyloxyethyl, isopropoxycarbonyloxymethyl, and isopropoxycarbonyloxyethyl. Other esters are described in European Patent No. 0,034.536.

The amidified carboxy are of the type



wherein R_6 and R_7 are individually selected from the group consisting of hydrogen and alkyl of 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and tert.butyl.

Examples of mono and dialkylamino are methylamino, ethylamino, dimethylamino, diethylamino, and methylethylamino. The heterocyclic of 5 to 6 ring members optionally containing another heteroatom of



may be pyrrolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidyl, indolyl, piperidino, morpholino, and piperazinyl, preferably piperidino or morpholino.

Examples of salts of salified carboxy are sodium, potassium, lithium, calcium, magnesium, ammonium, and organic bases such as methylamine, propylamine, trimethylamine, diethylamine, and triethylamine. Sodium salts are preferred.

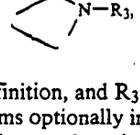
The alkylamino and dialkylamino are preferably alkyl of 1 to 4 carbon atoms such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, and ethylmethylamino. Examples of the heterocyclics containing at least one heteroatom are saturated monocyclics such as oxirannyl, oxolannyl, dioxolannyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, and morpholinyl.

The alkyl, alkenyl, and alkynyl are optionally interrupted by one or more sulfur, oxygen,or nitrogen heteroatoms. Examples are alkoxyalkyl such as methoxymethyl, methoxyethyl, methoxypropyl, and methoxybutyl, as well as alkoxy alkoxyalkyl such as methoxyethoxymethyl.

When the products of Formula I contain a salifiable amino group, the acid addition salts of non-toxic, pharmaceutically acceptable acids may be formed. Examples of said acids are inorganic acids such as nitric acid, hydrochloric acid, sulfuric acid, and phosphoric acid, as well as organic acids such as formic acid, acetic acid, propionic acid, benzoic acid, and methane sulfonic acid.

Among the preferred compounds of Formula I are those wherein Y is oxygen, -A-B- is

and X and R_3 are defined as above; those wherein -A-B- is

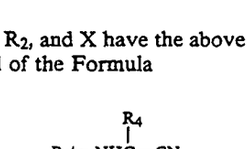


X has the above definition, and R_3 is hydrogen or alkyl of 1 to 6 carbon atoms optionally interrupted by at least one of —O—, —S—, and optionally substituted by —OH, —OH esterified with an acyl of an organic carboxylic acid of 1 to 7 carbon atoms, or free, esterified, or salified carboxy, are also worthy of special mention.

Among the preferred compounds of Formula I are those wherein R_3 is hydrogen or alkyl of 1 to 6, preferably 1 to 4, carbon atoms optionally substituted with —OH; those wherein R_2 is 3—CF_3 and R_1 is 4-CN; those wherein R_4 and R_5 are individually hydrogen, ethyl, or —CF_3; and those wherein R_4 and R_5 together with the carbon atoms form cyclobutyl or cyclopentyl.

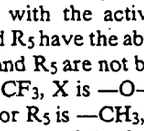
Specific preferred compounds of Formula I are 4-(3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-[1-methyl-4-oxo-2-thioxo-1,3-diazaspiro (4,4)-nonan-3-yl]-2(tri-fluoromethyl)-benzonitrile, and 4-(4,4-diethyl-3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile.

The inventive process for the preparation of a compound of Formula I comprises reacting the compound of the Formula



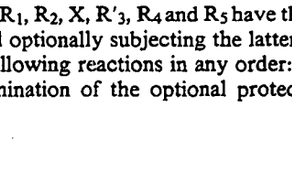
II

wherein R_1, R_2, and X have the above definitions, with a compound of the Formula



III

in the presence of a tertiary base, wherein R'_3 has the definition of R_3 with the active functions optionally protected, R_4 and R_5 have the above definitions with the proviso that R_4 and R_5 are not both methyl and, if R_1 is 4-NO_2, R_2 is 3—CF_3, X is —O—, and R'_3 is hydrogen; and if one of R_1 or R_5 is —CH_3, the other is —CH_2OH to obtain a compound of the formula



IV

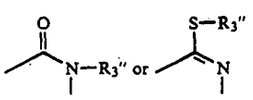
wherein R_1, R_2, X, R'_3, R_4 and R_5 have the above definitions and optionally subjecting the latter to at least one of the following reactions in any order:

a) elimination of the optional protective groups of R'_3;

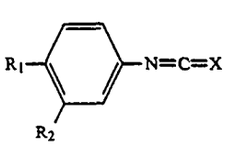
b) hydrolysis of C=NH to a ketone function and if appropriate of >C=S to >C=O;

c) transformation of >C=O to >C=S, and

d) reaction of the products of Formula IV wherein R'3 is hydrogen after hydrolysis of >C=NH to a ketone, with a compound of the formula R"3-Hal, wherein Hal is halogen and R"3 is R'3 except hydrogen to obtain a compound of Formula I wherein -A-B- is

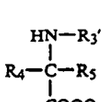


in which R"3 has the above meaning; then if desired, the reaction of these products with an elimination agent for the optional protective groups that can be carried by R"3 or, if appropriate, the reaction with an esterification, amidification, or salification agent, or reacting a compound of the Formula



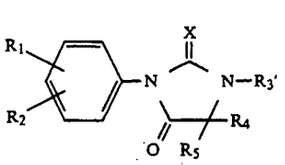
II

wherein R_1, R_2 and X have the above definitions, in the presence of a tertiary base, with a compound of the formula



III'

wherein R'3, R_4 and R_5 have the above definitions and Q is an alkali metal such as sodium or alkyl of 1 to 6 carbon atoms, to obtain a compound of the formula



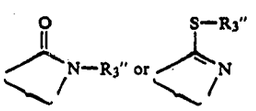
IVa

wherein R_1, R_2, X, R'3, R_4 and R_5 have the above definitions and optionally subjecting compound IVa to any one or more of the following reactions in any order:

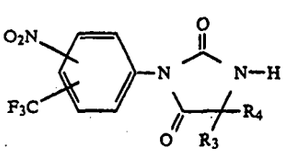
a) elimination of the optional protective groups that can be carried by R'3;

b) conversion of the >C=O group or groups into >C=S or, if appropriate conversion of >C=S into >C=O;

c) reaction of the products of Formula IVa, in which R'3 is hydrogen, with a reagent of formula Hal-R"3, wherein R"3 is the same as R'3 with the exception of hydrogen and Hal is halogen, to obtain the products of Formula I in which -A-B-is

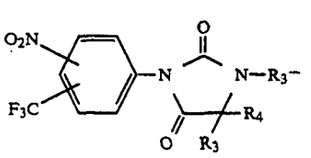


and optionally reaction of the latter to eliminate the protective group of R"3, or reaction of the same with an esterification, salification or amidification agent, or reaction of a compound of the formula R"3-Hal as defined above with a compound of the formula



IV'

to obtain a compound of the formula



IV"

and optionally subjecting the latter to at least one of the following reactions:

a) elimination of optional protective groups of R"3 and then reaction with an esterification, salification or amidification agent; and

b) transformation of >C=O to >C=S.

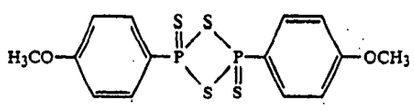
The reaction of the products of Formula II with the products; of Formula III is preferably effected in an organic solvent such as tetrahydrofuran, dichloroethane, ethyl ether, or isopropyl ether in the presence of a tertiary base such as triethylamine, pyridine, methylethyl pyridine.

The optional reactive functional groups of R_3 which are optionally protected in compounds of Formula III, IVa, or IV" are —OH or amino which are protected by the usual protective groups. Examples of such protective groups for —NH2 are tert.-butyl, tert.-amyl, trichloroacetyl, chloroacetyl, benzhydryl, trityl, formyl and benzyloxycarbonyl. Examples of hydroxy protective groups are formyl, chloroacetyl, tetrahydropyranyl, trimethylsilyl, and tert.butyldimethylsilyl.

The above list of protective groups is not intended to be exhaustive and any protective group known, for example, in peptide chemistry may be used. Other known protective groups are described in French Patent 2,499,995 which is incorporated herein by reference. The optional reactions to eliminate groups are indicated in the said patent and the preferred method of elimination is acid hydrolysis with hydrochloric acid, benzene sulfonic acid, p-toluene sulfonic acid, formic acid, or trifluoroacetic acid, preferably hydrochloric acid.

The optional hydrolysis of >C=NH to >C=O is preferably effected by reaction with refluxing aqueous hydrochloric acid. When the hydrolysis of >C=NH to >C=O is effected with a molecule also containing >C=S, the latter may be transformed into a >C=O group. The free hydroxy optionally contained in R3 may also be transformed into —SH.

The transformation of >C=O into >C=S is effected with a Lawesson reagent of the formula



which is commercial product sold, for example, by Fluka and is described in Bull. Soc. Chim. Belg., Vol. 87 No. 3 (1987), p. 229. When two >C=O groups are changed to >C=S, the reaction is effected with an excess of the Lawesson reagent. The same is also used when the molecule contains both >C=O to >C=S.

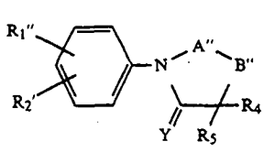
On the other hand, when part of the molecule contains two >C=O's, and it is desired to obtain a product with only one >C=S, a deficiency of the Lawesson reagent is used to obtain a mixture of 3 products, each of two products with a >C=O and >C=S and one containing two >C=S's. These products can be separated by known methods such as chromatography.

The reaction of the compounds of Formulas IV, IVA, or IV' with a compound of the formula R''_3-Hal is effected in the presence of a strong base such as sodium hydride or potassium hydride in a phase transfer reaction in the presence of quaternary ammonium salts such as tert.-butyl ammonium The protective groups of R''_3 may be those discussed above for R_3. The reaction to eliminate the protective groups are as discussed above. For example, a tert-butyl dimethylsilyl group may be removed by hydrochloric acid as described in the examples herein.

The optional esterification of the compounds of Formula I wherein R''_3 is free —OH is effected under classical conditions using, for example, an acid or a functional derivative thereof such as its anhydride, e.g. acetic acid anhydride, in the presence of a base such as pyridine. The optional esterification or salification of the compounds of Formula I wherein R''_3 is —COOH may be effected by known methods.

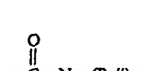
The optional amidification of the compounds of Formula I wherein R''_3 is —COOH is also effected under classical conditions with primary or secondary amines with functional derivatives of —COOH, such as a symmetrical or mixed anhydride thereof.

The process of the invention to prepare compounds of the Formula

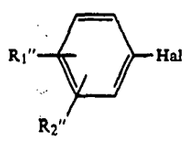


I''

wherein R''_1, R''_2, and -A''-B''- have the definitions of R_1 and R_2, and -A-B-, except that, when -A''-B''- is

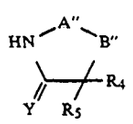


and R''_3 is hydrogen or alkyl of 1 to 7 carbon atoms and Y is oxygen R''_1 is —CN, comprises reacting a compound of the Formula



V

wherein R''_1 and R''_2 have the above definitions and Hal is halogen with a compound of the formula



VI

wherein -A''-B''-, R_4, and Y have the above definitions, in the presence of a catalyst and optionally a solvent. In the compounds of formula V, the halogen is preferably chlorine but may be iodine or bromine.

The role of the catalyst is obviously to trap the hydrogen halide as it forms and to facilitate the condensation reaction of the compounds of Formulas V and VI to form the desired product. The catalyst is preferably a metal in its native form, its oxide, its salt, or it may be a base. When the catalyst is metal, it is preferably copper or nickel and the metallic salts are preferably the chloride or acetate. When the catalyst is a base, it is preferably sodium hydroxide or potassium hydroxide and dimethylsulfoxide may be added to the reaction medium.

The catalyst of the process may be selected from cuprous oxide, cupric oxide, metallic copper, or a base such as sodium hydroxide or potassium hydroxide, preferably cuprous oxide in powdered form. The solvent used preferably is a high boiling point ether such as phenyl oxide, diglyme, triglyme, or dimethylsulfoxide; also useful are high boiling point oils such as paraffin or petroleum jelly. Preferably, the process is effected in an ether solvent such as phenyl oxide, diglyme, triglyme or dimethylsulfoxide, most preferably in phenyl oxide or triglyme.

The process may be effected at atmospheric pressure or under pressure at temperatures above 100° C., preferably above 150° C., for more than two hours. The reaction is preferably effected with cuprous oxide in triglyme at temperatures of 200° C. or higher for more than three hours.

The novel anti-androgenic compositions of the invention are comprised of an anti-androgenically effective amount of at least one compound of Formula I or its non-toxic, pharmaceutically acceptable acid addition salts and an inert pharmaceutical carrier. The compositions may be in the form of tablets, dragees, capsules, syrups, suppositories, creams, pomades, lotions, or injectable solutions prepared in the usual manner.

Examples of suitable excipients are aqueous or nonaqueous vehicles, gum arabic, lactose, starch, magnesium stearate, cocoa butter, fatty bodies of animal of vegetable origin, paraffinic derivatives, glycols, wetting agents, dispersants, emulsifiers, and preservatives.

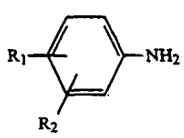
The compositions inhibit the effect of androgens on peripherical receptors and have an anti-androgenic activity useful for therapy in adults without the certain effects of a chemical castration. The compositions are useful for the treatment of adenoma and neoplasia of the prostate as well as benign hypertrophia of the prostrate, they are also useful for the treatment of benign or malig-

nant tumors of cells containing androgen receptors. They are particularly useful for the treatment of breast, brain, skin and ovarian cancer and bladder, lymphatic system, liver, and kidney cancers. They are equally useful for the treatment of hirsutism, acne, seborrhea, androgenic alopecia, hyperpilosity, and in the veterinary field.

The compositions of the invention are useful in dermatology and can contain another ingredient such as an antibiotic, e.g. derivatives of azelaic acid, fusidic acid, erythromycin or with a derivative of retinoids for the treatment of acne. They can also be used with a 5α-reductase inhibitor such as (5α, 17β)-1,1-dimethylethyl 3-oxo 4-azaΔ^1-androstene-17 carboxamide (or Finasteride Merck, 11th ed.) or with azelaic acid or a blocking agent of androgen receptors for the treatment of acne, alopecia or hirsutism. In addition, they can be used with a product stimulating the growth of hair such as Minoxidil for the treatment of alopecia. The compositions can also be used in the veterinary domain and in the form of radioactive products, as well as in diagnostics as specific labels for the androgen receptors. As radioactive products they can be labeled with tritium, carbon 14, and/or iodine 125.

The novel method of the invention for inducing anti-androgenic activity in warm-blooded animals, including humans, comprises administering to the warm-blooded animals an anti-androgenically effective amount of at least one compound of Formula I and its non-toxic, pharmaceutically acceptable acid addition salts. The compounds may be administered parenterally, buccally, perlingually, rectally, or topically and the usual daily dose is 0.13 to 6.66 mg/kg depends on the condition treated, the specific compound, and the method of administration.

The starting compounds of Formula II may be prepared by reacting phosgene, when X is oxygen, or thiophosgene, when X is sulfur, with an amine of the formula



A

A product of this type is described in French Patent No. 2,329,276. The amines of formula A are described in EP Patent No. 0,002,892 and French Patent No. 2,142,804.

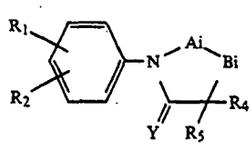
The products of Formula III or III' are known or can be prepared from the corresponding cyanhydrins by the process described in J. Am. Chem. Soc., Vol. 75 (1953), p. 4841, or Beil. I, 4 526, or J. Org. Chem., Vol. 27 (1962), p. 2901. The compounds of Formula III wherein R'$_3$ is other than hydrogen may be obtained by reacting a compound of the formula R"$_3$ Hal with 2-cyano-2-aminopropane under the conditions described above for reacting the said halide with the compounds of Formula IV. An example is described by Jilek et al, Collect. Czech. Chem. Comm., Vol. 54(8) 1989), p. 2248. The products of Formula IV' are described in French Patent No. 2,329,276.

The compounds of formulae V and VI are commercially available known compounds and can be prepared by known methods.

The preparation of the compounds of Formula VI are described in the following publications: Zhur Preklad Khim., Vol. 28 (1955), p. 969-75 (CA, Vol. 50 (1956), p. 4881 a); Tetrahedron, Vol. 43 (1987), p. 1753; J. Org. Chem., Vol. 52 (1987), p. 2407; Zh. Org. Khim., Vol. 21 (1985), p.2006; J. Fluor. Chem., Vol. 17 (1981), p. 345; German Patent 637,318, European Patent 0,130,875, and Japanese Patent No. 81-121,524.

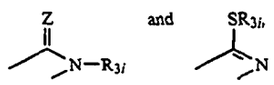
The products of Formula VI which are derivatives of hydantoin are largely used and are known in the literature such as J. Pharm. Pharmacal., 67, Vol. 19(4) (1967), p. 209-16; J. Chem. Soc., Vol. 74(2) (1972), p. 219-221; Khim. Farm. Zh., Vol 67(1)(5), p. 51-2; German Patent 2,217,914; European Patent 0,091,596 and J. Chem. Soc. Perkin. Trans. 1, Vol. 74(2), p. 48 and 219-221.

The novel intermediates of the invention are the compounds of the formula



IVi

wherein R_1, R2 and Y have the above definitions and -Ai-Bi- is



and

wherein X is oxygen or sulfur and R_{3i} is R_3 with the reactive groups, among which are —OH and —NH_2, protected as above for R_3.

In the following examples, there are described several preferred embodiments to illustrate the invention. However, it should be understood that the invention is not intended to be limited to the specific embodiments.

EXAMPLES

Example 1

4-(3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

a. A solution of 22 ml of distilled water and 1 ml of thilphosgene were slowly added to 2.23 g of 2-trifluoromethyl-4-amino-benzonitrile (prepared as in EP 000 2892) and the mixture was stirred for 1 hour and then extracted chloroform. The organic phase was washed with aqueous sodium chloride, dried, and evaporated to dryness under reduced pressure to obtain 3 grams of the desired product which was used as is.

b. A solution of 976 mg of N-methylglycyne in 3.65 ml of 3 mol sodium hydroxide solution was added to 2.5 grams of the thioisocyanate of Step a) in solution in 5 ml of ethanol. The mixture was stirred for 30 minutes at room temperature and then refluxed for 1 hour. After returning to room temperature, the mixture was poured into a mixture of 20 ml of water and 10 ml of N-hydrochloric acid and extracted with chloroform. After chromatography over silica (elution with methylene chloride-acetone (95-5)), there was obtain 1.78 grams of product which was crystallized from a mixture of methylene chloride and cyclohexane to obtain 1.66 g of the desired product melting at 220° to 221° C. and having an Rf=0.18 (cyclohexane-ethyl acetate 1—1).

IR Spectrum $CHCl_3$:

C=O	1788–1729 cm^{-1}
C=N	2235 cm^{-1}
conjugated system + Aromatics	1614–1580–1515 cm^{-1}

UV Spectrum (EtOH):

Max.	232 nm	ϵ = 17,300
Max.	254 nm	ϵ = 22,700

Example 2

4-[1-methyl-4-imino-2-thioxo-1,3-diazaspiro(4,4)nonan-3-yl]-2-trifluoromethyl-benzonitrile

A solution of 1.36 g of 1-methylamino-cyclopentane carbonitrile in 10 ml of tetrahydrofuran were added over about 2 minutes to 2.5 g of the isocyanate of step a of Example 1 and the mixture was stirred for 40 minutes. The solvent was evaporated and the residue was chromatographed over silica (elution with methylene chloride-ethyl acetate (87.5–12.5)) to obtain 3.32 g of the expected product melting at 165°–166° C. and having an Rf=0.3 (methylene chloride-ethyl-acetate (85–15)).

IR Spectrum $CHCl_3$:

=NH	3310–1672 cm^{-1}
C=N	2230 cm^{-1}
Aromatics	1614–1577–1505 cm^{-1}

Preparation of 1-methylamino-cyclopentane-carbonitrile:

A solution of 6.5 of potassium cyanide in 13 ml of water was added at 15°–20° C. to a solution of 8.5 g of cyclopentanone and 7 g of methylamine hydrochloride in 7.5 ml of water and returned to room temperature; the mixture was stirred for 18 hours and extracted with methylene chloride. The organic phase was washed with aqueous sodium chloride, dried, and evaporated to dryness, and the residue was distilled to obtain 4.1 g of the expected product with a boiling point of 60° C.±0.3° C. at 7 mm of Hg.

Example 3

4-(1-methyl-4-oxo-2-thioxo-1,3-diazaspiro(4,4)nonan-3-yl)-2-trifluoromethyl-benzonitrile

52 ml of methanol were added to a solution of 5.2 ml of chloroform and to 259 mg of the product of Example 2 and then 7.5 ml of 2N-hydrochloric acid were added thereto. The mixture was refluxed for 1 hour and, after cooling to room temperature, was poured into 150 ml of iced water. The mixture was extracted with chloroform and the organic phase was washed aqueous sodium chloride dried and evaporated to dryness. The residue was chromatographed over silica, eluting with ethyl acetate-cyclohexane(3–7) to obtain the fractions with Rf equal to 0.35. After crystallization, from a mixture of methylene chloride and cyclohexane, 247 mg of the desired product, melting at 162° C.–163° C. and with an Rf=0.35 (cyclohexane-ethyl acetate (7–3)) were obtained.

IR Spectrum $CHCl_3$:

C=O	1765 cm^{-1}
CN	2235 cm^{-1}
Aromatics	1609–1578–1505 cm^{-1}

UV Spectrum (EtOH):

Max.	234 nm	ϵ = 17,600
Max.	256 nm	ϵ = 23,800
Inf.	266 nm	ϵ = 20,300

Example 4

4-(4,4-diethyl-3-methyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 2, 2.5 g of the isothiocyanate of Step a) of Example 1 and 1.39 g of the appropriate amino nitrile were reacted to obtain 3.22 g of the expected product melting at 167° C.–168 ° C. and having an Rf=0.27 (methylene chloride-ethyl acetate (85–15)) .

IR Spectrum $CHCl_3$:

=NH	1304–1673 cm^{-1}
C=N	2230 cm^{-1}
Aromatics	1614–1576–1505 cm^{-1}

Preparation of 1-methyl amino-diethyl-carbonitrile

Using the procedure of Example 2, 8.6 g of diethyl ketone were reacted to obtain 4.8 g of the expected product with a boiling point of 77° C. at 40 mm of Hg.

Example 5

4-(4,4-diethyl-3-methyl-5-oxo-2-thioxo-1imidazolidinyl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 3, 321 mg of the product of Example 4 and 65 ml of methanol and 14 ml of 2 N-hydrochloride acid were reacted to obtain 249 mg of the expected product melting at 126° C.–127° C. and having an Rf=0.45 (cyclohexane-ethyl acetate (4–6)).

IR Spectrum $CHCl_3$:

C=O	1753 cm^{-1}
C=N	2235 cm^{-1}
Aromatics	1615–1580–1504 cm^{-1}

UV Spectrum (EtOH):

Max.	234 nm	ϵ = 17,800
Max,	254 nm	ϵ = 24,100
Inf.	265 nm	

Example 6

4-(5-methyl-8-imino-6-thioxo(5,7-diazaspiro(3,4))-octan-7-yl-2-trifluoromethyl-benzonitrile

A solution of 221 mg of 1-methyl amino-cyclobutanecarbonitrile in 1 mg of 1,2-dichloroethane was added over 3 minutes to a solution of 456 mg of the isothiocyanate of Example 1 Step a) in 2 ml of 1,2-dichloroethane in the presence of 0.2 ml of triethylamine and, after stirring the mixture for 45 minutes, the solution was evaporated. The residue was chromatographed over silica and diluted with a methylene chlo-

435

ride-acetate (95–5) mixture to recover the fraction with an Rf=0.32. After crystallization from ether 610 mg of the expected product melting at 172° C.–173° C. was obtained.

IR Spectrum $CHCl_3$:

C=NH	3015–1673 cm^{-1}
C≡N	2236 cm^{-1}
aromatics	1615–1580–1505 cm^{-1}

Using the procedure of Example 2, 7 g of cyclobutanone were reacted to obtain 10.6 g of 1-methylamino-cyclobutane-carbonitrile.

Example 7

4-(5-methyl-8-oxo-6-thioxo(5,7-diazaspiro(3,4))-octan-7-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 3, 514 mg of the product of Example 6 and 1.5 ml of 2N-hydrochloric acid were reacted to obtain, after chromatography over silica (cyclohexane-ethyl acetate (6–4)) to obtain a fraction with an Rf=0.34. Crystallization from ether yielded 499 mg of the expected product melting at 161° C.–162° C.

IR Spectrum $CHCl_3$:

C=O	1754 cm^{-1}
C≡N	2236 cm^{-1}
aromatics	1615–1583–1504 cm^{-1}

UV Spectrum (EtOH):

Inf.	239 nm	ε = 17,400
	257 nm	ε = 21,200
	268 nm	ε = 19,000

Example 8

4-(1-methyl-4-imino-2-oxo-1,3-diazaspiro (4,4))-nonan-3-yl)-2-trifluoromethyl-benzonitrile

1.5 ml of a solution of the isocyanate of 3-trifluoromethyl-4-benzonitrile of Example 1 starting from phosgene and 2-trifluoromethyl-4-benzonitrile (1.6M/l) in 1,2 dichloroethane were added at −3° C. to a solution 300 mg of 1-methylamino-cyclopentanecarbonitrile in 3 ml of 1,2 dichloroethane in the presence of 0.5 ml of triethylamine; after stirring for 40 minutes, the solution was evaporated to dryness. The residue was chromatographed over silica and diluted with a methylene chloride-ethyl acetate (95–5) mixture to obtain 620 mg of the expected product.

Example 9

4-(1-methyl-2,4-dioxo-1,3-diazaspiro(4,4))-nonan-3-yl)-2-trifluoromethyl-benzonitrile

A mixture of 535 mg of the product of Example 8 in 10 ml of methanol and 2 ml of 2N-hydrochloric acid was heated at 50° C. with stirring for 1 hour and, after returning to the room temperature, 20 ml of water were added thereto. The mixture was extracted with methylene chloride and the organic phase was evaporated to dryness under the reduced pressure. The residue was dissolved in acetone and chromatographed over silica (methylene chloride-acetone (98–2)) to obtain 325 mg of the expected product.

IR Spectrum $CHCl_3$:

C=O	1777(m), 1724 cm^{-1}(F)
C≡N	2238 cm^{-1}
Aromatics	1616–1576–1505 cm^{-1}

UV Spectrum (EtOH):

Inf.	236 nm	ε = 10,000
Max.	262 nm	ε = 13,900
Inf.	277 nm	ε = 7,200
Inf.	286 nm	ε = 3,700

Example 10

4-(5-methyl-8-imino-6-oxo-5,7-diazaspiro(3,4))-octan-7-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 8, 2 ml of a solution of isocyanate and 352 mg of 1-methylamino-cyclobutane-carbonitrile were reacted to obtain, after chromatography over silica (eluant methylene-chloride ethyl acetate (85–15)), the product with Rf=0.20 and finally to obtain 301 mg of the expected product melting at 144° C.–145° C.

IR Spectrum $CHCl_3$:

OH/NH	3295 cm^{-1}
C≡N	2240 cm^{-1}
C=O	1740 cm^{-1}
C=N	1664 cm^{-1}
aromatics	1611–1572–1508 cm^{-1}

Example 11

4-(6,8-dioxo-5-methyl-5,7-diazaspiro(3,4))-octan-7-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 9, 0.8 g of the product of Example 10 and 3 ml of 2N-hydrochloric acid were reacted and chloroform was used as the extraction solvent. After chromatography over silica (methylene chloride-ethyl acetate (95–5)), there were obtained 465 mg of the expected product melting at 165° C.–166° C.

IR Spectrum $CHCl_3$:

C≡N	2236 cm^{-1}
C=O	1778, 1726 cm^{-1}
Aromatics	1616–1579–1505 cm^{1}

UV Spectrum (EtOH):

Max.	238 nm	ε = 11,000
Max.	262 nm	ε = 14,000
Inf.	278–286 nm	

Example 12

4-(4-imino-2-oxo-1,3-diazaspiro(4,4))-nonan-3-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 8, 3.1 ml of 1.6M solution of isocyanate and 550 mg of 1-imino-cyclopentane-carbonitrile were reacted to obtain, after chromatography on silica (methylene chloride-acetone (90–10)), 1.24 g of the expected product melting at 212° C.–213° C.

IR Spectrum $CHCl_3$:

OH/NH	3350, 3290 cm^{-1}
C≡N	2240 cm^{-1}
C=O	1744 cm^{-1}
C=N	1678 cm^{-1}
Aromatics	1610–1574–1510 cm^{-1}

Preparation of 1-amino-cyclopentane-carbonitrile

8.8 ml of cyclopentane were added dropwise at 0° to 8° C. to a mixture of 7.9 g of ammonium chloride, 6.14 g of sodium cyanide and 40 ml of ammonium hydroxide and, after returning to room temperature, the mixture was stirred for 16 hours and extracted with methylene chloride. The organic phase was washed with aqueous sodium chloride, dried, and evaporated to dryness at a temperature less than 30° C. The residue was distilled to obtain 11 g of the expected product with a boiling point of 55° C.±2° at 11 mg of Hg.

Example 13

4-(2,4-thioxo-1,3-diazaspiro(4,4))-nonan-3-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 9, 1.17 g of the product of Example 12 and 5 ml of 2 N-hydrochloric acid were reacted to obtain, after chromatography on silica (methylene chloride-acetone (9–1)), 1.108 g of the expected product with a melting point of 184° C.–185° C. and having an Rf=0.23.

IR Spectrum $CHCl_3$:

=C–NH	3444 cm^{-1}
C≡N	2296 cm^{-1}
C=O	1786, 1731 cm^{-1}
Aromatics	1616–1505 cm^{-1}

UV Spectrum (EtOH):

Max.	258 nm	ε = 15,600
Max.	286 nm	ε = 3,500

Example 14

4-(8-imino-6-oxo-5,7-diazaspiro(3,4))-octan-7-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 8, 3.1 ml of an isocyanate solution and 480 mg of 1-amino-cyclobutane-carbonitrile were reacted to obtain 990 mg of the expected product melting at 192° C.–193° C. and having an Rf=0.25.

IR Spectrum $CHCl_3$:

OH/NH	3380, 3315 cm^{-1}
C≡N	2240 cm^{-1}
C=N	1754 cm^{-1}
Aromatics	1612–1571–1510 cm^{-1}

Using the procedure of Example 12, 7.4 ml of cyclobutanone were reacted to obtain 9.2 g of 1-amino-cyclobutane-carbonitrile.

Example 15

4-(6,8-dioxo-5,7-diazaspiro(3,4))-octan-7-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 9, a solution of 327 ml of the product of Example 14 in 1.5 ml of chloroform and 1.9 ml of 2N-hydrochloric acid were reacted to obtain, after chromatography on silica (methylene chloride-acetone (9–1)), 341 mg of the expected product melting at 210° C.–211° C. and having an Rf=0.32.

IR Spectrum $CHCl_3$:

OH/NH	3390 cm^{-1}
C≡N	2240 cm^{-1}
C=N	1787, 1737 cm^{-1}
Aromatics	1612–1577–1508 cm^{-1}

UV Spectrum (EtOH):

Max.	259 nm	ε = 15,700
Inf.	277, 286, 301 nm	

Example 16

4-[1-(4-hydroxybutyl(2,4-dioxo-1,3-diazaspiro(4,4))-nonan-3-yl]-2-trifluoromethyl-benzonitrile

A solution of 808 mg of the product of Example 13, in 7 ml of dimethylformamide were added dropwise over 35 minutes to 142 mg of sodium hydride and, 10 minutes after the evolution of hydrogen disengagement, 650 mg of 4-chloro-tert.-butyldimethylsilyl ether and 408 mg of sodium iodide were added. The mixture was heated at 70° C. for 3 hours and, after returning to room temperature, 71 mg of sodium hydride were added. The mixture was stirred for 10 minutes and 330 mg of the silyl were reacted and 222 mg of sodium iodide were added thereto. The mixture was heated for 45 minutes at 70° C. and, after cooling to room temperature, 60 ml of water containing about 500 mg of monopotassium phosphate were added thereto. The mixture was extracted with ethyl ether and then with ethyl acetate and the combined organic phases were dried and evaporated to dryness under reduced pressure. The residue was chromatographed over silica (methylene chloride-acetone (98–2)) to obtain 560 mg of the silyl intermediate. 550 mg of the silylated intermediate were added to 6 mg of methanol and 1.5 ml of 2N hydrochloric acid, and the mixture was stirred for 30 minutes. 30 ml of water was added and the mixture was extracted with methylene chloride. The organic phase was dried and evaporated to dryness and the residue was chromatographed over silica (methylene chloride-acetone (9–1)) and then crystallized from isopropylether to obtain 381 mg of the expected product melting at 125°–126° C. and having an Rf=0.17.

IR Spectrum $CHCl_3$:

OH	3625 cm^{-1}
C≡N	2235 cm^{-1}
C=N	1773, 1721 cm^{-1}
Aromatics	1615–1580–1505 cm^{-1}

UV Spectrum (EtOH):

Max.	239 nm	ε = 9,800
Max.	262 nm	ε = 14,600
Inf.	286 nm	

Example 17

4-[5-(4-hydroxybutyl(-6,8-dioxo-5,7-diazaspiro(3,4))-octan-7-yl]-2-trifluoromethyl-benzonitrile

Using the procedure of Example 16, the product of Example 15 was reacted to obtain the expected product melting at 92° C.–93° C.

IR Spectrum $CHCl_3$:

OH	3626 cm^{-1}
C≡N	2235 cm^{-1}
C=O	1775(m), 1784 cm^{-1}(F)
aromatics	1616–1578–1505 cm^{-1}

UV Spectrum (EtOH):

Max.	238 nm	ε = 11,200
Max.	262 nm	ε = 13,900
Inf.	288 nm	

Using the procedure of the above Examples, the appropriate isocyanate or thioisocyanate and 3,3,3-trifluoromethyl- 2-trifluoromethyl-2-methylamino-propionitrile prepared according to J. Org. Chem., Vol. 35, p. 1485 (1970) were reacted to obtain the following compounds.

Example 18

4-(4,4-bis,trifluoromethyl-3-methyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

Example 19

4-(4,4-bis,trifluoromethyl-3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

Example 20

4-(4,4-bis,trifluoromethyl-3-methyl-5-imino-2-oxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

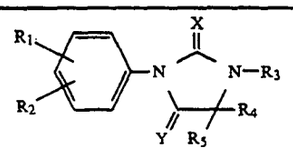
Example 21

4-(4,4-bis,trifluoromethyl-3-methyl-2,5-dioxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

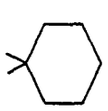
Example 22

Tablets were prepared by combining 100 ml of the product of Example 3, with sufficient excipient comprising lactose amido talc and magnesium stearate to form a final tablet weight of 300 mg.

In addition to the above products, other compounds falling within the scope of the invention are those having the following formula wherein R_1, R_2, R_3 R_4, R_5 and X are as indicated in the following table.



R_1	R_2	X	Y	R_4	R_5
C≡N	CF_3	S	O		
"	"	O	"	"	
"	"	S	"		



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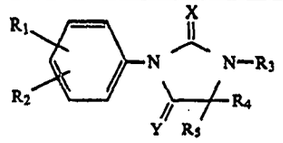


R_1	R_2	X	Y	R_4	R_5
"	"	O	"	"	

PHARMACOLOGICAL DATA

1) Study of androgenic Receptors

Male rats of the Sprague Dawley EOPS strain weighing 180 to 200 g, castrated 24 hours previously, were killed and the prostate was removed, weighed and homogenized at 0° C. with a potter glass in a buffered solution (Tris 10 mM, saccharose 0.25M, PMSF (phenyl methane sulfonyl fluoride) 0.1 mM, sodium molybdate 20 mM, HCl pH 7.4 into which was added extemporaneously 2 m of DTT (DL dithiothreitol) at a rate of 1 g of tissue per 8 ml of buffer solution. The homogenate was then ultracentrifuged at 0° C. for 30 minutes at 209,000 g and the aliquots of supernatant (=cytosol) were incubated for 30 minutes and 24 hours with a concentration (T) of tritiated testosterone and in the presence of increasing concentrations (0 to 2500×10^{-9}M) of cold testosterone or the test products. The concentration of bound tritiated testosterone (B) was then measured for each incubate by adsorption method of carbondextran. The relative affinity of bonding (RBA) was calculated.

The following two curves were graphed: the percentage of the bound tritiated hormone B/T as a logarithmic function of the concentration of the cold hormone and B/T as a logarithmic function of the concentration of the tested cold product. The line of the equation

$$I_{50} = \frac{(B/T\max + B/T\min)}{2}$$

was determined.

B/T max=% of the bound tritiated hormone for an incubation of this tritiated hormone at concentration (T).

B/T min=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T) in the presence of a large excess of cold hormone ($2,500\times10^{-9}$M).

The intersection of the straight line I_{50} and the curves permit an evaluation of the concentrations of the cold reference hormones (CH) and the cold test product (CX) which inhibit by 50% the bonding of the tritiated hormone on the receptor. The RBA of the test product was determined by the equation

$$RBA = 100(CH)/(CX)$$

and the following results expressed in RBA were obtained with testosterone=100.

Products of example	Incubation 24 H
3	27

-continued

Products of example	Incubation 24 H
5	8

2) Determination of the androgen or anti-androgen activity by the dosage of ornithine carboxylase

Six week old male Swiss mice castrated 24 hours received oral dose of the test products as a 0.5% suspension in methyl cellulose or in ethanol by oral or percutaneous route simultaneously with a sub-cutaneous injection of 3 mg/kg of testosterone propionate in solution in corn oil to determine the anti-androgen activity. Active agonists were determined in the absence of testosterone propionate. The test compounds as well as testosterone were administered in a volume of 10 ml/kg. 20 hours after the treatments , the animals were killed, the kidneys were removed and then homogenized at 0° C. with a teflon-glass grinding apparatus in 10 volumes of buffer Tris-HCl 50 mM at a pH 7.4 containing 250 μM of pyridoxal phosphate, 0.1 mM EDTA and 5 mM of dithiothreitol. The homogenate was centrifuged at 209,000 g for 30 minutes.

At 37° C., renal ornithine decarboxylase transforms an isotopic mixture of cold ornithine and tritiated ornithine in cold putrescine and tritiated putrescine. The putrescine was then collected on selective ion-exchange papers, after drying, excess non-transformed cold and tritiated ornithine were eliminated by washing 3 times with 0.1M ammonium hydroxide. The papers were dried and the radioactivity was determined after addition of an Aqualite sample. The results expressed in fmoles (10^{-15}M) of tritiated putrescine formed per hour/mg of protein are reported in the following table.

Products of Example	% Inhibition of ODL Test A
3	28
5	43

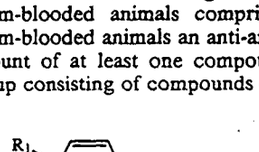
CONCLUSION

The tests show that the tested compounds of the invention possess a strong anti-androgen activity and are devoid of agonist activity.

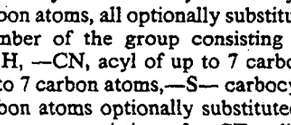
Various modifications of the compounds and method of the invention may be made without departing from the spirit or scope thereof and it is to be understood that the invention is intended to be limited only as defined in the appended claims.

What is claimed is:

1. A method of inducing anti-androgenic activity in warm-blooded animals comprising administering to warm-blooded animals an anti-androgenically effective amount of at least one compound selected from the group consisting of compounds of the formula

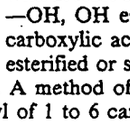


wherein R_1 and R_2 are individually selected from the group consisting of —CN, —NO_2, halogen, —CF_3, free carboxy, salified carboxy and carboxy esterified with lower alkyl; -A-B- is selected from the group consisting of



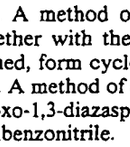
wherein X is=O or =S , R_3 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, carbocyclic aryl and carbocyclic aralkyl each of up to 12 carbon atoms, all optionally substituted with at least one member of the group consisting of —OH, halogen, —SH, —CN, acyl of up to 7 carbon atoms acyloxy of up to 7 carbon atoms,—S— carbocyclic aryl of up to 12 carbon atoms optionally substituted with a member of the group consisting of —CF_3, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, and alkynyloxy, with the sulfur being optionally oxidized to sulfone or sulfoxide, free, esterified, amidified or salified carboxy, —NH_2, mono and dialkylamino, and when the latter alkyl, alkenyl and alkynyl being optionally interrupted with at least one member of the group consisting of oxygen, nitrogen, and sulfur said sulfur being optionally oxidized to sulfoxide or sulfone, Y is =O, =S, or =NH; R_4 and R_5 taken together with the carbon atom to which they are attached, form cycloalkyl of 3 to 7 carbon atoms and their non-toxic, pharmaceutically acceptable acid addition salts.

2. A method of claim 1 wherein Y is —O—, -A-B- is



and X and R_3 are as defined in claim 1.

3. A method of claim 1 wherein -A-B- is



X is as defined is claim 1 and R3 is selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms optionally interrupted with at least one —O— or —S— and optionally substituted with at least one member of the group consisting of —OH, OH esterified with an acyl of an organic carboxylic acid of 1 to 7 carbon atoms, and free, esterified or salified carboxy.

4. A method of claim 1 wherein R_3 is hydrogen or alkyl of 1 to 6 carbon atoms optionally substituted by —OH.

5. A method of claim 1 wherein R_3 is alkyl of 1 to 4 carbon atoms optionally substituted by —OH.

6. A method of claim 1 wherein R_2 is 3—CF_3 and R_1 is 4—CN.

7. A method of claim 1 wherein R_4 and R_5 taken together with the carbon atom to which they are attached, form cyclopentyl or cyclobutyl.

8. A method of claim 1 which is 4-[1-methyl-4-oxo-2-thioxo-1,3-diazaspiro-(4,4)-nonan-3-yl]-2-trifluoromethylbenzonitrile.

* * * * *

Annexure VIII

US005589497A

United States Patent [19]

Claussner et al.

[11] Patent Number: 5,589,497

[45] Date of Patent: Dec. 31, 1996

[54] **PHENYLIMIDAZOLIDINES**

[75] Inventors: **André Claussner**, Villemomble; **François Goubet**, Paris; **Jean-Georges Teutsch**, Pantin, all of France

[73] Assignee: **Roussel Uclaf**, Romainville, France

[21] Appl. No.: **225,230**

[22] Filed: **Apr. 8, 1994**

Related U.S. Application Data

[62] Division of Ser. No. 68,736, May 28, 1993, Pat. No. 5,434,176.

[30] **Foreign Application Priority Data**

Jul. 8, 1992 [FR] France 92 08432

[51] **Int. Cl.**^{6} **C07D 233/74**

[52] **U.S. Cl.** **514/386**; 514/391; 548/319.1; 548/320.1; 548/320.5; 548/321.1

[58] **Field of Search** 548/319.1, 320.1, 548/320.5, 321.1; 514/386, 391

[56] **References Cited**

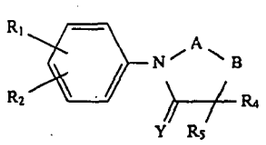
U.S. PATENT DOCUMENTS

4,407,814	10/1983	Bernauer	548/321.1
4,944,791	7/1990	Schroder	71/92
4,958,028	9/1990	Prisbylla	548/321.1
5,166,358	11/1992	Seuron	548/321.1

Primary Examiner—Robert Gerstl
Attorney, Agent, or Firm—Bierman and Muserlian

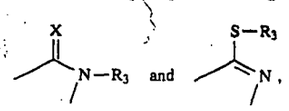
[57] **ABSTRACT**

A compound selected from the group consisting of compounds of the formula

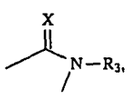


I

wherein R_1 and R_2 are individually selected from the group consisting of —CN, —NO_2, halogen, —CF_3, free carboxy, salified carboxy, and carboxy esterified with lower alkyl; -A-B- is selected from the group consisting of



wherein X is —O— or —S—, R_3 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and aralkyl each of up to 12 carbon atoms, all optionally substituted with at least one member of the group consisting of —OH, halogen, —SH, —CN, acyl and acyloxy of up to 7 carbon atoms, —S-aryl of up to 12 carbon atoms optionally substituted with a member of the group consisting of —CF_3, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl and alkynyloxy, with the sulfur being optionally oxidized to sulfone or sulfoxide, free, esterified, amidified or salified carboxy, =NH_2, mono and dialkylamino, and heterocyclic of 3 to 6 ring members and containing at least one heteroatom selected from the group consisting of oxygen, sulfur and nitrogen; the alkyl, alkenyl and alkynyl being optionally interrupted with at least one member of the group consisting of oxygen, nitrogen, and sulfur optionally oxidized to sulfoxide or sulfone, Y is —O—, —S—, or —NH, R_4 and R_5 are individually selected from the group consisting of hydrogen and alkyl of up to 12 carbon atoms optionally substituted with at least one halogen or, taken together with the carbon atom to which they are attached, form cycloalkyl of 3 to 7 carbon atoms; except the compounds wherein R_4 and R_5 are both methyl or one is hydroxymethyl, Y is —O— or =NH—, -A-B- is



X is oxygen, R_3 is hydrogen, R_1 is 4—NO_2 and R_2 is 3—CF_3; and their non-toxic, pharmaceutically acceptable acid addition salts having anti-androgenic activity.

17 Claims, No Drawings

PHENYLIMIDAZOLIDINES

PRIOR APPLICATION

This application is a divisional of U.S. patent application Ser. No. 08/068,736 filed May 28, 1993 now U.S. Pat. No. 5,434,176.

STATE OF THE ART

Japanese application No. J 48087030 describes 3-phenyl-2-thiohydantoins useful for inhibiting the germination of certain plants. U.S. Pat. No. 4,907,518 describes imidazolidines different from Formula I having anti-androgenic activity. Other pertinent art includes U.S. Pat. No. 3,823,240; No. 4,873,256; No. 4,407,814; No. 4,482,739 and No. 4,234,736.

OBJECTS OF THE INVENTION

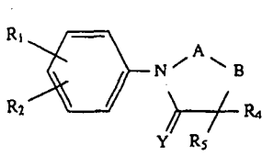
It is an object of the invention to provide novel compounds of Formula I and their non-toxic, pharmaceutically acceptable acid addition salts, novel intermediates, and a novel process for the preparation of the compounds.

It is another object of the invention to provide novel anti-androgenic compositions and a novel method of inducing anti-androgenic activity in warm-blooded animals.

These and other objects and advantages of the invention will become obvious from the following detailed description.

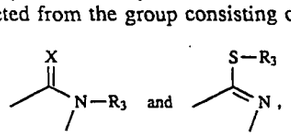
THE INVENTION

The novel phenylimidazolidines of the invention have the Formula



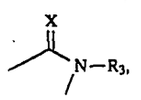
I

wherein R_1 and R_2 are individually selected from the group consisting of —CN, —NO_2, halogen, —CF_3, free carboxy, salified carboxy and carboxy esterified with lower alkyl, -A-B- is selected from the group consisting of



X, is —O— or —S—, R_3 is selected from the group consisting of hydrogen, alkyl, alkenyl and alkynyl all of up to 12 carbon atoms, aryl and aralkyl of up to 12 carbon atoms, all optionally substituted with at least one member of the group consisting of —OH, halogen, —SH, —CN, acyl of up to 7 carbon atoms, acyloxy of up to 7 carbon atoms, —S— aryl of up to 12 carbon atoms optionally substituted with a member of the group consisting of —CF_3, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl and alkynyloxy, with the sulfur being optionally oxidized to sulfone or sulfoxide, free, esterified, amidified or salified carboxy, —NH_2, mono and dialkylamino and heterocyclic of 3 to 6 ring members and containing at least one heteroatom selected from the group consisting of oxygen, sulfur, and nitrogen, the alkyl, alkenyl, and alkynyl being optionally interrupted with at least one member of the group consisting of oxygen, nitrogen, and sulfur optionally oxidized to sulfoxide or sulfone,

Y is —O—, —S— or =NH, R_4 and R_5 are individually selected from the group consisting of hydrogen and alkyl of up to 12 carbon atoms optionally substituted with at least one halogen or, taken together with the carbon atom to which they are attached, form cycloalkyl of 3 to 7 carbon atoms except the compounds wherein R_4 and R_5 are both methyl or one is hydroxymethyl, Y is —O— or =NH—, -A-B- is



X is oxygen, R_3 is hydrogen, R_1 is 4—NO_2 and R_2 is 3—CF_3; and their non-toxic, pharmaceutically acceptable acid addition salts.

The following examples of Alkyl of up to 12 carbon atoms includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, sec.- pentyl, tert.-pentyl, neopentyl, hexyl, isohexyl, sec.-hexyl, tert.-hexyl, heptyl, octyl, decyl, undecyl, and dodecyl, whether branched or linear. Preferred are alkyl of 1 to 4 carbon atoms, especially methyl, ethyl, propyl, isopropyl.

Examples of alkenyl of up to 12 carbon atoms are vinyl, allyl, 1-propenyl, butenyl, pentenyl, hexenyl, preferably alkenyl of 2 to 4 carbon atoms, and especially butenyl or allyl. Examples of alkynyl of up to 12 carbon atoms are ethynyl, propargyl, butynyl, pentynyl and hexynyl, preferably 2 to 4 carbon atoms such as propargyl. Examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Examples of aryl are carbocyclic aryl such as phenyl and naphthyl, heterocyclic aryl of 5 to 6 ring members containing at least one heteroatom selected from the group consisting of oxygen, sulfur, and nitrogen. Examples of 5 membered ring heteroaryls are furyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, thiadiazolyl, pyrazolyl, and isoxazolyl. Examples of 6 membered ring heteroaryl are pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl. Examples of condensed aryls are indolyl, benzofuranyl, benzothienyl and quinoleinyl. The preferred aryl is phenyl.

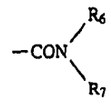
Examples of aralkyl include the alkyls recited above substituted with the aryls cited above. The preferred aralkyls are phenethyl and benzyl. Examples of halogen are fluorine, chlorine, bromine, and iodine, but preferred are fluorine, chlorine, and bromine. Examples of alkyl substituted with at least one halogen are fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, dichloromethyl, dibromomethyl, and trifluoromethyl.

Examples of substituents for aryl and aralkyl are phenyl substituted by fluorine, —OCH_3, or —CF_3 in the p-position. Examples of acyl are preferably those of up to 7 carbon atoms, such as acetyl, propionyl, butyryl, and benzoyl, as well as valeryl, hexanoyl, acryloyl, crotonoyl, carbamoyl, and formyl. The acyloxy may be derived from the same acids, especially acetyloxy and propionyloxy.

The esterified carboxy may be alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert.-butoxycarbonyl, cyclobutyloxy carbonyl, cyclopentyloxy carbonyl and cyclohexyloxy carbonyl.

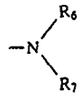
Examples of easily cleavable esters include methoxymethyl, ethoxymethyl, acyloxyalkyl such as pivaloyloxymethyl, pivaloyloxyethyl, acetoxymethyl, and acetoxyethyl; alkoxycarbonyloxyalkyl such as methoxycarbonyloxymethyl, methoxycarbonyloxyethyl, isopropoxycarbonyloxymethyl, and isopropoxycarbonyloxyethyl. Other esters are described in European Patent No. 0.034.536.

The amidified carboxy are of the type



wherein R_6 and R_7 are individually selected from the group consisting of hydrogen and alkyl of 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and tert.butyl.

Examples of mono and dialkylamino are methylamino, ethylamino, dimethylamino, diethylamino, and methylethylamino. The heterocyclic of 5 to 6 ring members optionally containing another heteroatom



may be pyrrolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidyl, indolyl, piperidino, morpholino, and piperazinyl, preferably piperidino or morpholino.

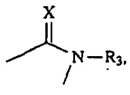
Examples of salts of salified carboxy are sodium, potassium, lithium, calcium, magnesium, ammonium, and organic bases such as methylamine, propylamine, trimethylamine, diethylamine, and triethylamine. Sodium salts are preferred.

The alkylamino and dialkylamino are preferably alkyl of 1 to 4 carbon atoms such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, and ethylmethylamino. Examples of the heterocyclics containing at least one heteroatom are saturated monocyclics such as oxirannyl, oxolannyl, dioxolannyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, and morpholinyl.

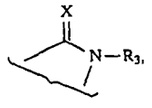
The alkyl, alkenyl, and alkynyl are optionally interrupted by one or more sulfur, oxygen, or nitrogen heteroatoms. Examples are alkoxyalkyl such as methoxymethyl, methoxyethyl, methoxypropyl, and methoxybutyl, as well as alkoxy alkoxyalkyl such as methoxyethoxymethyl.

When the products of Formula I contain a salifiable amino group, the acid addition salts of non-toxic, pharmaceutically acceptable acids may be formed. Examples of said acids are inorganic acids such as nitric acid, hydrochloric acid, sulfuric acid, and phosphoric acid, as well as organic acids such as formic acid, acetic acid, propionic acid, benzoic acid, and methane sulfonic acid.

Among the preferred compounds of Formula I are those wherein Y is oxygen, -A-B- is



and X and R_3 are defined as above; those wherein -A-B- is



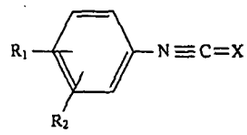
X has the above definition, and R_3 is hydrogen or alkyl of 1 to 6 carbon atoms optionally interrupted by at least one of —O—, —S—, and optionally substituted by —OH, —OH esterified with an acyl of an organic carboxylic acid of 1 to

7 carbon atoms, or free, esterified, or salified carboxy, are also worthy of special mention.

Among the preferred compounds of Formula I are those wherein R_3 is hydrogen or alkyl of 1 to 6, preferably 1 to 4, carbon atoms optionally substituted with —OH; those wherein R_2 is 3—CF_3 and R_1 is 4—CN; those wherein R_4 and R_5 are individually hydrogen, ethyl, or —CF_3; and those wherein R_4 and R_5 together with the carbon atoms form cyclobutyl or cyclopentyl.

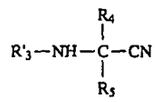
Specific preferred compounds of Formula I are 4-(3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-[1-methyl-4-oxo-2-thioxo-1,3-diazaspiro (4,4)-nonan-3-yl]-2(trifluoromethyl)-benzonitrile, and 4-(4,4-diethyl-3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile.

The inventive process for the preparation of a compound of Formula I comprises reacting the compound of the Formula



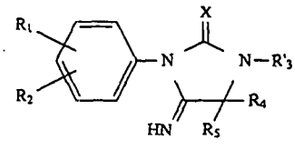
II

wherein R_1, R_2, and X have the above definitions, with a compound of the Formula



III

in the presence of a tertiary base, wherein R'_3 has the definition of R_3 with the active functions optionally protected, R_4 and R_5 have the above definitions with the proviso that R_4 and R_5 are not both methyl and, if R_1 is 4—NO_2, R_2 is 3—CF_3, X is —O—, and R'_3 is hydrogen; and if one of R_4 or R_5 is —CH_3, the other is —CH_2OH to obtain a compound of the formula



IV

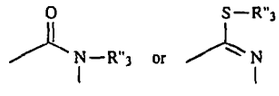
wherein R_1, R_2, X, R'_3, R_4 and R_5 have the above definitions and optionally subjecting the latter to at least one of the following reactions in any order:

a) elimination of the optional protective groups of R'_3;

b) hydrolysis of C═NH to a ketone function and if appropriate of >C═S to >C═O;

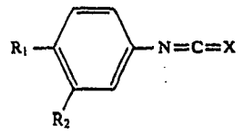
c) transformation of >C═O to >C═S, and

d) reaction of the products of Formula IV wherein R'_3 is hydrogen after hydrolysis of >C═NH to a ketone, with a compound of the formula R''_3-Hal wherein Hal is halogen and R''_3 is R'_3 except hydrogen to obtain a compound of Formula I wherein -A-B- is



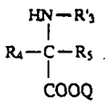
in which R''_3 has the above meaning; then if desired, the reaction of these products with an elimination agent for the optional protective groups that can be carried by R''_3 or, if appropriate, the reaction with an esterification, amidifica-

tion, or salification agent, or reacting a compound of the Formula



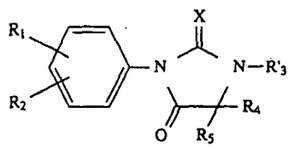
II

wherein R_1, R_2 and X have the above definitions, in the presence of a tertiary base, with a compound of the formula



III'

wherein R'_3, R_4 and R_5 have the above definitions and Q is an alkali metal such as sodium or alkyl of 1 to 6 carbon atoms, to obtain a compound of the formula



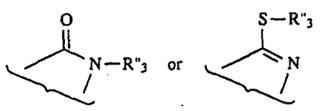
IVa

wherein R_1, R_2, X, R'_3, R_4 and R_5 have the above definitions and optionally subjecting compound IVa to any one or more of the following reactions in any order:

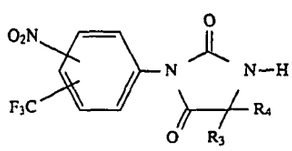
a) elimination of the optional protective groups that can be carried by R'_3;

b) conversion of the >C=O group or groups into >C=S or, if appropriate conversion of >C=S into >C=O;

c) reaction of the products of Formula IVa, in which R'_3 is hydrogen, with a reagent of formula Hal-R''_3, wherein R''_3 is the same as R'_3 with the exception of hydrogen and Hal is halogen, to obtain the products of Formula I in which -A-B- is

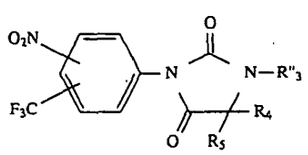


and optionally reaction of the latter to eliminate the protective group of R''_3, or reaction of the same with an esterification, salification or amidification agent, or reaction of a compound of the formula R''_3-Hal as defined above with a compound of the formula



IV'

to obtain a compound of the formula



IV"

and optionally subjecting the latter to at least one of the following reactions:

a) elimination of optional protective groups of R''_3 and then reaction with an esterification, salification or amidification agent; and

b) transformation of >C=O to >C=S.

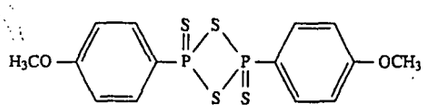
The reaction of the products of Formula II with the products of Formula III is preferably effected in an organic solvent such as tetrahydrofuran, dichloroethane, ethyl ether, or isopropyl ether in the presence of a tertiary base such as triethylamine, pyridine, methylethyl pyridine.

The optional reactive functional groups of R_3 which are optionally protected in compounds of Formula III, IVa, or IV" are—OH or amino which are protected by the usual protective groups. Examples of such protective groups for $—NH_2$ are tert.-butyl, tert.-amyl, trichloroacetyl, chloroacetyl, benzhydryl, trityl, formyl and benzyloxycarbonyl. Examples of hydroxy protective groups are formyl, chloroacetyl, tetrahydropyranyl, trimethylsilyl, and tert.-butyldimethylsilyl.

The above list of protective groups is not intended to be exhaustive and any protective group known, for example, in peptide chemistry may be used. Other known protective groups are described in French Patent 2,499,995 which is incorporated herein by reference. The optional reactions to eliminate groups are indicated in the said patent and the preferred method of elimination is acid hydrolysis with hydrochloric acid, benzene sulfonic acid, p-toluene sulfonic acid, formic acid, or trifluoroacetic acid, preferably hydrochloric acid.

The optional hydrolysis of >C=NH to >C=O is preferably effected by reaction with refluxing aqueous hydrochloric acid. When the hydrolysis of >C=NH to >C=O is effected with a molecule also containing >C=S, the latter may be transformed into a >C=O group. The free hydroxy optionally contained in R_3 may also be transformed into —SH.

The transformation of >C=O into >C=S is effected with a Lawesson reagent of the formula



which is commercial product sold, for example, by Fluka and is described in Bull. Soc. Chim. Belg., Vol. 87 No. 3 (1987), p. 229. When two >C=O groups are changed to >C=S, the reaction is effected with an excess of the Lawesson reagent. The same is also used when the molecule contains both >C=O to >C=S.

On the other hand, when part of the molecule contains two C=O's, and it is desired to obtain a product with only one >C=S, a deficiency of the Lawesson reagent is used to obtain a mixture of 3 products, each of two products with a >C=O and >C=S and one containing two >C=S's. These products can be separated by known methods such as chromatography.

The reaction of the compounds of Formulas IV, IVA, or IV' with a compound of the formula R''_3-Hal is effected in the presence of a strong base such as sodium hydride or potassium hydride in a phase transfer reaction in the presence of quaternary ammonium salts such as tert.-butyl ammonium The protective groups of R''_3 may be those discussed above for R_3. The reaction to eliminate the protective groups are as discussed above. For example, a tert-butyl dimethylsilyl group may be removed by hydrochloric acid as described in the examples herein.

The optional esterification of the compounds of Formula I wherein R''_3 is free —OH is effected under classical conditions using, for example, an acid or a functional derivative thereof such as its anhydride, e.g. acetic acid anhydride, in the presence of a base such as pyridine. The

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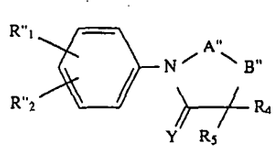
optional esterification or salification of the compounds of Formula I wherein R"$_3$is —COOH may be effected by known methods.

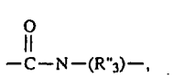
The optional amidification of the compounds of Formula I wherein R"$_3$is —COOH is also effected under classical conditions with primary or secondary amines with functional derivatives of —COOH, such as a symmetrical or mixed anhydride thereof.

The process of the invention to prepare compounds of the Formula

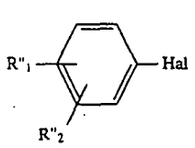


I"

wherein R"$_1$, R"$_2$, and -A"-B"- have the definitions of R_1 and R_2, and -A-B-, except that, when -A"-B"- is

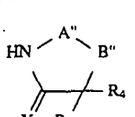


and R"$_3$ is hydrogen or alkyl of 1 to 7 carbon atoms and Y is oxygen R"$_1$ is —CN, comprises reacting a compound of the Formula



V

wherein R"$_1$ and R"$_2$ have the above definitions and Hal is halogen with a compound of the formula



VI

wherein -A"-B"- , R_4, R_5, and Y have the above definitions, in the presence of a catalyst and optionally a solvent. In the compounds of formula V, the halogen is preferably chlorine but may be iodine or bromine.

The role of the catalyst is obviously to trap the hydrogen halide as it forms and to facilitate the condensation reaction of the compounds of Formulas V and VI to form the desired product. The catalyst is preferably a metal in its native form, its oxide, its salt, or it may be a base. When the catalyst is metal, it is preferably copper or nickel and the metallic salts are preferably the chloride or acetate. When the catalyst is a base, it is preferably sodium hydroxide or potassium hydroxide and dimethylsulfoxide may be added to the reaction medium.

The catalyst of the process may be selected from cuprous oxide, cupric oxide, metallic copper, or a base such as sodium hydroxide or potassium hydroxide, preferably cuprous oxide in powdered form. The solvent used preferably is a high boiling point ether such as phenyl oxide, diglyme, triglyme, or dimethylsulfoxide; also useful are high boiling point oils such as paraffin or petroleum jelly. Preferably, the process is effected in an ether solvent such as phenyl oxide, diglyme, triglyme or dimethylsulfoxide, most preferably in phenyl oxide or triglyme.

The process may be effected at atmospheric pressure or under pressure at temperatures above 100° C., preferably above 150° C., for more than two hours. The reaction is preferably effected with cuprous oxide in triglyme at temperatures of 200° C. or higher for more than three hours.

The novel anti-androgenic compositions of the invention are comprised of an anti-androgenically effective amount of at least one compound of Formula I or its non-toxic, pharmaceutically acceptable acid addition salts and an inert pharmaceutical carrier. The compositions may be in the form of tablets, dragees, capsules, syrups, suppositories, creams, pomades, lotions, or injectable solutions prepared in the usual manner.

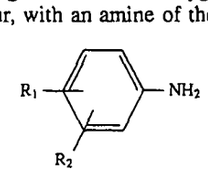
Examples of suitable excipients are aqueous or non-aqueous vehicles, gum arabic, lactose, starch, magnesium stearate, cocoa butter, fatty bodies of animal of vegetable origin, paraffinic derivatives, glycols, wetting agents, dispersants, emulsifiers, and preservatives.

The compositions inhibit the effect of androgens on peripherical receptors and have an anti-androgenic activity useful for therapy in adults without the certain effects of a chemical castration. The compositions are useful for the treatment of adenoma and neoplasia of the prostate as well as benign hypertrophia of the prostrate, they are also useful for the treatment of benign or malignant tumors of cells containing androgen receptors. They are particularly useful for the treatment of breast, brain, skin and ovarian cancer and bladder, lymphatic system, liver, and kidney cancers. They are equally useful for the treatment of hirsutism, acne, seborrhea, androgenic alopecia, hyperpilosity, and in the veterinary field.

The compositions of the invention are useful in dermatology and can contain another ingredient such as an antibiotic, e.g. derivatives of azelaic acid, fusidic acid, erythromycin or with a derivative of retinoids for the treatment of acne. They can also be used with a 5α- reductase inhibitor such as (5α, 17β)-1,1-dimethylethyl 3-oxo 4- azaΔ^1-androstene-17 carboxamide (or Finasteride Merck, 11th ed.) or with azelaic acid or a blocking agent of androgen receptors for the treatment of acne, alopecia or hirsutism. In addition, they can be used with a product stimulating the growth of hair such as Minoxidil for the treatment of alopecia. The compositions can also be used in the veterinary domain and in the form of radioactive products, as well as in diagnostics as specific labels for the androgen receptors. As radioactive products they can be labeled with tritium, carbon 14, and/or iodine 125.

The novel method of the invention for inducing anti-androgenic activity in warm-blooded animals, including humans, comprises administering to the warm-blooded animals an anti-androgenically effective amount of at least one compound of Formula I and its nontoxic, pharmaceutically acceptable acid addition salts. The compounds may be administered parenterally, buccally, perlingually, rectally, or topically and the usual daily dose is 0.13 to 6.66 mg/kg depends on the condition treated, the specific compound, and the method of administration.

The starting compounds of Formula II may be prepared by reacting phosgene, when X is oxygen, or thiophosgene, when X is sulfur, with an amine of the formula



A

A product of this type is described in French Patent No. 2,329,276. The amines of formula A are described in EP Patent No. 0,002,892 and French Patent No. 2,142,804.

The products of Formula III or III' are known or can be prepared from the corresponding cyanhydrins by the process described in J. Am. Chem. Soc., Vol. 75 (1953), p. 4841, or

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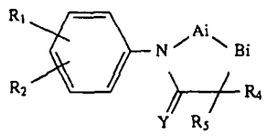
Beil. I, 4 526, or J. Org. Chem., Vol. 27 (1962), p. 2901. The compounds of Formula III wherein R'_3 is other than hydrogen may be obtained by reacting a compound of the formula $R"_3$ Hal with 2-cyano-2-aminopropane under the conditions described above for reacting the said halide with the compounds of Formula IV. An example is described by Jilek et al, Collect. Czech. Chem. Comm., Vol. 54(8) 1989), p. 2248. The products of Formula IV' are described in French Patent No. 2,329,276.

The compounds of formulae V and VI are commercially available known compounds and can be prepared by known methods.

The preparation of the compounds of Formula VI are described in the following publications: Zhur Preklad Khim., Vol. 28 (1955), p. 969–75 (CA, Vol. 50 (1956), p. 4881 a); Tetrahedron, Vol. 43 (1987), p. 1753; J. Org. Chem., Vol. 52 (1987), p. 2407; Zh. Org. Khim., Vol. 21 (1985), p.2006; J. Fluor. Chem., Vol. 17 (1981), p. 345; German Patent 637,318, European Patent 0,130,875, and Japanese Patent No. 81-121,524.

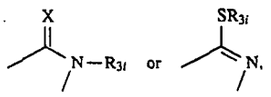
The products of Formula VI which are derivatives of hydantoin are largely used and are known in the literature such as J. Pharm. Pharmacal., 67, Vol. 19(4) (1967), p. 209–16; J. Chem. Soc., Vol. 74(2) (1972), p. 219–221; Khim. Farm. Zh., Vol 67(1)(5), p. 51–2; German Patent 2,217,914; European Patent 0,091,596 and J. Chem. Soc. Perkin. Trans. 1, Vol. 74(2), p. 48 and 219–221.

The novel intermediates of the invention are the compounds of the formula



IVi

wherein R_1, R_2 and Y have the above definitions and -Ai-Bi- is



wherein X is oxygen or sulfur and R_{3i} is R_3 with the reactive groups, among which are —OH and —NH_2, protected as above for R_3.

In the following examples, there are described several preferred embodiments to illustrate the invention. However, it should be understood that the invention is not intended to be limited to the specific embodiments.

EXAMPLES

Example 1

4-(3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

a. A solution of 22 ml of distilled water and 1 ml of thilphosgene were slowly added to 2.23 g of 2-trifluoromethyl-4-amino-benzonitrile (prepared as in EP 000 2892) and the mixture was stirred for 1 hour and then extracted chloroform. The organic phase was washed with aqueous sodium chloride, dried, and evaporated to dryness under reduced pressure to obtain 3 grams of the desired product which was used as is.

b. A solution of 976 mg of N-methylglycyne in 3.65 ml of 3 mol sodium hydroxide solution was added to 2.5 grams of the thioisocyanate of Step a) in solution in 5 ml of ethanol. The mixture was stirred for 30 minutes at room temperature and then refluxed for 1 hour. After returning to room temperature, the mixture was poured into a mixture of 20 ml of water and 10 ml of N-hydrochloric acid and extracted with chloroform. After chromatography over silica (elution with methylene chloride-acetone (95-5)), there was obtain 1.78 grams of product which was crystallized from a mixture of methylene chloride and cyclohexane to obtain 1.66 g of the desired product melting at 220° to 221° C. and having an Rf=0.18 (cyclohexane-ethyl acetate 1-1).

IR Spectrum $CHCl_3$:		
C=O	1788–1729 cm^{-1}	
C≡N	2235 cm^{-1}	
conjugated system + Aromatics	1614–1580–1515 cm^{-1}	
UV Spectrum (EtOH):		
Max.	232 nm	ϵ = 17,300
Max.	254 nm	ϵ = 22,700

Example 2

4-[1-methyl-4-imino-2-thioxo-1,3-diazaspiro(4,4)nonan-3-yl]-2-trifluoromethyl-benzonitrile

A solution of 1.36 g of 1-methylamino-cyclopentane carbonitrile in 10 ml of tetrahydrofuran were added over about 2 minutes to 2.5 g of the isocyanate of step a of Example 1 and the mixture was stirred for 40 minutes. The solvent was evaporated and the residue was chromatographed over silica (elution with methylene chloride-ethyl acetate (87.5-12.5)) to obtain 3.32 g of the expected product melting at 165°–166° C. and having an Rf=0.3 (methylene chloride-ethyl-acetate (85-15)).

IR Spectrum $CHCl_3$:	
=NH	3310–1672 cm^{-1}
C≡N	2230 cm^{-1}
Aromatics	1614–1577–1505 cm^{-1}

Preparation of 1-methylamino-cyclopentane-carbonitrile

A solution of 6.5 of potassium cyanide in 13 ml of water was added at 15°–20° C. to a solution of 8.5 g of cyclopentanone and 7 g of methylamine hydrochloride in 7.5 ml of water and returned to room temperature; the mixture was stirred for 18 hours and extracted with methylene chloride. The organic phase was washed with aqueous sodium chloride, dried, and evaporated to dryness, and the residue was distilled to obtain 4.1 g of the expected product with a boiling point of 60° C.±0.3° C. at 7 mm of Hg.

Example 3

4-(1-methyl-4-oxo-2-thioxo-1,3-diazaspiro(4,4)nonan-3-yl)-2-trifluoromethyl-benzonitrile

52 ml of methanol were added to a solution of 5.2 ml of chloroform and to 259 mg of the product of Example 2 and then 7.5 ml of 2N-hydrochloric acid were added thereto. The mixture was refluxed for 1 hour and, after cooling to room temperature, was poured into 150 ml of iced water. The mixture was extracted with chloroform and the organic phase was washed aqueous sodium chloride dried and

evaporated to dryness. The residue was chromatographed over silica, eluting with ethyl acetate-cyclohexane(3-7) to obtain the fractions with Rf equal to 0.35. After crystallization, from a mixture of methylene chloride and cyclohexane, 247 mg of the desired product, melting at 162° C.–163° C. and with an Rf=0.35 (cyclohexane-ethyl acetate (7-3)) were obtained.

IR Spectrum $CHCl_3$:		
C=O	1765 cm^{-1}	
CN	2235 cm^{-1}	
Aromatics	1609–1578–1505 cm^{-1}	
UV Spectrum (EtOH):		
Max.	234 nm	ϵ = 17,600
Max.	256 nm	ϵ = 23,800
Inf.	266 nm	ϵ = 20,300

Example 4

4-(4,4-diethyl-3-methyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 2, 2.5 g of the isothiocyanate of Step a) of Example 1 and 1.39 g of the appropriate amino nitrile were reacted to obtain 3.22 g of the expected product melting at 167 ° C.–168° C. and having an Rf=0.27 (methylene chloride-ethyl acetate (85-15)) .

IR Spectrum $CHCl_3$:	
=NH	1304–1673 cm^{-1}
C≡N	2230 cm^{-1}
Aromatics	1614–1576–1505 cm^{-1}

Preparation of 1-methyl amino-diethyl-carbonitrile

Using the procedure of Example 2, 8.6 g of diethyl ketone were reacted to obtain 4.8 g of the expected product with a boiling point of 77° C. at 40 mm of Hg.

Example 5

4-(4,4-diethyl-3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 3, 321 mg of the product of Example 4 and 65 ml of methanol and 14 ml of 2N-hydrochloride acid were reacted to obtain 249 mg of the expected product melting at 126° C.–127° C. and having an Rf=0.45 (cyclohexane-ethyl acetate (4-6)).

IR Spectrum $CHCl_3$:		
C=O	1753 cm^{-1}	
C≡N	2235 cm^{-1}	
Aromatics	1615–1580–1504 cm^{-1}	
UV Spectrum (EtOH):		
Max.	234 nm	ϵ = 17,800
Max.	254 nm	ϵ = 24,100
Inf.	265 nm	

Example 6

4-(5-methyl-8-imino-6-thioxo(5,7-diazaspiro(3,4))-octan-7-yl-2-trifluoromethyl-benzonitrile

A solution of 221 mg of 1-methyl amino-cyclobutanecarbonitrile in 1 mg of 1,2-dichloroethane was added over 3 minutes to a solution of 456 mg of the isothiocyanate of Example 1 Step a) in 2 ml of 1,2-dichloroethane in the presence of 0.2 ml of triethylamine and, after stirring the mixture for 45 minutes, the solution was evaporated. The residue was chromatographed over silica and diluted with a methylene chloride-acetate (95-5) mixture to recover the fraction with an Rf=0.32. After crystallization from ether 610 mg of the expected product melting at 172° C.–173° C. was obtained.

IR Spectrum $CHCl_3$:	
C=NH	3015–1673 cm^{-1}
C≡N	2236 cm^{-1}
aromatics	1615–1580–1505 cm^{-1}

Using the procedure of Example 2, 7 g of cyclobutanone were reacted to obtain 10.6 g of 1-methylamino-cyclobutane-carbonitrile.

Example 7

4-(5-methyl-8-oxo-6-thioxo(5,7-diazaspiro(3,4))-octan-7-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 3, 514 mg of the product of Example 6 and 1.5 ml of 2N-hydrochloric acid were reacted to obtain, after chromatography over silica (cyclohexane-ethyl acetate (6-4)) to obtain a fraction with an Rf=0.34. Crystallization from ether yielded 499 mg of the expected product melting at 161° C.–162° C.

IR Spectrum $CHCl_3$:		
C=O	1754 cm^{-1}	
C≡N	2236 cm^{-1}	
aromatics	1615–1583–1504 cm^{-1}	
UV Spectrum (EtOH):		
Inf.	239 nm	ϵ = 17,400
	257 nm	ϵ = 21,200
	268 nm	ϵ = 19,000

Example 8

4-(1-methyl-4-imino-2-oxo-1,3-diazaspiro(4,4))-nonan-3-yl)-2-trifluoromethyl-benzonitrile

1.5 ml of a solution of the isocyanate of 3-trifluoromethyl-4-benzonitrile of Example 1 starting from phosgene and 2-trifluoromethyl-4-benzonitrile (1.6 M/l) in 1,2 dichloroethane were added at –3° C. to a solution 300 mg of 1-methylamino-cyclopentanecarbonitrile in 3 ml of 1,2 dichloroethane in the presence of 0.5 ml of triethylamine; after stirring for 40 minutes, the solution was evaporated to dryness. The residue was chromatographed over silica and diluted with a methylene chloride-ethyl acetate (95-5) mixture to obtain 620 mg of the expected product.

Example 9

4-(1-methyl-2,4-dioxo-1,3-diazaspiro(4,4))-nonan-3-yl)-2-trifluoromethyl-benzonitrile

A mixture of 535 mg of the product of Example 8 in 10 ml of methanol and 2 ml of 2N-hydrochloric acid was heated at 50° C. with stirring for 1 hour and, after returning to the room temperature, 20 ml of water were added thereto. The mixture was extracted with methylene chloride and the organic phase was evaporated to dryness under the reduced pressure. The residue was dissolved in acetone and chromatographed over silica (methylene chloride-acetone (98-2)) to obtain 325 mg of the expected product.

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IR Spectrum $CHCl_3$:		
C=O	1777 (m), 1724 cm^{-1} (F)	
C≡N	2238 cm^{-1}	
Aromatics	1616–1576–1505 cm^{-1}	
UV Spectrum (EtOH):		
Inf.	236 nm	ε = 10,000
Max.	262 nm	ε = 13,900
Inf.	277 nm	ε = 7,200
Inf.	286 nm	ε = 3,700

Example 10

4-(5-methyl-8-imino-6-oxo-5,7-diazaspiro(3,4))-octan-7-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 8, 2 ml of a solution of isocyanate and 352 mg of 1-methylamino-cyclobutane-carbonitrile were reacted to obtain, after chromatography over silica (eluant methylene-chloride ethyl acetate (85-15)), the product with Rf=0.20 and finally to obtain 301 mg of the expected product melting at 144° C.–145° C.

IR Spectrum $CHCl_3$:	
OH/NH	3295 cm^{-1}
C≡N	2240 cm^{-1}
C=O	1740 cm^{-1}
C≡N	1664 cm^{-1}
aromatics	1611–1572–1508 cm^{-1}

Example 11

4-(6,8-dioxo-5-methyl-5,7-diazaspiro(3,4))-octan-7-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 9, 0.8 g of the product of Example 10 and 3 ml of 2N-hydrochloric acid were reacted and chloroform was used as the extraction solvent. After chromatography over silica (methylene chloride-ethyl acetate (95-5)), there were obtained 465 mg of the expected product melting at 165° C.–166° C.

IR Spectrum $CHCl_3$:		
C≡N	2236 cm^{-1}	
C=O	1778, 1726 cm^{-1}	
Aromatics	1616–1579–1505 cm^{-1}	
UV Spectrum (EtOH):		
Max.	238 nm	ε = 11,000
Max.	262 nm	ε = 14,000
Inf.	278–286 nm	

Example 12

4-(4-imino-2-oxo-1,3-diazaspiro(4,4))-nonan-3-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 8, 3.1 ml of 1.6M solution of isocyanate and 550 mg of 1-imino-cyclopentane-carbonitrile were reacted to obtain, after chromatography on silica (methylene chloride-acetone (90-10)), 1.24 g of the expected product melting at 212° C.–213° C.

IR Spectrum $CHCl_3$:	
OH/NH	3350, 3290 cm^{-1}
C≡N	2240 cm^{-1}
C=O	1744 cm^{-1}
C=N	1678 cm^{-1}
Aromatics	1610–1574–1510 cm^{-1}

Preparation of 1-amino-cyclopentane-carbonitrile

8.8 ml of cyclopentane were added dropwise at 0° to 8° C. to a mixture of 7.9 g of ammonium chloride, 6.14 g of sodium cyanide and 40 ml of ammonium hydroxide and, after returning to room temperature, the mixture was stirred for 16 hours and extracted with methylene chloride. The organic phase was washed with aqueous sodium chloride, dried, and evaporated to dryness at a temperature less than 30° C. The residue was distilled to obtain 11 g of the expected product with a boiling point of 55° C.±2° at 11 mg of Hg.

Example 13

4-(2,4-thioxo-1,3-diazaspiro(4,4))-nonan-3-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 9, 1.17 g of the product of Example 12 and 5 ml of 2N-hydrochloric acid were reacted to obtain, after chromatography on silica (methylene chloride-acetone (9-1)), 1.108 g of the expected product with a melting point of 184° C.–185° C. and having an Rf=0.23.

IR Spectrum $CHCl_3$:		
=C—NH	3444 cm^{-1}	
C≡N	2296 cm^{-1}	
C=O	1786, 1731 cm^{-1}	
Aromatics	1616–1505 cm^{-1}	
UV Spectrum (EtOH):		
Max.	258 nm	ε = 15,600
Max.	286 nm	ε = 3,500

Example 14

4-(8-imino-6-oxo-5,7-diazaspiro(3,4))-octan-7-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 8, 3.1 ml of an isocyanate solution and 480 mg of 1-amino-cyclobutane-carbonitrile were reacted to obtain 990 mg of the expected product melting at 192° C.–193° C. and having an Rf=0.25.

IR Spectrum $CHCl_3$:	
OH/NH	3380, 3315 cm^{-1}
C≡N	2240 cm^{-1}
C=N	1754 cm^{-1}
Aromatics	1612–1571–1510 cm^{-1}

Using the procedure of Example 12, 7.4 ml of cyclobutanone were reacted to obtain 9.2 g of 1-amino-cyclobutane-carbonitrile.

Example 15

4-(6,8-dioxo-5,7-diazaspiro(3,4))-octan-7-yl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 9, a solution of 327 ml of the product of Example 14 in 1.5 ml of chloroform and 1.9 ml of 2N-hydrochloric acid were reacted to obtain, after chromatography on silica (methylene chloride-acetone (9-1)), 341 mg of the expected product melting at 210° C.–211° C. and having an Rf=0.32.

IR Spectrum $CHCl_3$:		
OH/NH	3390 cm^{-1}	
C≡N	2240 cm^{-1}	
C=N	1787, 1737 cm^{-1}	
Aromatics	1612–1577–1508 cm^{-1}	
UV Spectrum (EtOH):		
Max.	259 nm	ε = 15,700
Inf.	2771 286, 301 nm	

Example 16

4-[1-(4-hydroxybutyl(2,4-dioxo-1,3-diazaspiro(4,4))-nonan-3-yl]-2-trifluoromethyl-benzonitrile

A solution of 808 mg of the product of Example 13, in 7 ml of dimethylformamide were added dropwise over 35 minutes to 142 mg of sodium hydride and, 10 minutes after the evolution of hydrogen disengagement, 650 mg of 4-chloro-tert.-butyldimethylsilyl ether and 408 mg of sodium iodide were added. The mixture was heated at 70° C. for 3 hours and, after returning to room temperature, 71 mg of sodium hydride were added. The mixture was stirred for 10 minutes and 330 mg of the silyl were reacted and 222 mg of sodium iodide were added thereto. The mixture was heated for 45 minutes at 70° C. and, after cooling to room temperature, 60 ml of water containing about 500 mg of monopotassium phosphate were added thereto. The mixture was extracted with ethyl ether and then with ethyl acetate and the combined organic phases were dried and evaporated to dryness under reduced pressure. The residue was chromatographed over silica (methylene chloride-acetone (98-2)) to obtain 560 mg of the silyl intermediate. 550 mg of the silylated intermediate were added to 6 mg of methanol and 1.5 ml of 2N hydrochloric acid, and the mixture was stirred for 30 minutes. 30 ml of water was added and the mixture was extracted with methylene chloride. The organic phase was dried and evaporated to dryness and the residue was chromatographed over silica (methylene chloride-acetone (9-1)) and then crystallized from isopropylether to obtain 381 mg of the expected product melting at 125°–126° C. and having an Rf=0.17.

IR Spectrum CHC_3:		
OH	3625 cm^{-1}	
C≡N	2235 cm^{-1}	
C=N	1773, 1721 cm^{-1}	
Aromatics	1615–1580–1505 cm^{-1}	
UV Spectrum (EtOH):		
Max.	239 nm	ε = 9,800
Max.	262 nm	ε = 14,600
Inf.	286 nm	

Example 17

4-[5-(4-hydroxybutyl(-6,8-dioxo-5,7-diazaspiro(3,4))-octan-7-yl]-2-trifluoromethyl-benzonitrile

Using the procedure of Example 16, the product of Example 15 was reacted to obtain the expected product melting at 92° C.–93° C.

IR Spectrum $CHCl_3$:		
OH	3626 cm^{-1}	

-continued

C≡N	2235 cm^{-1}	
C=O	1775(m), 1784 cm^{-1} (F)	
aromatics	1616–1578–1505 cm^{-1}	
UV Spectrum (EtOH):		
Max.	238 nm	ε = 11,200
Max.	262 nm	ε = 13,900
Inf.	288 nm	

Using the procedure of the above Examples, the appropriate isocyanate or thioisocyanate and 3,3,3-trifluoromethyl-2-trifluoromethyl- 2-methylamino-propionitrile prepared according to J. Org. Chem., Vol. 35, p. 1485 (1970) were reacted to obtain the following compounds.

Example 18

4-(4,4-bis,trifluoromethyl-3-methyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

Example 19

4-(4,4-bis,trifluoromethyl-3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

Example 20

4-(4,4-bis,trifluoromethyl-3-methyl-5-imino-2-oxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

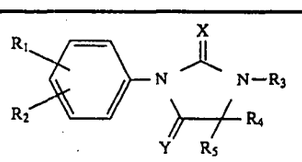
Example 21

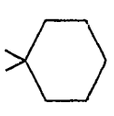
4-(4,4-bis,trifluoromethyl-3-methyl-2,5-dioxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

Example 22

Tablets were prepared by combining 100 ml of the product of Example 3, with sufficient excipient comprising lactose amido talc and magnesium stearate to form a final tablet weight of 300 mg.

In addition to the above products, other compounds falling within the scope of the invention are those having the following formula wherein R_1, R_2, R_3 R_4, R_5 and X are as indicated in the following table.



R_1	R_2	X	Y	R_4	R_5
C≡N	CF_3	S	O		
"	"	O	"	"	
"	"	S	"		
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PHARMACOLOGICAL DATA

1) Study of androgenic Receptors

Male rats of the Sprague Dawley EOPS strain weighing 180 to 200 g, castrated 24 hours previously, were killed and the prostate was removed, weighed and homogenized at 0° C. with a potter glass in a buffered solution (Tris 10 mM, saccharose 0.25M, PMSF (phenyl methane sulfonyl fluoride) 0.1 mM, sodium molybdate 20 mM, HCl pH 7.4 into which was added extemporaneously 2 m of DTT (DL dithiothreitol) at a rate of 1 g of tissue per 8 ml of buffer solution. The homogenate was then ultracentrifuged at 0° C. for 30 minutes at 209,000 g and the aliquots of supernatant (=cytosol) were incubated for 30 minutes and 24 hours with a concentration (T) of tritiated testosterone and in the presence of increasing concentrations (0 to 2500×10^{-9}M) of cold testosterone or the test products. The concentration of bound tritiated testosterone (B) was then measured for each incubate by adsorption method of carbon-dextran. The relative affinity of bonding (RBA) was calculated.

The following two curves were graphed: the percentage of the bound tritiated hormone B/T as a logarithmic function of the concentration of the cold hormone and B/T as a logarithmic function of the concentration of the tested cold product. The line of the equation $I_{50}=(B/Tmax+B/Tmin)/2$ was determined.

B/T max=% of the bound tritiated hormone for an incubation of this tritiated hormone at concentration (T). B/T min=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T) in the presence of a large excess of cold hormone ($2,500\times10^{-9}$M).

The intersection of the straight line I_{50} and the curves permit an evaluation of the concentrations of the cold reference hormones (CH) and the cold test product (CX) which inhibit by 50% the bonding of the tritiated hormone on the receptor. The RBA of the test product was determined by the equation

$$RBA=100(CH)/(CX)$$

and the following results expressed in RBA were obtained with testosterone=100.

Products of example	Incubation 24 H
3	27
5	8

2) Determination of the androgen or anti-androgen activity by the dosage of ornithine carboxylase

Six week old male Swiss mice castrated 24 hours received oral dose of the test products as a 0.5% suspension in methyl cellulose or in ethanol by oral or percutaneous route simultaneously with a sub-cutaneous injection of 3 mg/kg of testosterone propionate in solution in corn oil to determine the anti-androgen activity. Active agonists were determined in the absence of testosterone propionate. The test compounds as well as testosterone were administered in a volume of 10 ml/kg. 20 hours after the treatments, the animals were killed, the kidneys were removed and then homogenized at 0° C. with a teflon-glass grinding apparatus in 10 volumes of buffer Tris-HCl 50 mM at a pH 7.4 containing 250 μM of pyridoxal phosphate, 0.1 mM EDTA and 5 mM of dithiothreitol. The homogenate was centrifuged at 209,000 g for 30 minutes.

At 37° C., renal ornithine decarboxylase transforms an isotopic mixture of cold ornithine and tritiated ornithine in cold putrescine and tritiated putrescine. The putrescine was then collected on selective ion-exchange papers, after drying, excess non-transformed cold and tritiated ornithine were eliminated by washing 3 times with 0.1M ammonium hydroxide. The papers were dried and the radioactivity was determined after addition of an Aqualite sample. The results expressed in fmoles (10^{-15}M) of tritiated putrescine formed per hour/mg of protein are reported in the following table.

Products of Example	% Inhibition of ODL Test A
3	28
5	43

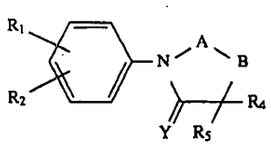
CONCLUSION

The tests show that the tested compounds of the invention possess a strong anti-androgen activity and are devoid of agonist activity.

Various modifications of the compounds and method of the invention may be made without departing from the spirit or scope thereof and it is to be understood that the invention is intended to be limited only as defined in the appended claims.

What is claimed is:

1. A compound selected from the group consisting of compounds of the formula



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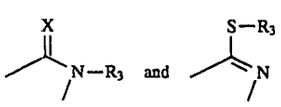
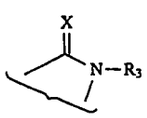
wherein one of R_1 and R_2 is —CN, and the other is —CF_3, -A-B- is selected from the group consisting of



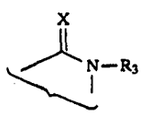
wherein X is —O— or —S—, R_3 is alkyl of up to 12 carbon atoms optionally substituted with —OH, Y is —O—, —S—, or NH; R_4 and R_5 are individually selected from the group consisting of hydrogen and alkyl of up to 12 carbon atoms optionally substituted with at least one halogen and their non-toxic pharmaceutically acceptable acid addition salts.

2. A compound of claim 1 wherein Y is —O— and -A-B- is



and X and R_3 are as defined in claim 1.

3. A compound of claim 1 wherein -A-B- is



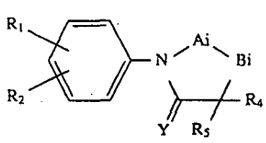
X is as defined in claim 1 and R_3 is alkyl of 1 to 6 carbon atoms optionally substituted with —OH.

4. A compound of claim 3 wherein R_3 is alkyl of 1 to 4 carbon atoms optionally substituted by —OH.

5. A compound of claim 1 wherein R_2 is 3—CF_3 and R_1 is 4—CN.

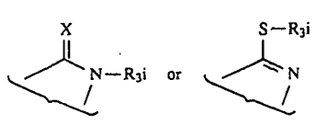
6. A compound of claim 1 wherein R_4 and R_5 are individually hydrogen, ethyl, or —CF_3.

7. A compound of the formula



wherein R_1, R_2, R_4, R_5 and Y have the definitions of claim 1 and

is

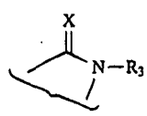


X is —O— or —S— and R_{3i} is R_3 with reactive functions protected.

8. An anti-androgenic composition comprising an anti-androgenically effective amount of at least one compound of claim 1 and an inert pharmaceutical carrier.

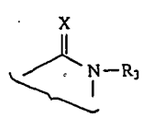
9. A method of inducing anti-androgenic activity in warm-blooded animals comprising administering to warm-blooded animals an anti-androgenically effective amount of at least one compound of claim 1.

10. A method of claim 9 wherein Y is —O—, -A-B- is



and X and R_3 are as defined in claim 1.

11. A method of claim 9 wherein -A-B- is



X is as defined in claim 1 and R_3 is alkyl of 1 to 6 carbon atoms optionally substituted with —OH.

12. A method of claim 9 wherein R_3 is alkyl of 1 to 4 carbon atoms optionally substituted by —OH.

13. A method of claim 9 wherein R_2 is 3—CF_3 and R_1 is 4—CN.

14. A method of claim 9 wherein R_4 and R_5 are individually hydrogen, ethyl, or —CF_3.

15. A compound of claim 1 selected from the group consisting of 4-(3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile and 4-(4,4-diethyl-3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile.

16. An anti-androgenic composition of claim 8 wherein the active compound is selected from the group consisting of 4-(3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile and 4-(4,4-diethyl-3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile.

17. A method of claim 9 wherein the compound is selected from the group consisting of 4-(3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile and 4-(4,4-diethyl-3-methyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile.

* * * * *

450

Annexure IX

US00RE35956E

United States Patent [19]

Gaillard-Kelly et al.

[11] E Patent Number: Re. 35,956

[45] Reissued Date of Patent: Nov. 10, 1998

[54] **PHENYLIMIDAZOLIDINES HAVING ANTIANDROGENIC ACTIVITY**

[75] Inventors: **Martine Gaillard-Kelly**; **Francois Goubet**, both of Paris; **Daniel Philbert**, Laverenne Saint Hiliare; **Jean-Georges Teutsch**, Pantin, all of France

[73] Assignee: **Roussel Uclaf**, France

[21] Appl. No.: **807,760**

[22] Filed: **Feb. 27, 1997**

Related U.S. Patent Documents

Reissue of:

[64] Patent No.: **5,411,981**
Issued: **May 2, 1995**
Appl. No.: **64,257**
Filed: **May 18, 1993**

U.S. Applications:

[63] Continuation-in-part of Ser. No. 819,910, Jan. 9, 1992, abandoned.

[30] **Foreign Application Priority Data**

Jan. 9, 1991 [FR] France 91 00185
Jul. 8, 1992 [FR] France 92 08431

[51] **Int. Cl.**[6] **A61K 31/415**; C07D 233/72

[52] **U.S. Cl.** **514/386**; 514/342; 514/391; 548/311; 548/317.1; 548/318.5; 548/320.1; 548/320.5

[58] **Field of Search** 514/386, 391, 514/342; 548/311.1, 317.1, 318.5, 320.1, 320.5

[56] **References Cited**

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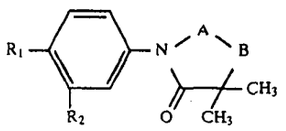
Primary Examiner—Floyd D. Higel

Attorney, Agent, or Firm—Bierman, Muserlian and Lucas

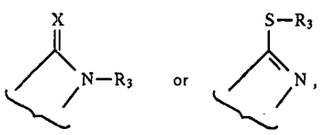
[57] **ABSTRACT**

A compound of the formula

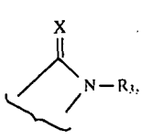


I

wherein R_1 is —CN, —NO_2 or halogen, R_2 is —CF_3 or halogen, —A—B— is of



X is —O— or —S—, R_3 is hydrogen, alkyl, alkenyl or alkynyl of up to 12 carbon atoms, aryl and aralkyl of up to 12 carbon atoms, all optionally substituted by —OH, halogen, —SH, —CN, acyl and acyloxy of up to 7 carbon atoms, —aryl, —O—aryl, —O—aralkyl —S— aryl of up to 12 carbon atoms the aryl and aralkyl being optionally substituted by halogen, —CF_3, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl or alkynyloxy with the sulfur being optionally oxidized to sulfone or sulfoxide, free, esterified, amidified or salified carboxy, —NH_2, mono and dialkylamino and heterocyclic of 3 to 6 ring members and containing at least one heteroatom selected from the group consisting of oxygen, sulfur and nitrogen, the alkyl, alkenyl and alkynyl being optionally interrupted by at least one oxygen, nitrogen or sulfur optionally oxidized to sulfoxide or sulfone, trialkylsilyl with the alkyl having 1 to 6 carbon atoms and acyl and acyloxy of an organic carboxylic acid of 1 to 7 carbon atoms and Y is —O—, —S— or —NH—, except the compounds wherein —A-B— is



X is oxygen, R_3 is hydrogen and Y is oxygen or —NH—, R_2 is —CF_3 or halogen and R_1 is —NO_2 or halogen and their non-toxic, pharmaceutically acceptable acid addition salts.

20 Claims, No Drawings

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PHENYLIMIDAZOLIDINES HAVING ANTIANDROGENIC ACTIVITY

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

PRIOR APPLICATION

This application is a continuation-in-part of U.S. Patent application Ser. No. 819,910, filed Jan. 9, 1992, now abandoned.

Japanese application No J 48087030 describes 3-phenyl-2-thiohydantoins useful for inhibiting the germination of certain plants. U.S. Pat. No. 4,097,578 describes imidazolidines different from formula I having antiandrogenic activity. Other pertinent art includes U.S. Pat. Nos. 3,823,240; No. 4,873,256; No. 4,407,814; No 4,482,739 and No. 4,234,736.

OBJECTS OF THE INVENTION

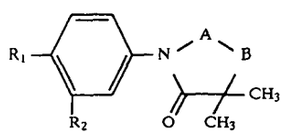
It is an object of the invention to provide the novel compounds of formula I and a novel process and novel intermediates for their preparation.

It is another object of the invention to provide novel anti-androgenic compositions and a novel method of inducing anti-androgenic activity in warm-blooded animals.

These and other objects and advantages of the invention will become obvious from the following detailed description.

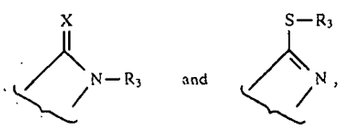
THE INVENTION

The novel phenylimidazolidines of the invention have the formula



I

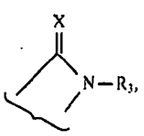
wherein R_1 is selected from the group consisting of —CN, —NO_2 and halogen, R_2 is —CF_3 or halogen, —A-B— is selected from the group consisting of



and

X is —O— or —S—, R_3 is selected from the group consisting of hydrogen, alkyl, alkenyl and alkynyl of up to 12 carbon atoms, aryl and aralkyl of up to 12 carbon atoms, all optionally substituted with at least one member of the group consisting of —OH, halogen, —SH, —CN, acyl and acyloxy of up to 7 carbon atoms, —aryl, —O—aryl, —O—aralkyl —S—aryl of up to 12carbon atoms, the aryl and aralkyl being optionally substituted with a member of the group consisting of halogen, —CF_3, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl and alkynyloxy with the sulfur being optionally oxidized to sulfone or sulfoxide, free, esterified, amidified or salified carboxy, —NH_2, mono and dialkylamino and heterocyclic of 3 to 6 ring members and containing at least one heteroatom selected from the group

consisting of oxygen, sulfur and nitrogen, the alkyl, alkenyl and alkynyl being optionally interrupted with at least one member of the group consisting of oxygen, nitrogen and sulfur optionally oxidized to sulfoxide or sulfone, trialkylsilyl with the alkyl having 1 to 6 carbon atoms and acyl and acyloxy of an organic carboxylic acid of 1 to 7 carbon atoms and Y is —O—, —S— or —NH—, except the compounds wherein —A-B— is



X is oxygen, R_3 is hydrogen and Y is oxygen or —NH—, R_2 is —CF_3 or halogen and R_1 is —NO_2 or halogen and their non-toxic, pharmaceutically acceptable acid addition salts.

The following examples are given for the values of R_3. Alkyl of up to 12 carbon atoms includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, sec.-pentyl, tert.-pentyl, neopentyl, hexyl, isohexyl, sec.-hexyl, tert.-hexyl, heptyl, octyl, decyl, undecyl and dodecyl, branched or linear. Preferred are alkyl of 1 to 6 carbon atoms, especially methyl, ethyl, propyl and isopropyl, n-butyl, isobutyl, tert-butyl and branched or linear pentyl and hexyl.

Examples of alkenyl of up to 12 carbon atoms are vinyl, allyl, 1-propenyl, butenyl, pentenyl and hexenyl and preferably alkenyl of 2 to 4 carbon atoms and especially vinyl, allyl or butenyl. Examples of alkynyl of up to 12 carbon atoms are ethynyl, propargyl, butynyl, pentynyl and hexynyl and preferably 2 to 4 carbon atoms such as ethynyl and propargyl.

Examples of aryl are carbocyclic aryl such asphenyl and naphthyl, heterocyclic aryl of 5 to 6 ring members containing at least one heteroatom selected from the group consisting of oxygen, sulfur and nitrogen. Examples of 5 ring heteroaryls are furyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, thiadiazolyl, pyrazolyl and isoxazolyl. Examples of 6 ring heteroaryl are pyridyl, pyrimidinyl, pyridazinyl and pyrazinyl. Examples of condensed aryls are indolyl, benzofurannyl, benzothienyl and quinoleinyl. The preferred aryl is phenyl.

Examples of aralkyl include the alkyl recited above substituted with the aryl cited above. The preferred aralkyl are triphenylmethyl, phenethyl and benzyl. Examples of halogen are fluorine, chlorine, bromine and iodine but preferred are fluorine, chlorine and bromine. Examples of alkyl substituted with at least one halogen are fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, dichloromethyl, dibromomethyl and trifluoromethyl.

Examples of substituents for aryl and aralkyl are phenyl substituted by fluorine, —OCH_3 or —CF_3 in the p-position.

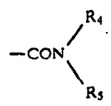
Examples of acyl are preferably those of up to 7 carbon atoms such as acetyl, propionyl, butyryl and benzoyl as well as valeryl, hexanoyl, acryloyl, crotonoyl, carbamoyl or formyl. The acyloxy may be derived for the same acids, especially acetyloxy and propionyloxy.

The esterified carboxy may be alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert.-butoxycarbonyl, cyclobutyloxy carbonyl, cyclopentyloxy carbonyl and cyclohexylocy carbonyl.

Examples of easily cleavable esters includes methoxymethyl, ethoxymethyl; acyloxyalkyl such as pivaloyloxymethyl, pivaloyloxyethyl, acetoxymethyl and

acetoxyethel; alkoxycarbonyloxyalkyl such as methoxycarbonyloxymethyl, methoxycarbonyloxyethyl, isopropoxycarbonyloxymethyl and isopropoxycarbonyloxyethyl. Other esters are described in European Patent No. 0.034.536.

The amidified carboxy are of the type



wherein R_4 and R_5 are individually selected from the group consisting of hydrogen and alkyl of 1 to 4carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and tert.-butyl.

Examples of the mono and dialkylamino are methylamino, ethylamino, dimethylamino, diethylamino and methylethylamino. The hetero-cyclic of 5 to 6 ring members optionally containing another heteroatom may be pyrrolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidyl, indolyl, piperidino, morpholino and piperazinyl, preferably piperidino or morpholino.

Examples of salts of salified carboxy are sodium, potassium, lithium, calcium, magnesium, ammonium and organic bases such as methylamine, propylamine, trimethylamine, diethylamine and triethylamine. Sodium salt is preferred.

The alkylamino and dialkylamino are preferably alkyl of 1 to 4 carbon atoms such as methylamino, ethylamino, propylamino, isopropylamino, dimethylamino, diethylamino and ethylmethylamino.

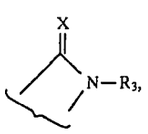
Examples of the heterocyclics containing at least one heteroatom are saturated monocyclics such as oxirannyl, oxolannyl, dioxolannyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl and morpholinyl.

The alkyl, alkenyl and alkynyl may be optionally interrupted by one or more sulfur, oxygen or nitrogen heteroatoms. Examples are alkoxyalkyl such as methoxymethyl, methoxyethyl, methoxypropyl or methoxybutyl or alkoxy alkoxyalkyl such as methoxyethoxymethyl.

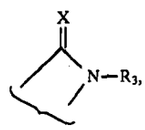
Examples of trialkylsilyl groups are trimethylsilyl, triethylsilyl and (1,1-dimethylethyl) dimethylsilyl.

When the products of formula I contain a salifiable amino group, the acid addition salts of non-toxic, pharmaceutically acceptable acids may be formed. Examples of said acids are inorganic acids such as nitric acid, hydrochloric acid, sulfuric acid and phosphoric acid and organic acids such as formic acid, acetic acid, propionic acid, benzoic acid and methane sulfonic acid.

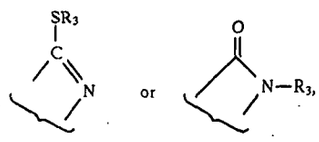
Among the preferred compounds of formula I are those wherein Y is oxygen except for the compounds wherein —A-B— is



X is oxygen, R_3 is hydrogen, R_2 is $—CF_3$ or halogen and R_1 is $—NO_2$ or halogen. Other preferred compounds of formula I are those wherein —A-B— is



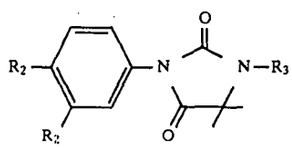
X is sulfur and R_3 has the above definition, those wherein R_3 is hydrogen or alkyl of 1 to 4 carbon atoms optionally substituted with —OH or methoxy, those wherein R_1 is cyano or halogen, preferably chlorine and those wherein —A-B— is



and R_3 is optionally substituted alkyl or alkenyl of up to 6 carbon atoms and optionally interrupted by oxygen or optionally oxidized sulfur or optionally substituted aralkyl, acyl or trialkylsilyl.

Other preferred examples of the invention are those in which R_3 is alkyl of up to 6 carbon atoms optionally substituted by at least one member of the group consisting of halogen, free or esterified hydroxy or carboxy, heterocyl, O-aralkyl or S-aryl in which the aryl radical is optionally substituted by at least one halogen or alkoxy and the sulfur atom is optionally oxidized in the form of the sulfoxide or sulfone and quite particularly those in which R_3 is alkyl of 2 to 4 carbon atoms substituted by a member of the group consisting of chlorine, ethoxycarbonyl, terbutoxycarbonyl, cyclopentyloxycarbonyl, 4-fluorophenylthio optionally oxidized in the form of the sulfoxide or sulfone, morpholino, phenylmethoxy, triphenylmethoxy and methylsulfonyloxy.

Other preferred compounds of formula I are those wherein R_3 is acetyl or benzoyl or (1,1-dimethylethyl) dimethylsilyl, those wherein R_1 is nitro and R_3 is alkyl or alkenyl of up to 4 carbon atoms optionally substituted with esterified or salified or free carboxy and those of the formula



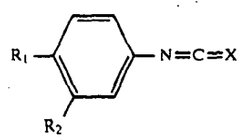
I

in which R_1, R_2 and R_3 have the above meaning with the exception of the products in which R_1 is nitro, R_2 is trifluoromethyl and R_3 is hydrogen.

Examples of specific preferred compounds of formula I are 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-(4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-[4,4-dimethyl 3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl]-2-(trifluoromethyl) benzonitrile, 3-(3,4-dichlorophenyl)-2-thioxo-1,5,5-trimethyl-4-imidazolidinone, 1-(4-nitro-3-(trifluoromethyl)-phenyl)-3,4,4-trimethyl-2,5-imidazolidinedione, 4-[[4,5-dihydro-4,4-dimethyl-5-oxo-2-benzyl-thio]-1H-imidzao-1-yl]-2-trifluoromethyl) benzonitrile, 4-[4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo

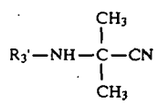
2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile and 3-(4-cyano 3-(trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoic acid.

The process of the invention for the preparation of a compound of formula I comprises either reacting a compound of the formula



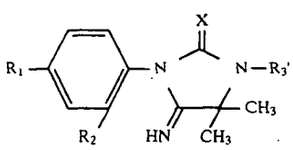
II

wherein R_1, R_2 and X have the above definitions with a compound of the formula



III

in the presence of a tertiary base wherein R'_3 has the definition of R_3 with reactive group optionally protected and if R_1 is $—NO_2$ or halogen, R_2 is halogen or $—CF_3$ and X is oxygen, R'_3 is not hydrogen to obtain a compound of the formula



IV

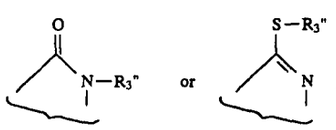
wherein R_1, R_2, X and R'_3 have the above definitions and optionally subjecting the latter to one or more of the following reactions in any order:

a) reaction to eliminate the optional protective groups of R'_3

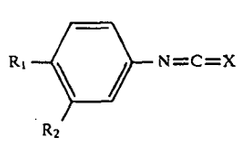
b) reaction of hydrolysis of C═NH to a ketone function or transformation of C═S to C═O

c) transformation reaction of C═O to C═S

d) and reacting the products of formula IV wherein R'_3 is hydrogen and after hydrolysis of C═NH to a ketone with a compound of the formula $R"_3$-Hal where Hal is a halogen and $R"_3$ is R'_3 except hydrogen to obtain a compound of formula I wherein —A-B— is

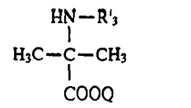


and optionally reacting the latter to eliminate the protective group of $R"_3$ or reacting the same with an esterification, salification or amidification agent or reacting a compound of the formula



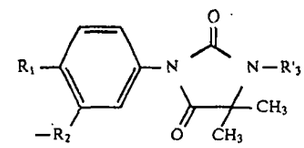
II

in which R_1, R_2 and X have the above meaning in the presence of a tertiary base with a product of the formula



III

in which R'_3 has the above meaning and Q is either an alkali metal for example sodium or alkyl of 1 to 6 carbon atoms to obtain a product of the formula



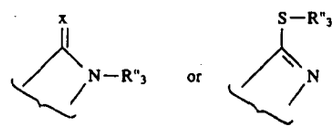
IVa

in which X, R_1, R_2 and R'_3 have the above meaning which if desired is subjected to any one or more of the following reactions in any order:

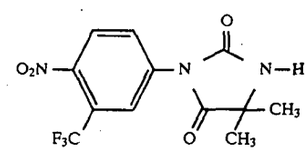
a) elimination reaction of the optional protective groups that can be carried by R'_3;

b) conversion reaction of the >C═O group or groups into the >C═S or if appropriate of >C═S into >C═O;

c) the action on the products of formula IVa in which R'_3 is hydrogen of a reagent of formula Hal—$R"_3$ in which $R"_3$ has the values of R'_3 with the exception of hydrogen and Hal is halogen to obtain the products of formula I in which —A-B— is

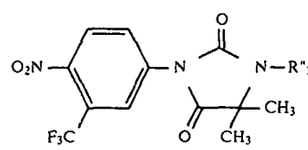


in which $R"_3$ has the above meaning, then, if desired, the action of these products of an elimination agent of the optional protective groups that can be carried by $R"_3$ or if appropriate, the action of an esterification, amidification or salification agent, or reacting a reagent of the formula $R"_3$—Hal as defined above with a compound of the formula



IV'

to obtain a compound of the formula



IV"

and optionally subjecting the latter to one or more of the following reactions:

a) elimination reaction of optional protective groups of $R"_3$ and then to reaction with an esterification, salification or amidification reagent

b) reaction of transformation of C═O to C═S.

The reaction of the products of formula II with the products of formula III is preferably effected in an organic solvent such as tetrahydrofuran or dichloroethane or ethyl ether or isopropyl ether in the presence of a tertiary base such as pyridine or methylethyl pyridine.

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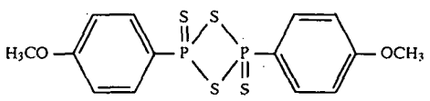
The optional reactive functional groups of R_3 which are optionally protected in compounds of formula III, IVa or IV" are —OH or amino which are protected by the usual protective groups. Examples of such protective groups for $—NH_2$ are tert.-butyl, tert.-amyl, trichloroacetyl, chloroacetyl, benzhydryl, trityl, formyl and benzyloxycarbonyl. Examples of hydroxy protective groups are formyl, chloroacetyl, tetrahydropyrannyl, trimethylsilyl and tert.-butyldimethylsilyl.

The above list of protective groups is not intended to be exhaustive and any protective group known, for example, in peptide chemistry may be used. Other known protective groups are described in French Patent No. 2,499,995 which is incorporated herein by reference. The optional reactions to eliminate groups are indicated in the said patent and the preferred method of elimination is acid hydrolysis with hydrochloric acid, benzene sulfonic acid, p-toluene sulfonic acid, formic acid or trifluoroacetic acid, preferably hydrochloric acid.

The optional reaction of hydrolysis of C=NH to C=O is preferably effected with an acid suchas refluxing aqueous hydrochloric acid. When the hydrolysis of C=NH into a C=O is effected with a molecule also containing C=S, the latter may be transformed in C=O group. The free hydroxy optionally contained in R_3 may also be transformed into —SH.

The transformation of the group C=O into C=S is effected with a Lawesson reagent of the formula



which is a commercial product sold by Fluka for example and is described in Bull. Soc. Chim. Belg., Vol 87 No. 3 (1987), p. 229. When two C=O groups are to be changed to C=S, the reaction is effected in an excess of the Lawesson reagent. The same is used also when the molecule contains both C=S and C=O and it is desired to change the C=O to C=S.

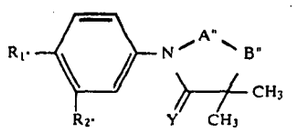
On the contrary, when part of the molecule contain two C=O and it is desired to obtain a product with only one C=S, a deficiency of the Lawesson reagent is used to obtain a mixture of 3 products, each of two products with a C=O and C=S and one containing two C=S. The said products can be separated by known methods such as chromatography.

The reaction of the compounds of formulae IV, IVA or IV' with a compound of the formula $R"_3$—Hal is effected in the presence of a strong base such as sodium hydride or potassium hydride in a phase transfer reaction in the presence of quaternary ammonium salts such as tert.-butyl ammonium. The protective groups of $R"_3$ may be those discussed above for R_3. The reaction to eliminate the protective groups are as discussed above. For example, a tert-butyl dimethylsilyl group may be removed by hydrochloric acid as described in the examples infra.

The optional esterification of the compounds of formula I wherein $R"_3$ is free —OH is effected under the classical conditions using for example an acid or a functional derivative thereof such as its anhydride like acetic acid anhydride in the presence of a base such as pyridine. The optional esterification or salification of the compounds of formula I wherein $R"_3$ is —COOH may be effected by known methods.

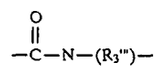
The optional amidification of the compounds of formula I wherein $R"_3$ is —COOH is effected also under classical conditions with primary or secondary amine with a functional derivative of —COOH such as a symetrical or mixed anhydride thereof.

The process of the invention to prepare compounds of the formula

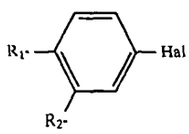


I

wherein $R"_1$, $R"_2$ and —A"-B"— have the definitions of R_1, R_2 and —A-B— except when —A"-B"— is

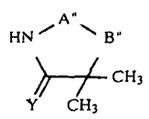


and $R'"_3$, is hydrogen or alkyl of 1 to 7 carbon atoms and Y is oxygen, $R"_1$ is —CN comprises reacting a compound of the formula



V

wherein $R"_1$ and $R"_2$ have the above definitions and Hal is halogen with a compound of the formula



VI

wherein —A"-B"— and Y have the above definitions in the presence of a catalyst and optionally a solvent. In the compounds of formula V, the halogen is preferably chlorine but may be iodine or bromine.

The role of the catalyst is obviously to trap the hydrogen halide as it forms and to facilitate the condensation reaction of the compounds of formulae V and VI to form the desired product. The catalyst is preferably a metal in its native form or its oxide or salt form or it may be a base. When the catalyst is a metal, it is preferably copper or nickel and the metallic salts are preferably the chloride or acetate. When the catalyst is a base, it is preferably sodium hydroxide or potassium hydroxide and dimethylsulfoxide may be added to the reaction medium.

The catalyst of the process may be selected from cuprous oxide, cupric oxide, metallic copper or a base such as sodium hydroxide or potassium hydroxide, preferably cuprous oxide in powdered form. The solvent used preferably is a high boiling point ether such as phenyl oxide, diglyme, triglyme and dimethylsulfoxide but also useful are high boiling point oils such as paraffin or vaseline. Preferably, the process is effected in another solvent such as phenyl oxide, diglyme, triglyme or dimethylsulfoxide, most preferably in phenyl oxide or triglyme.

The process may be effected at atmospheric pressure or under pressure at temperatures above 100° C., preferably above 150° C. for more than two hours. The reaction is preferably effected with cuprous oxide in triglyme at temperatures of 200° C. or higher for more than three hours.

The novel anti-androgenic compositions of the invention are comprised of an anti-androgenically effective amount of at least one compound of formula I and its non-toxic,

pharmaceutically acceptable acid addition salts and an inert pharmaceutical carrier. The compositions may be in the form of tablets, dragees, capsules, syrups, suppositories, creams, pomades, lotions or injectable solutions prepared in the usual manner.

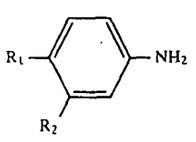
Examples of suitable excipients are aqueous or non-aqueous vehicles, arabic gum, lactose, starch, magnesium stearate, cocoa butter, fatty bodies of animal or vegetable origin, paraffinic derivatives, glycols, diverse wetting agents, dispersants or emulsifiers and preservatives.

The compositions inhibit the effect of androgens on peripherical receptors and have an anti-androgenic activity useful for therapy in adults without the certain effects of a chemical castration. The compositions are useful for the treatment of adenomas and neoplasies of the prostateas well as benign hypertrophia of the prostate as well as the treatment of benign or malignant tumors of cells containing androgen receptors. They are particularly useful for the treatment of breast, brain, skin and ovarian cancer and bladder, lymphatic system, liver and kidney cancers. They are equally useful for the treatment of hirsutism, acne, seborrhea, androgenic alopecia and hyperpilosity and in the veterinary field.

The compositions of the invention are useful in dermatology and can contain another ingredient such as an antibiotic such as derivatives of retinoids for the treatment of acne, or with a 5α-reductase inhibitor such as (5═, 17β)-1,1-dimethylethyl 3-oxo 4-aza-Δ^1-androstene-17 carboxamide (or Finasteride Merck, 11th ed.) or azelaic acid or a blocking agent of androgen receptors for the treatment of acne, alopecia or hirsutism, or with a product stimulating the growth of hair such as Minoxidil for the treatment of alopecia. The compositions can also be used in the veterinary domain and in the form of radioactive products, can also be used in diagnostics as specific labels for the androgen receptors. As radioactive products, the products labelled with tritium, with carbon 14 or also with iodine 125 can be used.

The novel method of the invention for inducing anti-androgenic activity in warm-blooded animals, including humans, comprises administering to warm-blooded animals an anti-androgenically effective amount of at least one compound of formula I and its non-toxic, pharmaceutically acceptable acid addition salts. The compounds may be administered parenterally, buccally, perlingually, rectally or topically and the usual daily dose is 0.133 to 6.66 mg/kg depending on the condition treated, the specific compound and the method of administration.

The starting compounds of formula II may be prepared by reacting phosgene when X is oxygen or thiophosgene when X is sulfur with an amine of the formula



A

A product of this type is described in French Patent No. 2,329,276. The amines of formula A are described in EP Patent No. 0,002,892 and French Patent No. 2,142,804.

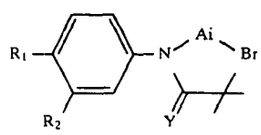
The products of formula III or III' are known or can be prepared from the corresponding cyanhydrin by the process of J. Am. Chem. Soc., Vol 75 (1953), p. 4841. The compounds of formula III wherein R'_3 is other than hydrogen may be obtained by reacting a compound of the formula R''_3 Hal with 2-cyano-2-amino-propane under the conditions described above for reacting the said halide with the compounds of formula IV. An example is described by Jilek et al, Collect. Czech. Chem. Comm., Vol 54(8) (1989), p. 2248. The products of formula IV' are described in French Patent No. 2,329,276.

The compounds of formulae V and VI are commercially available known compounds and can be prepared by known methods.

The preparation of the compounds of formula VI are described in the following publications: Zhur Preklad Khim., Vol. 28 (1955), p. 969–75 (CA, Vol. 50 (1956), p 4881a); Tetrahedron, Vol. 43 (1987), p. 1753; J. Org. Chem., Vol. 52 (1987), p. 2407; Zh. Org. Khim., Vol. 21 (1985), p. 2006; J. Fluor. Chem., Vol. 17 (1981), p. 345; German Patent No. 637,318, European Patent No. 0,130,875 and Japanese Patent No. 81-121,525.

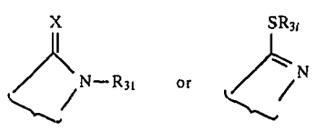
The products of formula VI which are derivatives of hydantoin are largely used and are known in the literature such as J. Pharm. Pharmacal., 67, Vol. 19(4) (1967), p. 209–16; J. Chem. Soc., Vol. 74(2) (1972), p. 219–221; Khim. Farm. Zh., Vol. 67(1)(5), p. 51–2; German Patent No. 2,217,914; European Patent No. 0,091,596 and J. Chem. Soc. Perkin. Trans. 1, Vol. 74(2), p. 48 and 219–221.

The novel intermediates of the invention are the compounds of the formula



[Vi

wherein R_1, R_2 and Y have the above definitions and —Ai-Bi— is



wherein X is oxygen or sulfur and R_3, is R_3 with the reactive groups protected among which are —OH or —NH_2 protected as above for R_3.

In the following examples, there are described several preferred embodiments to illustrate the invention. However, it should be understood that the invention is not intended to be limited to the specific embodiments.

EXAMPLE 1

1-(4-nitro-3-trifluoromethyl-phenyl)-3,4,4-trimethyl-2,5-imidazolidinedione

A solution of 3.17 g of 1-(3-trifluoromethyl-4-nitrophenyl)-4,4-dimethyl-imidazoline-2,5-dione (French Patent No. 2,329,276) and 32 ml of dimethylformamide were added at 23° C. to 26° C. to a 50% suspension of 492 mg of sodium hydride in oil and 3 ml of dimethylformamide and after stirring for 15 minutes, a solution of 0.7 ml of methyl iodide in 2 ml of dimethylformamide was added. The mixture was stirred for 25 minutes at 24° C. to 28° C. and was then poured into 200 g of a 1—1 water-ice mixture. The mixture was extracted with ether and the organic phase was washed with saturated aqueous sodium chloride, dried, filtered and evaporated to dryness under reduced pressure to obtain 3.6 g of the desired product melting at 116° C. An analytical sample was crystallized from isopropyl alcohol to obtain 2.73 g of the product melting at 116° C.

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Analysis: $C_{13}H_{12}F_3N_3O_4$: molecular weight = 331.25				
	% C	% H	% F	% N
Calculated:	47.14	3.65	17.20	12.68
Found:	47.0	3.5	17.1	12.5

IR Spectrum ($CHCl_3$):	
C=O	1780, 1727 cm^{-1}
aromatics	1615, 1596, 1497 cm^{-1}
NO_2	1545, 1357 cm^{-1}

EXAMPLE 2

5,5-dimethyl-1-ethyl-3-(4-nitro-3-trifluoromethylphenyl)-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazoline-2, 5-dione prepared as in French Patent No. 2,329,276 was reacted with 0.37ml of ethyl iodide and a 50% suspension of 166 mg of sodium hydride in oil to obtain 1.19 g of the desired product melting at 110° C. to 111° C. which was crystallized from isopropanolto obtain 934 mg of the product melting at 110° C. to 111° C.

Analysis: $C_{14}H_{14}F_3N_3O_4$: molecular weight = 345.28				
	% C	% H	% F	% N
Calculated:	48.70	4.09	16.51	12.17
Found:	48.6	4.0	16.8	12.1

IR Spectrum ($CHCl_3$):	
C=O	1777, 1724 cm^{-1}
NO_2	1545, 1356 cm^{-1}
aromatics	1614, 1596, 1497 cm^{-1}

EXAMPLE 3

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-propyl-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazoline-2, 5-dione was reacted with 0.35 ml of 1-iodopropane and a 50% suspension of 155mg of sodium hydride in oil to obtain after chromatography on silica with an eluant of acetone-methylene chloride (1–99), 3.087 g of raw product melting at 102° C. The product was crystallized from isopropanol to obtain 945 mg of the desired product melting at 102° C.

Analysis: $C_{15}H_{16}F_3N_3O_4$: molecular weight = 359.31				
	% C	% H	% F	% N
Calculated:	50.14	4.49	15.86	11.69
Found:	50.1	4.4	15.9	11.5

IR Spectrum ($CHCl_3$):	
C=O	1778, 1724 cm^{-1}
NO_2	1544, 1358 cm^{-1}
aromatics	1615, 1596, 1497 cm^{-1}

EXAMPLE 4

5,5-dimethyl-1-isopropyl-3-(4-nitor-3-trifluoromethylphenyl)-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazoline-2, 5-dione was reacted with 0.4 ml of 2-iodopropane and a 50% suspension or 166 mg of sodium hydride in oil for 18 hours at 50° C. to obtain after chromatography over silica (eluant methylene chloride-acetone 99–1), 685 mg of product melting at 130° C. which after crystallization from isopropanol yielded 661 of the desired product melting at 130° C.

Analysis: $C_{15}H_{16}N_3F_3O_4$: molecular weight = 359.31				
	% C	% H	% F	% N
Calculated:	50.14	4.49	15.86	11.69
Found:	50.1	4.4	16.2	11.6

IR Spectrum ($CHCl_3$):	
C=O	1779, 1771, 1723 cm^{-1}
NO_2	1544, 1361 cm^{-1}
aromatics	1615, 1596, 1497 cm^{-1}

EXAMPLE 5

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-(2-propenyl)-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-(henyl)-4,4-dimethyl imidazoline-2, 5-dione was reacted with 0.35 ml of allyl bromide and a 50% suspension of 166 mg of sodium hydride in oil to obtain after chromatography over silica (eluant—methylene chloride-acetone (99–1)) 1.10 g of product which after crystallization from isopropanol yielded 1.01 g of the desired product melting at 105° C.

Analysis: $C_{15}H_{14}F_3N_3O_4$: molecular weight = 357.29				
	% C	% H	% F	% N
Calculated:	50.42	3.95	15.95	11.76
Found:	50.4	3.8	15.8	11.7

IR Spectrum ($CHCl_3$):	
C=O	1779, 1724 cm^{-1}
NO_2	1545, 1358 cm^{-1}
aromatics	1615, 1596, 1497 cm^{-1}
$CH=CH_2$	1643, 930 cm^{-1}

EXAMPLE 6

5,5-dimethyl-3-(3-trifluoromethyl-4-nitro-phenyl)-1-benzyl-2,4-imidazolidinedione

Using the procedure of Example 1, 2 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazolidine-2,5-dione was reacted with 0.71 ml of benzyl bromide and a 50% suspension of 332 mg of sodium hydride in oil to obtain after chromatography on silica and elution with 99–1 methylene chloride-acetone 2.375 g of the desired product which as crystallized from isopropanol to obtain 2.165 g of product melting at 99° C.

Analysis: $C_{19}H_{16}N_3F_3O_4$: molecular weight = 407.3				
	% C	% H	% F	% N
Calculated:	56.02	3.96	10.31	14.00
Found:	56.1	3.8	10.2	13.9

-continued

IR Spectrum ($CHCl_3$):	
C=O	1799, 1723 cm^{-1}
aromatics	1608 cm^{-1}
+	1594 cm^{-1} (m)
NO_2	1545 cm^{-1} (F)
	1497 cm^{-1}

EXAMPLE 7

4-(4,4-dimethyl-5-imino-2-oxo-1-imidazolidinyl)-2-trifluoromethylbenzonitrile

A solution of 10 g of 4-cyano-3-trifluoromethyl-aniline (described in European Paten No. 0,002,892) in 30 ml of ethyl acetate was added at 0° to 5° C. to 33.6 ml of a toluene solution of 1.93 M/l of phosgene and after stirring at 0 to 5° C. for 30 minutes, the temperature was raised to 25° C. The mixture was distilled while introducing fresh toluene maintaining to constant level for compensate the distilled volume of toluene until a temperature of about 110° C. was reached. The mixture was held at reflux until the disengagement of hydrogen chloride ceased (4 ½ hours). The temperature returned to room temperature and the white solid was dried over sodium sulfate and was rinsed with toluene 3 times. The organic phase was evaporated to dryness under reduced pressure, heated at60° C. for one hour and then cooled under argon to obtain 11.6 g of 4-isocyanate of 2-trifluoromethylbenzonitrile.

IR Spectrum:	
—NC=O	2268 cm^{-1}
—CN	2233 cm^{-1}

A solution of 6.6 g of 4-isocyanate of 2-trifluoromethylbenzonitrile in 10 ml of dichloroethane was added at 5° C. to a solution of 2.63 g of 2-amino-2-cyano-propane and 36 ml of dichloroethane and 0.9 ml of triethylamine and after stirring 16hours at room temperature, the mixture was evaporated to dryness. The 7.7 g of residue were chromatographed on silica and eluted with a 85–15 methylene chloride-acetone mixture to obtain 3.54 g of the desired product melting at 228° C. An analytical sample was prepared by crystallizing 300 mg from isopropanol to obtain 267 mg of the product melting at 228° C.

Analysis: $C_{13}H_{11}F_3N_3O_4$: molecular weight = 296.25

	% C	% H	% F	% N
Calculated:	52.71	3.74	19.24	18.91
Found:	52.7	2.6	19.1	18.6

IR Spectrum (Nujol):	
NH/OH	3340, 3290 cm^{-1}
CN	2240 cm^{-1}
C=O	1760 cm^{-1}
C=N	1655 cm^{-1}
aromatics	1606, 1570, 1502 cm^{-1}

EXAMPLE 8

4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-trifluoromethylbenzonitrile

A solution of 2.76 g of the product of Example 7 and 60 ml of 0.5 hydrochloric acid was refluxed for 35 minutes and was poured into 100 g of water and ice. The mixture was extracted with ethyl acetate and the organic phase was washed with water, dried and evaporated to dryness under reduced pressure to obtain 2.70 g of the desired product melting at 210° C. An analytical sample was obtained by crystallizing 440 mg of product from isopropanol to obtain 383 mg of product melting at 210° C. to 211° C.

Analysis: $C_{13}H_{10}F_3N_3O_4$: molecular weight = 297.24

	% C	% H	% F	% N
Calculated:	52.53	3.39	19.17	14.14
Found:	52.4	3.2	19.4	13.9

IR Spectrum ($CHCl_3$):	
CN	2245 cm^{-1}
C=O	1788, 1722 cm^{-1}
aromatics	1610, 1572, 1502 cm^{-1}
NH(max)	3340 cm^{-1}

EXAMPLE 9

3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2,4-dioxo-1-imidazolidine acetic acid

A solution of 600 mg of the product of Example 8 in 6 ml of dimethylformamide was added with stirring over 15 minutes to a suspension of a 50% suspension of 210 mg of sodium hydride in oil in 3 ml of dimethylformamide and after the addition of 290 mg of bromoacetic acid, the mixture was stirred for 16 hours at room temperature. After another 105 mg of sodium hydride were added, 145 mg of bromoacetic acid were added to the mixture which was stirred for 30 minutes and then poured into a mixture of 50 ml of water and 5 ml of 2N hydrochloric acid. The mixture was extracted with ether and the organic phase was washed with saturated aqueous sodium chloride, dried, filtered and evaporated to dryness under reduced pressure. The 1.22 g of residue were chromatographed on silica and eluted with a 90-10-0.5 methylene chloride-methanol-acetic acid mixture to obtain 367 mg of the desired product.

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}
C=O hydantoin & acid	1784, 1725, 1710 cm^{-1}
aromatic	1616, 1580, 1508 cm^{-1}

Ultra-violet Spectrum:		
ETOH - 0.1N HCl	max 258 nm	ϵ = 13,300
	inflex 277 nm	ϵ = 5,000
	inflex 285 nm	ϵ = 2,600
ETOH 0.1N NaOH	max 287 nm	ϵ = 19,100
	max 342 nm	ϵ = 1,900

EXAMPLE 10

Ethyl3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2,4-dioxo-1-imidazolidine-acetate

A solution of 600 mg of the product of Example 8 in6 ml of dimethylformamide was added to a 50% suspension of 100 mg of sodium hydride in oil and 3 ml of dimethylformamide and after stirring for 15 minutes, 0.25 ml of ethyl bromoacetate was slowly added at less than 30° C. The mixture was stirred for 30 minutes and then was poured into

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50 g of a 1—1 ice-water mixture. 0.5 g of monopotassium phosphate was added and the mixture was extracted with ether. The organic phase was washed with water, dried and evaporated to dryness to obtain 1.1 g of residue which was chromatographed on silica and eluted with 97-3 methylene chloride-acetone to obtain 709 mg of the desired product melting at 152° C. An analytical sample was prepared by crystallization from isopropanol to obtain 667 mg of the desired product melting at 152° C.

Analysis: $C_{12}H_{16}N_3F_3O_4$: molecular weight = 383.33

	% C	% H	% F	% N
Calculated:	53.21	4.21	14.83	10.96
Found:	53.3	4.0	14.9	10.8

IR Spectrum ($CHCl_3$):

CN	2225 cm^{-1}
imidazolidine	1786, 1729 cm^{-1}
COOEt	1751 cm^{-1}
aromatics	1616, 1572, 1505 cm^{-1}

EXAMPLE 11

4-(5-imino-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

2.23 of 1-trifluoromethyl-4-amino-benzonitrile (described in European Patent No. 0,002,892)were slowly added to a solution of 22 ml of distilled water and 1 ml of thiophosgene and after stirring for one hour, the mixture was extracted with chloroform. The organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness under reduced pressure to obtain 3 g of isocyanate product which as used as is.

A mixture of the 3 g of product, 1.33 ml of 2-methylamino-2-cyano-propane, 23 ml of tetrahydrofuran and 0.23 ml of triethylamine was refluxed for 40 minutes and was evaporated to dryness. The 3.07 g of residue were chromatographed on silica and eluted with a 1—1 cyclohexane-ethyl acetate mixture and then a 95-5 methylene chloride-acetone mixture to obtain 2.83 g of product which was crystallized from isopropanol to obtain 2.63 g of the desired product melting at 173° C. to 174° C.

Analysis: $C_{14}H_{13}F_3N_4S$: molecular weight = 326.35

	% C	% H	% F	% N	% S
Calculated:	51.53	4.01	17.17	17.46	9.82
Found:	51.7	3.9	17.2	17.2	9.9

IR Spectrum ($CHCl_3$):

C=NH	3308, 1679 cm^{-1}
C=S + aromatics	1608, 1575, 1505, 1488 cm^{-1}
CN	2230 cm^{-1}
CF_3	1185 cm^{-1}

EXAMPLE 12

4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

A mixture of 2.21 g of the product of Example 11and 44 ml of 0.5 N hydrochloric acid was refluxed with stirring for one hour and was then poured into 200 g of an ice-water (1—1) mixture. The mixture was extracted with methylene chloride and the organic phase was washed with saturated aqueous sodium chloride, dried and evaporated to dryness. The residue was chromatographed on silica and eluted with a 1—1cyclohexane-ethyl acetate mixture to obtain 2.1 g of product melting at171° C. which was crystallized from isopropanol to obtain 1.99 g of the desired product melting at 171° C.

Analysis: $C_{14}H_{12}F_3N_3OS$: molecular weight = 327.33

	% C	% H	% F	% N	% S
Calculated:	51.37	3.69	12.84	17.41	9.79
Found:	51.4	3.5	12.7	17.6	10.79

IR Spectrum ($CHCl_3$):

C=O	1761, 1756 cm^{-1}
aromatics	1610, 1578, 1505 cm^{-1}
CN	2230 cm^{-1}
CF_3	1178 cm^{-1}

EXAMPLE 13

4-(2,5-dithioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

A mixture of 839 mg of the product of Example 12, 518 mg of Lawesson reagent and 4.7 ml of toluene was refluxed for 24 hours and was then evaporated to dryness under reduced pressure. The 1.36 g of residue were chromatographed on silica and eluted with a 99-1 methylene chloride-ethyl acetate mixture and then an 85-15 cyclohexane-ethylacetate mixture to obtain 783 mg of product which was crystallized from isopropanol to obtain 690 mg of the desired product melting at 211° C. to 212° C.

Analysis: $C_{14}H_{12}F_3N_3S_2$: molecular weight = 343.40

	% C	% H	% F	% N	% S
Calculated:	48.97	3.52	16.60	12.24	18.67
Found:	49.0	3.4	16.6	12.2	18.6

IR Spectrum ($CHCl_3$):

CN	2230 cm^{-1}
aromatics + conjugated system	1612, 1582, 1508 cm^{-1}
CF_3	1178 cm^{-1}

EXAMPLE 14

4-(4,4-dimethyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

1 g of 2-amino-2-cyano-propane and 1 ml of tetrahydrofuran were added with stirring to a mixture of 2.54 g of the isocyanate product of Example 11, 20 ml of tetrahydrofuran and 0.2 ml of triethylamine at room temperature and was then evaporated to dryness. The 3.5 g of residue were chromatographed on silica and eluted with a 7-3 ethyl acetate-cyclohexane mixture and then a 1—1 ethyl acetate-cyclohexane mixture to obtain 940 mg of the desired product. 300 g were crystallized from isopropanol to obtain 263 mg of product melting at296° C.

Analysis: $C_{12}H_{11}F_3N_4S$: molecular weight = 312.32

	% C	% H	% F	% N	% S
Calculated:	50.00	3.55	18.25	17.94	10.27
Found:	49.9	3.4	18.3	17.6	10.4

IR Spectrum (Nujol):

OH/NH	3260 cm^{-1}
CN	2230 cm^{-1}
C=S	1764 cm^{-1}
aromatic + C=C	1612, 1575, 1530, 1501 cm^{-1}

A new preparation was effected using 1,2-dichloroethane in place of tetrahydrofuran to obtain the product in a 60% yield.

EXAMPLE 15

4-(4,4-dimethyl-5-oxo-3-thioxo-1-imidazolidinyl)-1-trifluoromethyl-benzonitrile

A mixture of 635 mg of the product of Example 14 and 14 ml of 0.5 N hydrochloric acid was stirred for one hour at reflux and after cooling, 100 ml of water were added. The mixture was extracted with ethyl acetate and the organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness. The 600 mg of residue were chromatographed and eluted with a 95-5 methylene chloride-acetone mixture to obtain 590 mg of product melting at 190° C. to 191° C. The latter was crystallized from isopropanol to obtain 490 mg of product melting to 190° C. to 191° C.

Analysis: $C_{13}H_{10}F_3N_5OS$: molecular weight = 313.50

	% C	% H	% F	% N	% S
Calculated:	49.84	3.22	18.19	13.41	10.23
Found:	49.6	3.1	18.4	13.2	10.0

IR Spectrum ($CHCl_3$):

=C—NH	3430 cm^{-1}
CN	2230 cm^{-1}
C=O	1766 cm^{-1}
aromatics and conjugated system	1612, 1578, 1505 cm^{-1}

EXAMPLE 16

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-pentyl-2,4-imidazolidine

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazolidien-2,5-dione was reacted with 170 mg of sodium hydride and 0.47 ml of 1-bromo-pentane to obtain after chromatography on silica and elution with an 8-2 methylene chloride-cyclohexane mixture 1.23 g of product which as crystallized from isopropanol to obtain 995 mg of the desired product melting at 84° C.

Analysis: $C_{17}H_{20}O_4F_3N_3$: molecular weight = 387.35

	% C	% H	% F	% N
Calculated:	52.71	5.20	14.71	10.85
Found:	52.8	5.1	14.8	10.7

-continued

IR Spectrum ($CHCl_3$):

C=O	1778, 1723 cm^{-1}
NO_2	1544, 1360 cm^{-1}

EXAMPLE 17

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-nonyl-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazolidine-2,5-dione was reacted with a 50% suspension of 170 mg of sodium hydride in oil and 0.7 ml of 1-bromononane to obtain after chromatography on silica 1.08 g of the desired product melting at 63° C.

Analysis: $C_{21}H_{28}O_4F_3N_3$: molecular weight = 443.46

	% C	% H	% F	% N
Calculated:	56.87	6.36	12.85	9.48
Found:	57.0	6.5	12.8	9.5

IR Spectrum ($CHCl_3$):

C=O	1788, 1723 cm^{-1}
NO_2	1544, 1359 cm^{-1}
C=O	1778, 1723 cm^{-1}
NO_2	1544, 1360 cm^{-1}

EXAMPLE 17

5,5-dimethyl-3-(4-nitro-3-trifluoromethyl-phenyl)-1-nonyl-2,4-imidazolidinedione

Using the procedure of Example 1, 1 g of 1-(3-trifluoromethyl-4-nitro-phenyl)-4,4-dimethyl imidazolidine-2,5-dione prepared from a 50% suspension of 170 mg of sodium hydride in oil and 0.7 ml of 1-bromononane were reacted to obtain after chromatography on silica 1.08 g of the desired product melting at 63° C.

Analysis: $C_{21}H_{28}O_4F_3N_3$: molecular weight = 443.46

	% C	% H	% F	% N
Calculated:	56.87	6.36	12.85	9.48
Found:	57.0	6.5	12.8	9.5

IR Spectrum ($CHCl_3$):

C=O	1788, 1723 cm^{-1}
NO_2	1544, 1359 cm^{-1}

EXAMPLE 18

4-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile

Using the procedure of Example 1, 300 mg of the product of Example 8 were reacted to obtain 275 mg of the desired product melting at 158° C.

IR Spectrum ($CHCl_3$):	
C=O	1780, 1727 cm^{-1}
aromatics	1615, 1574, 1505 cm^{-1}
CN	2238 cm^{-1}

EXAMPLE 19

4-(5-thioxo-2-oxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (product A), 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl benzonitrile (product B) and 4-(2,5-dithioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (product C)

A suspension of 230 mg of the product of Example 18, 1.4 ml of toluene and 78 mg of Lawesson reagent was refluxed for 9 hours and then returned to room temperature and evaporated to dryness. The 330 mg of residue was chromatographed on silica and eluted with a 99–1 methylenechloride-acetone mixture to obtain in the following order of elution 46 mg of product C with a melting point of 210° C. to 211° C. and a Rf=0.63 (identical to the product of Example 13), 26 mg of product B with a melting point of 170° C. to 171° C. and a Rf=0.49 (identical to the product of Example 12) and 42 mg of product A with a melting point of 194° C. and a Rf=0.34.

Analysis for Product A		
IR Spectrum ($CHCl_3$):		
C=O	1760 cm^{-1}	
CN	2235 cm^{-1}	
aromatics	1615, 1580, 1506 cm^{-1}	
UV Spectrum (ethanol):		
max	228 nm	ϵ = 19,400
	256 nm	ϵ = 12,100
	298 nm	ϵ = 8,600
	390 nm	ϵ = 70

EXAMPLE 20

4-(4,5-dihydro-4,4-dimethyl-2-methylthio-5-oxo-1H-imidazolidin-1-yl)-2-trifluoromethyl benzonitrile

A solution of 626 mg of the product of Example 15 in 6 ml of dimethylformamide was added to a 50% suspension of 108 mg of sodium hydride in oil and 1.8 ml of dimethylformamide and after rinsing with 0.3 ml of dimethylformamide, the mixture was stirred for 10 minutes after cessation of hydrogen evolution. A mixture of 0.19 ml of methyliodide in 1 ml of dimethylformamide was added dropwise and after 45 minutes of reaction, the mixture was poured into 50 g of an ice-water mixture containing 0.5 g of monosodium phosphate. The mixture was extracted4times with ether and the combined organic phases were washed with aqueous sodium chloride, dried over magnesium sulfate and evaporated to dryness. The 668 mg of residue were chromatographed on silica and eluted with a 95-5 dichloromethane-ethyl acetate mixture to obtain 640mg of the desired product which chromatographed again on silica. Elution with a 7-3 cyclohexane-ethyl acetate mixture yielded after taking up in ether 507mg of the desired product melting at62° C.

IR Spectrum:	
C=O	1747 cm^{-1}
C=N and aromatics	1614, 1581, 1563, 1503 cm^{-1}

UV Spectrum (ethanol):		
max	209 nm	ϵ = 26,000
inflex.	236 nm	ϵ = 11,500
inflex.	264 nm	ϵ = 8,700

EXAMPLE 21

4-(4,5-dihydro-4,4-dimethyl-5-oxo-2-benzylthio)-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile

A solution of 313 mg of 4-(4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile in 3 ml of dimethylformamide were added to a suspension of 53 mg of sodium hydride in oil and 0.5 ml of dimethylformamide and after stirring for 10 minutes, 0.1 ml of benzyl bromide were added. The mixture was stirred for 30 minutes and then poured into an ice-water mixture containing 500 mg of monosodium phosphate. The mixture was extracted with ether and the organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness. The 450 mg of residue were chromatographed on silica and eluted with a 97.5-2.5 methylene chloride-ethyl acetate mixture to obtain 316mg of the desired product with a RF=0.38.

Analysis:	% C	% H	% F	% N
Calculated:	59.54	4.0	14.12	10.41
Found:	59.6	4.0	14.1	10.2

IR Spectrum ($CHCl_3$):	
C=O	1746 cm^{-1}
CN	2236 cm^{-1}
aromatics and conjugated system	1614, 1580, 1570, 1503, 1499 cm^{-1}

EXAMPLE 22

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-imino-2-thioxo-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile

8 ml of ethanoline were added dropwise at 20° C. to 30° C. to 12.3 ml of the cyanhydrin of acetone and after stirring for 18 hours, the mixture was distilled to obtain 2.3 g of a mixture of 2-(2-hydroxyethyl)-amino-2-methyl-propanenitrile and 2,2-dimethyloxazolidine which was used as is for the next step.

A mixture of 1.18 g of the said mixture, 2.11 g of the isothiocyanate of Example 11 and 20 ml of tetrahydrofuran and 0.5 ml of triethylamine was refluxed for 30 minutes and then evaporated to dryness. The residue was chromatographed on silica and eluted with a 95–5 methylene chloride-acetone mixture to obtain 1.26 g of the desired product and 686 mg of N-(4-cyano-2-trifluoromethyl-phenyl)-2,2-dimethyl-3-oxazolidine carbothioamide. The 686 mg were dissolved in 10 ml of ethyl acetate and after the addition of 30 ml of cyclohexane, the mixture was concentrated to 4 ml and vacuum filtered and dried to obtain

another 518 mg of product. The raw product was dissolved in 20 ml of isopropanol and the solution was concentrated to 5 ml, vacuum filtered and dried to obtain 1.04 g of the desired product melting at 181° C.

Analysis:	% C	% H	% F	% N	% S
Calculated:	50.55	4.24	16.00	15.72	9.00
Found:	50.4	4.1	15.9	15.6	9.0

IR Spectrum ($CHCl_3$):	
OH	3630 cm^{-1}
=NH	3314, 1677 cm^{-1}
CN	2230 cm^{-1}
aromatics	1611, 1576, 1504 cm^{-1}

EXAMPLE 23

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile (Product A) and 4-(4,4-dimethyl-2,5-dioxo-3-(2-mercaptoethyl) 1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (Product B)

A mixture of 680 mg of the product of Example 22, 7 ml of water and 7 ml of hydrochloric acid was refluxed for 10 minutes and after cooling to room temperature, the mixture was extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness. The residue was chromatographed on silica and eluted with a 1—1 cyclohexane-ethyl acetate mixture to obtain 119 mg of product B with a Rf=0.35 and 569 mg of product A with a Rf=0.14 and a melting point of ≈130° C.

Analysis: $C_{15}H_{14}F_3N_3O_2S$: molecular weight = 357.36

	% C	% H	% F	% N	% S
Calculated:	50.42	3.95	15.95	11.76	8.97
Product A Found:	50.7	4.0	15.7	11.5	9.2
Product B Found:	50.6	3.8	15.9	11.6	9.1

IR Spectrum ($CHCl_3$):	
Product A:	
OH	3626 cm^{-1}
CN	2236 cm^{-1}
C=O	1763 cm^{-1}
aromatics	1615, 1578, 1504 cm^{-1}
Product B:	
Absence of OH	
CN	2228 cm^{-1}
C=O	1780, 1726 cm^{-1}
aromatics	1615, 1578, 1505 cm^{-1}

Using 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile of Example 8 and the appropriate reactants, the following products were prepared.

EXAMPLE 24

4-(4,4-dimethyl-2,5-dioxo-3-ethyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile with a melting point of 100° C. to 101° C.

Analysis: $C_{15}H_{14}F_3N_3O_2$: molecular weight = 325.29

	% C	% H	% F	% N
Calculated:	55.39	4.34	17.52	12.92
Found:	55.7	4.3	17.6	12.8

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}
C=O	1777, 1724 cm^{-1}
aromatics	1617, 1575, 1505 cm^{-1}

EXAMPLE 25

4-(4,4-dimethyl-2,5-dioxo-3-(2-propenyl)-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 109° C. to 110° C.

Analysis: $C_{15}H_{14}F_3N_3O_2$: molecular weight = 337.35

	% C	% H	% F	% N
Calculated:	56.97	4.18	16.90	12.46
Found:	57.0	4.1	16.2	12.3

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}
C=O	1728, 1725 cm^{-1}
$HC=CH_2$	1645 cm^{-1}
aromatics	1616, 1575, 1505 cm^{-1}

EXAMPLE 26

4-(4,4-dimethyl-2,5-dioxo-3-benzyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 98° C. to 99° C.

Analysis: $C_{20}H_{16}F_3N_3O_2$: molecular weight = 387.36

	% C	% H	% F	% N
Calculated:	62.01	4.16	14.71	10.85
Found:	62.0	4.1	14.7	10.8

IR Spectrum ($CHCl_3$): C—NH: 3430 cm^{-1}

CN	2238 cm^{-1}
C=O	1779, 1724 cm^{-1}
aromatics	1615, 1605, 1575, 1504, 1497 cm^{-1}

EXAMPLE 27

4-(4,4-dimethyl-2,5-dioxo-3-(4-fluorobenzyl)-1-imidazolidinyl-2-trifluoromethyl-benzonitrile melting at 101°° C. to 102° C.

Analysis: $C_{20}H_{15}F_4N_3O_2$: molecular weight = 405.35

	% C	% H	% F	% N
Calculated:	59.26	3.73	18.75	10.37
Found:	59.1	3.5	18.9	10.3

-continued

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}
C=O	1780, 1724 cm^{-1}
aromatics	1615, 1612, 1505 cm^{-1}

EXAMPLE 28

4-(4,4-dimethyl-2,5-dioxo-3-(4-methoxybenzyl)-1-imidazolidinyl-benzonitrile melting at 95° C. to 96° C.

Analysis: $C_{21}H_{18}F_3N_3O_3$: molecular weight = 417.39

	% C	% H	% F	% N
Calculated:	60.43	4.35	13.65	10.07
Found:	59.1	3.5	18.9	10.3

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}
C=O	1778, 1723 cm^{-1}
aromatics	1615, 1584, 1514, 1505 cm^{-1}

EXAMPLE 29

4-(4,4-dimethyl-2,5-dioxo-3-(4-trifluoromethyl-benzyl)-1-imidazolidinyl)-2-trifluoromethyl benzonitrile melting at ≈89° C. to 90° C.

Analysis: $C_{21}H_{15}F_6N_3O_2$: molecular weight = 313.30

	% C	% H	% F	% N
Calculated:	55.39	3.32	25.03	9.23
Found:	55.2	3.2	25.3	9.2

IR Spectrum ($CHCl_3$):	
CN	2238 cm^{-1}
C=O	1615, 1505 cm^{-1}
aromatics	1615, 1505 cm^{-1}

EXAMPLE 30

4-(4,4-dimethyl-2,5-dioxo-3-(2-epoxymethyl)-1-imidazolidinyl 2-trifluoromethyl-benzonitrile melting at 112° C. to 113° C.

Analysis: $C_{16}H_{14}F_3N_3O_3$: molecular weight = 353.30

	% C	% H	% F	% N
Calculated:	54.39	3.99	16.13	11.89
Found:	54.7	4.0	16.1	11.8

IR Spectrum ($CHCl_3$):	
CN	2235 cm^{-1}
C=O	1781, 1725 cm^{-1}
aromatics	1615, 1576, 1505 cm^{-1}

EXAMPLE 31

4-(4,4-dimethyl-2,5-dioxo-3-propyl-1H-imidazolidinyl)-2-trifluoromethyl benzonitrile melting at 113° C. to 114° C.

Analysis: $C_{16}H_{16}F_3N_3O_2$: molecular weight = 339.32

	% C	% H	% F	% N
Calculated:	56.64	4.75	16.80	12.38
Found:	56.7	4.7	16.7	12.2

IR Spectrum ($CHCl_3$):	
CN	2236 cm^{-1}
C=O	1778, 1725 cm^{-1}
aromatics	1616, 1505 cm^{-1}

EXAMPLE 32

4-(4,4-dimethyl-2,5-dioxo-3-isopropyl-1-imidazolidinyl) -2-trifluoromethyl benzonitrile melting at 138° C. to 139° C.

Analysis: $C_{16}H_{16}F_3N_3O_2$: molecular weight = 339.32

	% C	% H	% F	% N
Calculated:	56.64	4.75	16.80	12.38
Found:	56.5	4.7	17.1	12.3

IR Spectrum ($CHCl_3$):	
CN	2236 cm^{-1}
C=O	1778, 1724 cm^{-1}
aromatics	1616, 1575, 1505 cm^{-1}

Using 4-(4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile of Example 15 and the appropriate reactants, the following compounds were prepared:

EXAMPLE 33

4-(4,5-dihydro-4,4-dimethyl-2-nonylthio-5-oxo-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile were a Rf=0.35 (97.5–2.5 methylene chloride-ethyl acetate eluant).

EXAMPLE 34

4-(4,5-dihydro-4,5-dimethyl-2-(3-hydroxypropylthio)-5-oxo-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile with a Rf=0.17 (8–2 methylene chloride-ethyl acetate eluant).

EXAMPLE 35

Ethyl [1-(4-cyano-3-trifluoromethyl-phenyl)-4,5-dihydro-4,4-dimethyl-5-oxo-1H-imidazol 2-yl)-thio]-acetate with a Rf=0.20 (65–35 cyclohexane-ethyl acetate eluant).

Using the isocyanate or Example 11 and the appropriate reactants, the following compounds were prepared.

EXAMPLE 36

4-(4,4-dimethyl-3-ethyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile with a Rf=0.16 (95-5 methylene chloride-acetone eluant).

EXAMPLE 37

4-(4,4-dimethyl-5-imino-3-pentyl-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile with a RF=0.35 (8-2 ethyl acetate-cyclohexane eluant)

Using the 4-(4,4-dimethyl-3-ethyl-5-imino-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile of Example

36 and the 4-(4,4-dimethyl-5-imino-3-pentyl-2-thioxo-1-imidazolidinyl) 2-trifuoromethyl-benzonitrile of Example 37 and 0.5 N hydrochloric acid, the following compounds were prepared.

EXAMPLE 38

4-(4,4-dimethyl-3-ethyl-5-oxo-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile with a Rf=0.38 (1—1 ethyl acetate-cyclohexane eluant).

EXAMPLE 39

4-(4,4-dimethyl-5-oxo-3-pentyl-2-thioxo-1-imidazolidinyl)-2-trifluoromethyl benzonitrile with a melting point of 78° C. and a Rf=0.66 (8-2 ethyl acetate-cyclohexane eluant)

Using 4-(4,5-dihydro-4,4-dimethyl-2-methylthio-5-oxo-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile of Example 20 and 4-(4,5-dihydro-4,4-dimethyl-5-oxo-2-benzylthio-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile of Example 21 and the Lawesson reagent, the following compounds were prepared.

EXAMPLE 40

4-(4,5-dihydro-4,4-dimethyl-2-methylthio-5-thioxo-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile with a Rf=0.36 (97.5-2.5 methylene chloride-ethyl acetate eluant).

EXAMPLE 41

4-(4,5-dihydro-4,4-dimethyl-2-benzylthio-5-thioxo-1H-imidazol-1-yl) 2-trifluoromethyl-benzonitrile with a Rf=0.62 (98-2 methylene chloride-ethyl acetate eluant).

EXAMPLE 42

3-(4-cyano-3-trifluoromethyl-penyl)-5,5-dimethyl-2,4-dioxo-N-methyl-N-isopropyl-1-imidazolidine acetamide

0.1 ml of N-methyl-morpholine was added to a suspension of 3-(4-cyano-3-trifluoromethyl-phenyl)-5,5-dimethyl-2,4-dioxo-1-acetic acid in 4 ml of methylene chloride and after cooling the solution to −10° C., 0.1 ml of isobutyl chloroformate was added dropwise. After stirring for 25 minutes at −10° C., 0.15 ml of N-methyl-N-isopropylamine was added and the mixture was allowed to return to room temperature over 40 minutes. 5 ml of an aqueous saturated sodium bicarbonate solution were added and after stirring for 30 minutes, the mixture was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The residue was chromatographed on silica and eluted with a 96-4 methylene chloride-acetone mixture to obtain 147 mg of the desired product.

IR Spectrum ($CHCl_3$):	
CN	2236 cm^{-1}
hydantoin C=O	1783, 1728 cm^{-1}
amide C=O	1661 cm^{-1}

IR Spectrum ($CHCl_3$):	
aromatics	1615, 1575, 1505 cm^{-1}

EXAMPLE 43

4-(4,4-dimethyl-2,5-dioxo-3-(2-hydroxyethyl)-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile

Using the procedure of Example 9, 900 mg of the product of Example 8 and 1.91 g of 2-bromoethane tert.-butyldimethylsilyl ether were reacted to obtain 1 g of the silyloxy ether derivative melting at 86° C. to 87° C. after chromatography on silica and elution with a 7 g cyclohexane-ethyl acetate mixture.

1 ml of 2 N hydrochloric acid were added to a mixture of 380 mg of the silyloxy ether, 4 ml of methanol and 1 ml of methylene chloride and after stirring for 40 minutes at room temperature,the mixture was poured into 15 ml of water and was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness and the residue was chromatographed on silica. Elution with a 7-3 methylene chloride-ethyl acetate mixture yielded the desired product which after crystallization from isopropanol melted at 109° C. to 110° C. and had a Rf=0.9.

	Analysis:			
	% C	% H	% F	% N
Calculated:	52.79	4.23	16.70	12.31
Found:	52.5	4.2	16.7	12.1

EXAMPLE 44

Using the procedure of Example 43, 2-bromopropanol tert.-butyldimethylsilyl ether was reacted to obtain 4-(4,4-dimethyl-2,5-dioxo-3-(3-hydroxypropyl) 1-imidazolidinyl)-2-trifluoromethyl-benzonitrile melting at 131° C. to 132° C. and a Rf=0.13 (3-1 methylene chloride-ethyl acetate eluant).

EXAMPLE 45

4-[3-(2-acetyloxyethyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]2-trifluoromethyl-benzonitrile

A mixture of 215 mg of the product of Example 43, 15 mg of 4-dimethylamino-pyridine, 1 ml of pyridine and 0.5 ml of acetic acid anhydride was stirred at room temperature for 30 minutes and was then poured into 20 ml of a saturated aqueous sodium bicarbonate solution. After stirring for 20 minutes, the mixture was extracted with ethyl acetate. The organic phase was washed with water and evaporated to dryness and the pyridine and residual acetic acid were distilled. The residue was chromatographed on silica and eluted with a 65-35 methylene chloride-ethyl acetate mixture. The residue with a Rf=0.35 was taken up in isopropanol, partially concentrated, iced and vacuum filtered to obtain after drying 210 mg of the desired product melting at 99° C. to 100° C.

	Analysis:			
	% C	% H	% F	% N
Calculated:	53.27	4.21	14.87	10.96
Found	53.5	4.3	15.2	10.9

Using the above procedure, the following products were prepared.

EXAMPLE 46

4-(4,4-dimethyl-2,5-dioxo-3-(5-hydroxypentyl)-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile melting at 101° C. to 102° C.

EXAMPLE 47

4-(4,4-dimethyl-2,5-dioxo-3-(2-methoxyethyl)-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile melting at 68° C. to 69° C.

EXAMPLE 48

4-(4,4-dimethyl-2,5-dioxo-3-cyanomethyl-1-imidazolidinyl)-2-trifluoromethyl benzonitrile melting at 186° C. to 187° C.

EXAMPLE 49

4-(4,4-dimethyl-2,5-dioxo-3-[(1,3-dioxolan-2-yl)-methyl]-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile melting at 135° C. to 136° C.

EXAMPLE 50

4-(4,4-dimethyl-2,5-dioxo-3-(2-chloroethyl)-1-imidazolidinyl) 2-trifluoromethyl-benzonitrile melting at 120° C. to 121° C.

EXAMPLE 51

1-(3,4-dichlorophenyl)-5-imino-3,4,4-trimethyl-2-imidazolidine thione

A mixture of 2.4 g of the isocyanate of 3,4-dichlorophenyl, 1.3 ml of 2-methylamino-2-cyano-propane, 23 ml of tetrahydrofuran and 0.23 ml of triethylamine was refluxed for 16 hours and then evaporated to dryness under reduced pressure. The residue was chromatographed on silica and eluted with a 96-4 methylene chloride-acetone mixture to obtain after crystallization from ether, 2.54 g of the desired product melting at 133° C.

EXAMPLE 52

3-(3,4-dichlorophenyl)-2-thioxo-1,5,5-trimethyl-1-imidazolidinone

A suspension of 1.88 g of the product of Example 51 in 14 ml of 6 N hydrochloric acid was refluxed for 45 minutes and after the addition of another 14 ml of 6 N hydrochloric acid, the mixture was refluxed for 2 more hours. Another 4 ml of 6 N hydrochloric acid were added and the mixture was refluxed for 90 minutes and then returned to room temperature. 100 g of ice were added and the mixture was extracted with ethyl acetate. The organic phase was washed with water, dried and evaporated to dryness. The residue was chromatographed on silica and eluted with a 1—1 cyclohexane-ethyl acetate mixture to obtain 1.84 g of the desired product melting at 129° C. after crystallization from isopropanol.

Analysis: $C_{12}H_{12}Cl_2N_2OS$: molecular weight = 303.21

	% C	% H	% Cl	% N	% S
Calculated:	47.54	3.99	23.38	9.24	10.57
Found:	47.5	3.8	23.2	9.3	10.5

Using the above procedures, the following compounds were prepared:

EXAMPLE 53

3-(3,4-dichlorophenyl)-3,5-dihydro-5,5-dimethyl-2-methylthio-4H-imidazol 4-one melting at 110° C.

EXAMPLE 54

1-(3,4-dichlorophenyl)-3,4-4-trimethyl-2,5-imidazolidine-dithione melting at ≈146° C.

EXAMPLE 55

1-(4-chloro-3-trifluoromethyl-phenyl)-4,4-dimethyl-2-thioxo-5-imidazolidinone melting at 176° C.

EXAMPLE 56

1-(4-chloro-3-trifluoromethyl-phenyl)-4,4-dimethyl-5-imino-2-imidazolidinethione melting at 173° C. to 174° C.

EXAMPLE 57

3-(3,4-dichlorophenyl)-3,5-dihydro-5,5-dimethyl-2-benzylthio 4H-imidazol-4-one

IR Spectrum ($CHCl_3$):	
C=O	1736 cm^{-1}
CN + aromatics	1578, 1496 cm^{-1}

EXAMPLE 58

4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxy butyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

a) Condensation

600 mg of 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl) benzonitrile obtained as in Example 8—in 5 ml of dimethylformamide were added to a suspension of 104 mg of sodium hydride in 0.8 ml of dimethylformamide, while maintaining the temperature below 20° C. After 10 minutes of stirring, 445 mg of 4-chloro-t-butyl-dimethylsilylether and 300 mg of sodium iodide were added. The mixture was heated for 16 hours at 50° C. and then, cooled to ambient temperature. 87 mg of sodium hydride were added followed by another 400 mg of the chlorinated ether and 267 mg of sodium hydride were added. The mixture was heated for another hour and then, returned to ambient temperature, and poured into 60 ml of water containing 600 mg of monopotassium phosphate. Extraction was carried out with ether and the organic phase was washed with water, dried and the solvent was evaporated. The residue was chromatographed on silica (eluant: methylene chloride—acetone (99-1)) to obtain 526 mg of product which as used as is for the stage following the cleavage.

The said product was mixed in 5 ml of methanol and 1.5 ml of 2 N hydrochloric acid and the mixture was stirred for 40 minutes at ambient temperature. The mixture was poured into 30 ml of water and was extracted with methylene chloride. The organic phase was washed with water, dried and the solvent was evaporated. After chromatographing the residue on silica (eluant methylene chloride—acetone (9-1), the fractions with a Rf=0.15, were recovered, and after crystallization from isopropyl ether, 307 mg of the expected product melting at 102°–103° C. were obtained.

Analysis: $C_{17}H_{18}F_3N_3O_3$: molecular weight = 369.35

	C %	H %	F %	N %
Calculated	55.28	4.91	15.43	11.38
Found	55.2	4.9	15.3	11.1

IR Spectrum ($CHCl_3$);	
OH	3628 cm^{-1}
C=N	2236 cm^{-1}
C=O	1778-1724 cm^{-1}
Aromatics	1615-1575-1505 cm^{-1}

Preparation of the 4-chloro t-buryl dimethylsilylether used at the start of Example 58.

9.9 ml of 4-chloro-1-butanol and 24.3 g of imidazole in 50 ml of tetrahydrofuran were stirred and 2.82 g of terbutyldimethylsilyl chloride in 20 ml of tetrahydrofuran were added dropwise at a temperature of less than 20° C. The mixture was stirred for 18 hours at ambient temperature, followed by separating, rinsing with tetrahydrofuran and eliminating the solvent under reduced pressure. The residue was purified by chromatography on silica (eluant: cyclohexane—ethyl acetate (95-5)) to obtain 17.5 g of the expected product.

EXAMPLE 59

(1,1-dimethyl) ethyl 3-(4-cyano 3-trifluoro-methylphenyl)5,5-dimethyl 2,4-dioxo-1-imidazolidine acetate

450 mg of the product of Example 8—in solution in 4 ml of dimethylformamide were added to a suspension of 78 mg of sodium hydride at 50% in oil and 0.5 ml of dimethylformamide. The mixture was stirred for 15 minutes and then without exceeding 30° C., 0.22 ml of terbutyl bromoacetate were slowly added. The mixture was stirred for 16 hours and then, was poured into 50 g of a water and ice mixture (1—1). 0.5 g of monopotassium phosphate were added and extraction was carried out with ether. The organic phase was washed with water, dried and evaporated to dryness. The 1.1 g of crude product was chromatographed on silica (eluant: methylene chloride—acetone (99-1)) to obtain 425 mg of the expected product melting at 122°–123° C. with a Rf=0.28 (eluant: methylene chloride—acetone (99-1))

IR Spectrum ($CHCl_3$);	
C=O	1788-1729 cm^{-1} (hydantoin) 1745 cm^{-1} (ester)
C≡N	2235 cm^{-1}
Aromatics	1616-1505 cm^{-1}
UV Spectrum (EtOH)	
Max. 258 nm = 16100 Infl. 277 nm = 6000 Infl. 285 nm = 3000	

EXAMPLE 60

cyclopentyl 3-(4-cyano-3-trifluoromethyl phenyl)-5,5-dimethyl 2,4-dioxo 1-imidazolidine acetate

A solution of 355 mg of the product of Example 9,—49 mg of 4-dimethylamino-pyridine 130 mg of cyclopentanol and 6.5 ml of methylene chloride was cooled to −10° C. and then 226 mg of dicyclohexylcarbodiimide in 2 ml of methylene chloride were added. The mixture was allowed to return to ambient temperature, stirred for 25 minutes, heated at reflux for 2 hours, returned to ambient temperature, filtered and the solvent was evaporated. The residue was chromatographed on silica (eluant: methylene chloride—acetone (99-1)) to obtain 281 mg of the expected product with a Rf=0.25 (eluant: methylene chloride—acetone (99-1))

IR Spectrum ($CHCl_3$);	
C=O	1786-1729 cm^{-1} (hydantoin) 1748 cm^{-1} (ester)
C≡N	2235 cm^{-1}
Aromatics	1615-1602-1576-1505 cm^{-1}

-continued

UV Spectrum (EtOH)
Max. 258 nm = 16800 Infl. 276 nm = 5800 Infl. 286 nm = 3000

EXAMPLE 61

ethyl 3-(4-cyano 3-(trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoate

Using the procedure or Example 59, the product of Example 8—and ethyl 4-bromobutyrate were reacted to obtain the expected product melting at 66°–67° C. with a Rf=0.16 (eluant: methylene chloride—acetone (99-1))

IR Spectrum ($CHCl_3$);	
C=O	1770-1726 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1616-1576-1505 cm^{-1}
UV Spectrum (EtOH)	
Max. 260 nm = 15500 Infl. 277 nm = 7000 Infl. 286 nm = 3600	

EXAMPLE 62

3-(4-cyano 3-trifluoromethyl-phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidine butanoic acid

1 g of the product or Example 61 in 20 ml of methanol was stirred for 3 hours at ambient temperature in the presence of 3 ml of 2 N sodium hydroxide and the mixture was poured into 20 ml of water and acidified to pH=1 using 7 ml of N hydrochloric acid. The mixture was extracted with ether and the extracts were washed with water and dried and the solvents were eliminated under reduced pressure to obtain 863 mg of crude product melting at 179°–180° C. which was purified by chromatography on silica (eluant: methylene chloride—methanol (92.5-7.5)). After crystallization from isopropanol, 614 mg of the expected product melting at 184°–185° C. and with a Rf=0.25 (eluant: methylene chloride—methanol (92.5-7.5)) were obtained.

IR Spectrum (nujol);	
C=O	1770-1753-1735-1712-1690-1645 cm^{-1}
C≡N	2230 cm^{-1}
Aromatics	1613-1587-1533-1502 cm^{-1}

EXAMPLE 63

(1,1-dimethyl) ethyl 3-(4-cyano 3-trifluoro-methylphenyl)-5,5-dimethyl 2,4-dioxo-1-imidazolidinebutanoate

By carrying out the esterification of the product of Example 62, with terbutanol in the presence of dicyclohexylcarbodiimide and 4-dimethylamino-pyridine as in Example 60, the expected product melting at 96°–97° C. with a Rf=0.32 (eluant: methylene chloride—acetone (98-2)) was obtained.

IR Spectrum ($CHCl_3$);	
C=O	1779-1725 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1616-1576-1505 cm^{-1}
UV Spectrum (EtOH)	
Max. 261 nm = 15600	
Infl. 276 nm = 7800	
Infl. 286 nm = 3700	

EXAMPLE 64

cyclopentyl 3-(4-cyano 3-trifluoromethyl-phenyl) 5, 5-dimethyl-2,4-dioxo-1-imidazolidine butanoate

Using the procedure of Example 63, cyclopentanol was reacted to obtain the expected product melting at 85°–86° C. with a Rf=0.33 (eluant: methylene chloride—acetone (98-2)).

IR Spectrum ($CHCl_3$)	
C=O	1779-1728 cm^{-}
C≡N	2236 cm^{-1}
Aromatics	1616-1578-1505 cm^{-1}
UV Spectrum (EtOH)	
Max. 261 nm = 16000	
Infl. 277 nm = 7600	
Infl. 286 nm = 3700	

EXAMPLE 65

4-(4,4-dimethyl-2,5-dioxo 3-(2-(4-fluorophenylthio) ethyl)-1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile

a) Formation of the phenolate

0.16 ml of 4-fluorothiophenol in 1.6 ml of dimethylformamide were added at a temperature of less than 28° C. to a suspension of 80 mg of sodium hydride in 0.5 ml of dimethylformamide, and the solution was stirred for 10 minutes.

b) Substitition

548 mg of 4-[4,4-dimethyl-2,5-dioxo-3-(2-chloroethyl) 1-imidazolidinyl]-2-(trifluoromethyl) benzonitrile (Example 50—in solution in 4 ml of dimethylformamide were added to the solution of a) and the mixture was stirred for 2 hours, poured into 50 ml of water with 0.5 g of monopotassium phosphate. Extraction was carried out with ether and the organic phase was washed with water and dried and the solvent was evaporated. After chromatographing the residue on silica (eluant: cyclohexane—ethyl acetate (75-25)), 570 mg of the expected product melting at 93°–94° C. with a Rf=0.29 (eluant: cyclohexane—ethyl acetate (75-25)) were obtained.

IR Spectrum ($CHCl_3$)	
C=O	1780-1726 cm^{-1}
C≡N	2238 cm^{-1}
Aromatics	1616-1579-1506 cm^{-1}
(fluorophenyl) thio	1591-1492 cm^{-1}
UV Spectrum (EtOH)	
Max. 254 nm = 18600	
Infl. 277 nm = 7500	
Infl. 286 nm = 4200	

EXAMPLE 66

4-(4,4-dimethyl-2,5-dioxo-3-(2-(4-fluorophenyl sulfonyl) ethyl)-1-imidazolidinyl-2-(trifluoromethyl) benzonitrile

1.21 g of metachloroperbenzoic acid in 24 ml of methylene chloride were added dropwise at a temperature of less than 29° C. to 222 mg of the product of Example 65 in 4.4 ml of methylene chloride. After 30 minutes of stirring, the mixture was poured into 30 ml of sodium thiosulfate (0.5 M/l). The mixture was stirred for 10 minutes, followed by decanting and extracting with methylene chloride. The organic phase was washed with a saturated aqueous solution of sodium bicarbonate, then with water, dried, and the solvent was evaporated. After chromatographing the residue on silica (eluant: cyclohexane—ethyl acetate (1—1)), 220 mg of product were obtained which was crystallized from isopropanol to obtain 196 mg of the expected product melting at 155°–156° C. with a RF=0.22 (eluant: ethyl acetate—cyclohexane (1—1)).

IR Spectrum ($CHCl_3$);	
C=O	1783-1727 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1615-1593-1505-1497 cm^{-1}
SO_2	1314-1150 cm^{-1}
UV Spectrum (EtOH)	
Max. 258 nm = 16700	
Infl. 286 nm	

EXAMPLE 67

4-(4,4-dimethyl 2,5-dioxo 3-(2-((4-fluorophenyl) sulfinyl) ethyl) 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile

222 mg of the product of Example 65 in 15 ml of methanol were stirred for 30 minutes at ambient temperature in the presence of 5 ml of an aqueous solution of sodium metaperiodate (0.1 M/l). The suspension was heated for one hour at 40° C. and 10 ml of methanol and 5 ml of oxidizing solution were added. The methanol was evaporated off and after 10 ml of a saturated solution of sodium chloride were added, extraction was carried out with ethyl acetate. The organic phase was washed with salt water, dried, and the solvent was evaporated. After chromatographing the residue on silica (eluant: methylene chloride—acetone (9-1)), 205 mg of product were obtained which was crystallized from isopropanol to obtain 180 mg of the expected product melting at 145°–146° C. with a Rf=0.10 (eluant: methylene chloride—acetone (9-1)).

IR Spectrum ($CHCl_3$);	
C=O	1782-1727 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1615-1592-1505-1493 cm^{-1}

UV Spectrum (EtOH)	
Max. 258 nm	ε = 17600
Infl. 285 nm	

Using the procedure of the preceding examples, 4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile of Example 8—and the appropriate reagents, the compounds of the following examples were obtained:

EXAMPLE 68

4-(4,4-dimethyl 2,5-dioxo 3-((3-methoxyphenyl) methyl) 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile Melting at 88°–89° C. with a Rf=0.21 (eluant: cyclohexane—ethyl acetate (7-3))

IR Spectrum ($CHCl_3$)	
C=O	1779-1724 cm^{-1}
C≡N	2238 cm^{-1}
Aromatics	1614-1602-1588-1575-1504-1491

UV Spectrum (EtOH)	
Max. 260 nm	ε = 16800
Infl. 210 nm	ε = 28500
Infl. 280 nm	ε = 8900

EXAMPLE 69

4-(4,4-dimethyl 2,5-dioxo 3-(2-(4-morpholinyl) ethyl) 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile with a Rf=0.20 (eluant: methylene chloride—acetone (70-30))

IR Spectrum ($CHCl_3$)	
C=O	1779-1725 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1616-1576-1505 cm^{-1}
morpholinyl	1117 cm^{-1}

UV Spectrum (EtOH)	
Max. 261 nm	ε = 14000
Infl. 277 nm	ε = 6900
Infl. 286 nm	ε = 3600

EXAMPLE 70

4-(4,4-dimethyl 3-(2-hydroxyethyl) 5-imino 2-thioxo 1-inidazolidinyl) 2-(trifluoromethyl)-benzonitrile

a) Preparation of the isothiocyanate

2.23 g of 1-trifluoromethyl-4-amino benzonitrile (prepared accord to EP 0002892) were added slowly to a solution of 22 ml of distilled water and 1 ml of thiophosgene and the mixture was stirred for one hour and then extracted with chloroform. The extracts were washed with salt water, dried and evaporated to dryness under reduced pressure to obtain 3 g of product which was used as is for obtaining the imine.

b) Obtaining the imine

5 g of the said isothiocyanate were mixed with 37 ml of tetrahydrofuran in the presence of 1.5 ml of triethylamine and 2.8 g of 2-[(2-hydroxy ethyl) amino] 2-methyl propane nitrile (prepared in Example 22)—in solution in 10 ml of tetrahydrofuran were added all at once. The temperature spontaneously increased to 34° C. and the resultant mixture was allowed to return to ambient temperature while stirring for one hour. The solvent was evaporated off and the residue was chromatographed on silica (eluant: methylene chloride—methanol (7-3)) to obtain 5.87 g of the expected product melting at 181° C., after crystallization from isopropanol.

EXAMPLE 71

4-(4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

4.6 g of the product of Example 70 in 65 ml of methanol was refluxed for one hour in the presence or 10 ml of 2 N hydrochloric acid. The mixture was cooled to ambient temperature and poured into 300 ml of ice-cooled water. Extraction was carried out with ethyl acetate and the organic phase was washed with salt water, dried, and the solvent was evaporated off. The residue was chromatographed on silica (ethyl acetate—cyclohexane (1—1)) and the fractions were collected with a Rf=0.14. After crystallization from methylene chloride and cyclohexane, 4.37 g of the expected product melting at 130° C. were obtained

Analysis; $C_{15}H_{14}F_3N_3O_2S$; molecular weight = 357.36

	C %	H %	F %	N %	S %
Calculated	50.42	3.95	15.95	11.76	8.97
Found	50.3	3.9	15.9	11.6	8.9

IR Spectrum ($CHCl_3$);	
OH	3626 cm^{-1}
C≡N	2236 cm^{-1}
C=O	1763 cm^{-1}
Aromatics	1615-1578-1504 cm^{-1}

EXAMPLE 72

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-imino-2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl)-5-^{3}H-benzonitrile

a) Preparation of the tritiated benzonitrile

15 mg of 2-trifluoromethyl 4-amino 5-bromo benzonitrile were mixed with 200 μl of ethyl acetate in the presence of 6.5 μl of triethylamine and 2 mg of palladium on activated charcoal and then tritium (1.42 bar) was introduced. After filtering, rinsing with ethyl acetate and evaporating to dryness at ambient temperature, approximately 66.6 G.Bq (1.8 Ci) of product were obtained.

b) Preparation of the tritiated isothiocyanate

150 μl of a 10% solution of thiophosgene in chloroform were added to the above product, in 150 μl of water and the mixture was stirred for 45 minutes at ambient temperature. Dilution was carried out with 0.5 ml of water and 1 ml of chloroform, followed by extraction with chloroform. The solvent was evaporated off under reduced pressure and the

residue was taken up in toluene to obtain 50.7 G.Bq (1.37 Ci) of the expected product which was kept at −80° C.

c) Preparation of the tritiated imine

Having eliminated the toluene from the above mixture under reduced pressure, 130 μl of tetrahydrofuran with 1% triethylamine were added and 13 μl of 2-[(2-hydroxyethyl) -amino] 2-methylpropane-nitrile (Example 22)—were added. Then, another 130 μl of tetrahydrofuran with 1% triethylamine were added and the mixture was stirred for 30 minutes at ambient temperature and the solvents were eliminated under reduced pressure.

Preparation of the 2-trifluoromethyl 4-amino 5-bromo benzonitrile used in Example 72.

A solution of 2-trifluoromethyl 4-amino benzonitrile (prepared according to EP 0002892) (5 moles) in 25 ml of methanol was cooled to 0° C. and bomine was added (5.2 moles). The mixture was allowed to return to ambient temperature, stirred for 3 hours, alkalinized with triethylamine and then an aqueous solution of sodium thiosulfate was added. The solvents were eliminated and extraction was carried out with chloroform. The organic phase was washed with water, dried, and the solvent was evaporated to obtain the product which was used as is for the following stage.

IR Spectrum ($CHCl_3$);	
NH_2	3612-3408 cm^{-1}
C≡N	2230 cm^{-1}
Aromatics	1621-1556-1506 cm^{-1}

EXAMPLE 73

4-(4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo 1-imidazolidinyl)-2-(trifluoromethyl) 5-^{3}H-benzonitrile

The product of Example 72 in 180 μl of water was heated to 100° C. and 60 μl of 2 N hydrochloric acid was added. The mixture was stirred for 5 minutes at reflux and then approximately 600 mg of ice were added. Extraction is carried out with ethyl acetate and the extracts were washed with salt water and dried to obtain 34.7 G.Bq (937 mCi) of product. After chromatography on silica (eluant: cyclohexane—ethyl acetate (60-40)), 19 G.Bq (513 mCi) of the expected product were obtained.

EXAMPLE 74

4-(4,4-dimethyl-3-hydroxypropyl)-5-imino-2-thioxo-1-imidazolidinyl) 2-(trifluoromethyl)-benzonitrile

Using the procedure of Example 22—2 g of the isothiocyanate of Example 70 (a) and 1.2 g of the appropriate aminonitrile were reacted to obtain 1.70 g of the expected product with a Rf=0.25 (methylene chloride—acetone (65-35)).

IR Spectrum ($CHCl_3$);	
OH	3630 cm^{-1}
=NH	3314-1676 cm^{-1}
C≡N	2235 cm^{-1}

EXAMPLE 75

4-(4,4-dimethyl-3-(3-hydroxypropyl)-5-oxo-2-thioxo-1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 71, 240 mg of the product of Example 74 were reacted to obtain 226 mg of the expected product melting at 149°–150° C. with a Rf=0.32 (eluant; methylene chloride—acetone (75-25)).

IR Spectrum ($CHCl_3$);	
OH	3626 cm^{-1}
C=O	1763 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1615-1580-1504-1483 cm^{-1}

EXAMPLE 76

4-(4,4-dimethyl 3-(4-hydroxybutyl)-5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 22,—2 g of isothiocyanate and 1.38 g of the appropriate aminoitrile were reacted to obtain 2.08 g of the expected product with a Rf=0.25 (methylene chloride—acetone (65-35)).

IR Spectrum ($CHCl_3$);	
OH	3630 cm^{-1}
=NH	3314-1675 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1614-1577-1504 cm^{-1}

EXAMPLE 77

4-(4,4-dimethyl 3-(4-hydroxybutyl)-5-oxo 2-thioxo-1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 71, 300 mg of the product of Example 76 were reacted to obtain 236 mg of the expected product melting at 78°–79° C. with a Rf=0.31 (eluant: methylene chloride—acetone (75-25)).

IR Spectrum ($CHCl_3$);	
OH	3624 cm^{-1}
C=O	1762 cm^{-1}
C=N	2237 cm^{-1}
Aromatics	1615-1580-1504 cm^{-1}

UV Spectrum (EtOH)	
Max. 232 nm	ε = 19500
Max. 254 nm	ε = 24000
Infl. 266 nm	

EXAMPLE 78

4-(4,4-dimethyl 3-(2-methoxyethyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 22,—2.5 g of isothiocyanate and 1.56 g of the appropriate aminoitrile were reacted to obtain 2.36 g of the expected product with a Rf=0.23 (methylene chloride—acetone (92.5-7.5)).

IR Spectrum ($CHCl_3$);	
=NH	3314 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1614-1578-1504 cm^{-1}
C=N	1675 cm^{-1}

EXAMPLE 79

4-(4,4-dimethyl 3-(2-methoxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 71, the product of Example 78 was reacted to obtain the expected product melting at 98°–99° C. with a Rf=0.32 (eluant: methylene chloride—acetone (99-1))

IR Spectrum ($CHCl_3$);	
C=O	1757 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1615-1580-1504 cm^{-1}

UV Spectrum (EtOH)	
Max. 232 nm	ε = 18200
Max. 254 nm	ε = 22400
Infl. 265 nm	

EXAMPLE 80

4-(4,4-dimethyl 3-(1-methylethyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 22,—2.5 g of the isothiocyanate and 1.32 g of the appropriate aminonitrile were reacted to obtain 880 mg of the expected product with a Rf=0.20 (eluant: methylene chloride—acetone (96-4)).

IR Spectrum ($CHCl_3$);	
=NH	3310-1675 cm^{-1}
C≡N	2236 cm^{-1}
Aromatics	1614-1580-1504 cm^{-1}

EXAMPLE 81

4-(4,4-dimethyl 3-(1-methylethyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 71, 880 mg of the product of Example 80 and 35 ml of 6 N hydrochloric acid were reacted to obtain after extraction with chloroform, 744 mg of the expected product melting at 203°–204° C. with a Rf=0.45 (eluant: cyclohexane—ethyl acetate (1—1)).

IR Spectrum ($CHCl_3$);	
OH	3626 cm^{-1}
C=O	1753 cm^{-1}
C≡N	2232 cm^{-1}
Aromatics	1615-1580-1504 cm^{-1}

-continued

UV Spectrum (EtOH)	
Max. 232 nm	ε = 18900
Max. 235 nm	ε = 22500
Infl. 273 nm	

EXAMPLE 82

3-(3,4-dichlorophenyl 5,5-dimethyl 1-(3-hydroxypropyl) 4-imino 2-imidazolidine thione

Using the procedure of Example 51,—2.4 g of 3,4-dichlorophenyl isocyanate and 1.6 g of the appropriate aminonitrile were reacted to obtain, after chromatography on silica (eluant: methylene chloride—acetone (6-4)), 2.16 g of expected product with a Rf=0.25

IR Spectrum ($CHCl_3$);	
OH	3630 cm^{-1} + associated
C=NH	3294-1676 cm^{-1} (F)
Aromatics	1595-1569-1482 cm^{-1}

EXAMPLE 83

3-(3,4-dichlorophenyl 5,5-dimethyl 1-(3-hydroxypropyl) 2-thioxo 4-imidazolidinone

Using the procedure of Example 52,—0.88 g of the product of Example 82 and 35 ml of 6 N hydrochloric acid were reacted to obtain, after extraction with chloroform, 0.79 g of the expected product melting at 202°–203° C.

IR Spectrum ($CHCl_3$);	
C=O	1753 cm^{-1}
C≡N	2232 cm^{-1}
Aromatics	1615-1580-1504 cm^{-1}

UV Spectrum (EtOH)	
Max. 232 nm	ε = 18900
Max. 235 nm	ε = 22500
Infl. 273 nm	

EXAMPLE 84

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

a) 4-amino 2-(trifluoromethyl) (5-^{3}H) benzonitrile

The following were cooled to −180° C. and mixed under an inert atmosphere: 16 mg of 2-trifluoromethyl 4-amino 5-bromo benzonitrile, 2 mg of palladium on activated charcoal, 200 μl of ethyl acetate and 6.5 μl of triethylamine. Then the mixture was left under a tritium atmosphere and taken to 20° C. and the pressure was then 1.68 bar. The mixture was stirred until absorption was complete (p=0.42 bar), followed by cooling to −180° C. The excess tritium was recovered, taken to 20° C. and then filtered. The filtrate was rinsed with ethyl acetate and concentrated at 40° C. under reduced pressure to obtain 68 G.Bq of the expected product.

b) 4-thioisocyanate 2-(trifluoromethyl) (5-^{3}H) benzonitrile

The following were mixed under an argon atmosphere: 34 G.Bq of the above tritiated amino derivate, 150 μl of

demineralized water and 150 μl of 10% thiophosgene solution in chloroform. The mixture was stirred at 20° C. for 45 minutes, decanted and reextraction was carried out with chloroform. The extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The thioisocyanate obtained was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) ($5-^3H$) benzonitrile

The following were mixed under an argon atmosphere with the thioisocyanate of stage b): 350 μl of tetrahydrofuran with 1% triethylamine and 20 μl of propanonitrile prepared as indicated below. The mixture was stirred for 2 hours at 20° C., followed by concentration at 20° C. under reduced pressure. The imine was used as is for the following stage.

Preparation of the 2-(4-hydroxybutylamino) 2-methylpropano-nitrile used in stage c)

550 μl of acetone cyanohydrin and 500 μl of 4-amino 1-butanol were mixed together and the mixture was stirred for 16 hours at 20° C. to obtain the desired product which was used as is for the following stage.

EXAMPLE 85

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) ($5-^3H$) benzonitrile

200 μl of 2 N hydrochloric acid were added to the imine of Example 84 and the mixture was refluxed for 5 minutes, then returned to 20° C. and diluted with 1 ml of water. Extaction was carried out with ethyl acetate and the extracts were washed with water and concentrated under reduced pressure. The crude product was purified by chromatography on silica (eluant: cyclohexane—ethyl acetate (6-4)) to obtain 2.8 G.Bq of the expected product.

EXAMPLE 86

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

a) 4-amino 2-(trifluoromethyl) benzo (^{14}C) nitrile

377 mg of cuprous cyanide ^{14}C (9 G.Bq) and 1.0732 g of 4-bromo 3-(trifluoromethyl) benzenamine were mixed together under a nitrogen atmosphere in 8 ml of dimethylformamide and the mixture was refluxed for 4 hours, then cooled to 0° C. and diluted with 20 ml of acetone. The insoluble part was filtered off and the filtrate was concentrated at 70° C. under reduced pressure. The residue was taken up in methylene chloride, filtered and the filtrate was concentrated under reduced pressure. The benzonitrile (^{14}C) was purified by chromatography on silica (eluant: methylene chloride—cyclohexane (70-30)) to obtain 0.558 g (6.62 G.Bq) of the expected product.

b) 4-thioisocyanate 2-(trifluoromethyl) benzo (^{14}C) nitrile

The following were mixed under a nitrogen atmosphere: 189 mg of benzonitrile (^{14}C) of stage a), 2.7 ml of water and 85 μl of thiophosgene. The mixture was agitated vigorously stirred for 5 minutes, and after 30 μl of thiophosgene were added, stirring was continued for one hour at 20° C. Then extraction was carried out with chloroform and the extracts were washed with water, dried and concentrated under reduced pressure. The thioisocyanate obtained was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

2 ml of tetrahydrofuran, the propanonitrile prepared below in solution in 1.5 ml of methylene chloride and 150 μl of triethylamine were added under a nitrogen atmosphere to the thioisocyanate of stage b). The mixture was heated for 30 minutes under reflux and concentrated under reduced pressure to obtain the imine which was used as is for the following stage.

Preparation of the 2-(4hydroxybutylamino) 2-methylpropano-nitrile of stage c

220 μl of acetone cyanohydrin and 200 μl of 4-amino 1-butanol were mixed together with stirring for 16 hours at 20° C. and then was diluted with 2 ml of methylene chloride, dried, filtered and the filtrate was concentrated under reduced pressure to obtain the propanonitrile which was used as is for the following stage.

EXAMPLE 87

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

6 ml of methanol and 1.6 ml of 2 N hydrochloric acid were added to the imine of Example 86 and the mixture was refluxed for 45 minutes, cooled to 20° C. and diluted with 10 ml of water. Extraction was carried out with methylene chloride and the extracts were washed with water and concentrated under reduced pressure. The crude product was purified by chromatography on silica (eluant: ether—acetonitrile—cyclohexane (50-15-35)) to obtain 328 mg of the expected product.

EXAMPLE 88

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl) ($5-^3H$) benzonitrile

a) 4-amino 2-(trifluoromethyl) ($5-^3H$) benzonitrile

Using the procedure of stage a) of Example 84, 16 mg of 4-amino 5-bromo 2-trifluoromethyl benzonitrile, 2 mg of palladium on activated charcoal, 200 μl of ethyl acetate and 6.5 μl of triethylamine were reacted to obtain 68 G.Bq of the expected product.

b) 4-isocyanate 2-(trifluoromethyl) ($5-^3H$) benzonitrile

34 G.Bq of tritiated amino derivate of step a) and 100 μl of 20% phosgene in toluene were mixed together under an argon atmosphere and the mixture was taken to 80° C. for one hour. A further 100 μl of phosgene were added and the mixture heated for one hour at 80° C. This operation was repeated one more time, then concentration was carried out at 20° C. under reduced pressure to obtain the isocyanate which was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl) ($5-^3H$) benzonitrile

The following were added under an argon atmosphere to the isocyanate of stage b): 200 μl of methylene chloride, 50

μl of the propanonitrile chloromethylene solution prepared as below and 20 μl of triethylamine and the mixture was stirred for 30 minutes. A further 50 μl of the propanonitrile solution were added and stirring was continued for 30 minutes followed by concentration at 20° C. under reduced pressure. The imine was used as is for the following stage.

Preparation of the 2-(4-hydroxybutylamino) 2-methyl propano-nitrile, of stage c)

220 μl of acetone cyanohydrin and 200 μl of 4-amino 1-butanol were mixed together and the mixture was stirred for 16 hours at 20° C., then diluted with 3 ml of methylene chloride and dried over magnesium sulfate. The decanted solution was used as is for the following stage.

EXAMPLE 89

4-(4,4-dimethyl2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) (5-^{3}H) benzonitrile

200 μl of methanol and 50 μl of 2 N hydrochloric acid were added to the imine of Example 88 and the mixture was refluxed for 45 minutes, then returned to 20° C. and diluted with 1 ml of water. Extraction was carried out with methylene chloride and the extracts were washed with water and concentrated at 20° C. under reduced pressure. The crude product was purified by chromatography on silica (eluant: methylene chloride—ethyl acetate (7-3 then 5—5)) to obtain 16 G.Bq of the expected product.

EXAMPLE 90

4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

a) 4-amino 2-(trifluoromethyl) benzo (^{14}C) nitrile

Using the procedure of Example 86, stage a), 377 mg of cuprous cyanide ^{14}C, 1.0732 g of 4-bromo 3-trifluoromethyl benzenamine and 8 ml of dimethylformamide were reacted to obtain 0.558 g (6.62 G.Bq) of the expected product.

b) 4-isocyanato 2-(trifluoromethyl) benzo (^{14}C) nitrile

182.4 mg of benzonitrile (^{14}C) (0.97 mmole), 2 ml of dioxane and 1 ml of 20% phosgene in toluene were mixed together under a nitrogen atmosphere and the solution was heated at 60° C. for 22 hours, then concentrated at 60° C. under reduced pressure. The isocyanate was used as is for the following stage.

c) 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-imino 2-oxo 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

1.5 ml of methylene chloride (on siliporite NK 30), the propanonitrile of Example 88 in solution in 1.5 ml of methylene chloride, and 150 μl of triethylamine were added under a nitrogen atmosphere to the isocyanate of stage b). The mixture was stirred for one hour at 20° C. and concentrated under reduced pressure. The imine was used as is for the following stage.

EXAMPLE 91

4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzo (^{14}C) nitrile

5 ml of methanol and 1.2 ml of 1 N hydrochloric acid were added to the imine of Example 90 and the mixture was refluxed for 40 minutes, then returned to 20° C. and diluted with 10 ml of water. Extraction was carried out with methylene chloride and the extracts were washed with water and concentrated under reduced pressure. The crude product was purified by chromatography on silica (eluant: ether—acetonitrile—cyclohexane (50-15-35)) to obtain 289 mg (1.26 G.Bq) of the expected product.

EXAMPLE 92

4-(2,5-dioxo 4,4-dimethyl 3-(4-triphenylmethoxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

370 mg of the product of Example 58, 307 mg of trityl chloride in the presence of 10 mg of 4-dimethylaminopyridine, 0.25 ml of triethylamine and 4 ml of dimethylformamide were stirred at ambient temperature for 16 hours. The mixture was heated to 40° C. for 4 hours, poured into water and extraction was carried out with ether. The extracts were washed with water and dried and the solvent was eliminated under reduced pressure. The residue was chromatographed on silica (eluant: cyclohexane—ethyl acetate 75-25) to obtain 467 mg of the expected product with a Rf=0.25.

IR Spectrum ($CHCl_3$):	
C=O	1778, 1725 cm^{-1} (F)
C≡N	2235 cm^{-1}
Aromatics	1615, 1597, 1505, 1490 cm^{-1}

EXAMPLE 93

4-(2,5-dioxo 4,4-dimethyl 3-(4-phenylmethoxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

48 mg of sodium hydride were added in several lots to 370 mg of the product of Example 58 in solution in 4 ml of dimethylformamide and the mixture was stirred for 30 minutes. Then, 0.12 ml of benzyl bromide and 40 mg of tetrabutylammonium iodide were added and after 90 minutes of reaction, the same amount of each reagent was added. The mixture was stirred for one hour and the reaction medium was poured into an ice-cooled aqueous solution of monopotassium phosphate. Extraction was carried out with ether and the extracts were washed with water and dried. The solvent was eliminated under reduced pressure and the residue was chromatographed on silica (eluant: methylene chloride—acetone 99-1) to obtain 140 mg of the expected product melting at 75°–76° C.

IR Spectrum ($CHCl_3$):	
C=O	1779, 1725 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1615, 1580, 1505, 1497 cm^{-1}

EXAMPLE 94

4-[4,4-dimethyl 2,5-dioxo 3-(4-methoxybutyl) 1-imidazolidinyl] 2-(trifluoromethyl)-benzonitrile

50 mg of sodium hydride were added in several lots to 370 mg of the product of Example 58 in solution in 3 ml of dimethylformamide and the mixture was stirred for 20

minutes. 0.06 ml of methyl iodide were added and the mixture was stirred for one hour. A further 50 mg of sodium hydride were added and then after 20 minutes, 0.06 ml of methyl iodide were added. The reaction medium was poured into water and extracted with ether. The extracts were washed with water, dried and the solvent was evaporated. The residue was chromatographed on silica (eluant: methylene chloride—acetone 98-2) to obtain 135 mg of the expected product melting at 80°–81° C.

IR Spectrum ($CHCl_3$);	
C=O	1779, 1725 cm^{-1} (F)
C=N	2234 cm^{-1}
Aromatics	1616, 1576, 1505 cm^{-1}
OCH_3 approx.	2830 cm^{-1}

EXAMPLE 95

4-[3-(4-chlorobutyl) 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrile

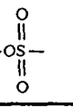
Using the procedure of Example 59, 600 mg of the product of Example 8—and 660 mg of 1-chloro 4-iodobutane in solution in 1 ml of dimethylformamide cooled down to +5° C. were reacted to obtain 604 mg of the expected product melting at 80°–81° C.

IR Spectrum ($CHCl_3$);	
C=O	1779, 1725 cm^{-1} (F)
C≡N	2238 cm^{-1}
Aromatics	1616, 1575, 1505 cm^{-1}

EXAMPLE 96

4-[3-[4-[(methylsulphoneyl) oxyl] butyl] 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrile

0.17 ml of methanesulfonyl chloride were added to 740 mg of the product of Example 58 in solution in 7.4 ml of pyridine and 24 mg of 4-dimethylamino-pyridine and the mixture was stirred for one hour. The mixture was poured into ice-cooled water and extraction was carried out with methylene chloride. The extracts were washed with water and the residual pyridine was eliminated by distillation. The residue was chromatographed on silica (eluant: methylene chloride—ethyl acetate 8-2) to obtain 771 mg of the expected product.

IR Spectrum ($CHCl_3$);	
C=O	1779, 1725 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1615, 1575, 1505 cm^{-1}
	1361, 1175 cm^{-1}

-continued

UV Spectrum (EtOH)		
max.	261 nm	ε = 14900
infl.	279–297 nm	

EXAMPLE 97

4-(3-acetyl 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 59, 420 mg of the product of Example 8—and two lots of 0.1 ml of acetyl chloride were reacted to obtain after chromatography on silica (eluant: methylene chloride—ethyl acetate 98-2), 334 mg of the expected product melting at 129°–130° C.

IR Spectrum ($CHCl_3$);	
C=O	1800, 1740, 1717 cm^{-1}
C≡N	2240 cm^{-1}
Aromatics	1616, 1505 cm^{-1}

UV Spectrum (EtOH)		
max.	250 nm	ε = 12000
infl.	274–284 nm	

EXAMPLE 98

4-(3-benzoyl 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

Using the procedure of Example 59, 300 mg of the product of Example 8—and two lots of 0.12 ml of benzoyl chloride in solution in 0.5 ml of dimethylformamide were reacted to obtain after chromatography on silica (eluant: cyclohexane—ethyl acetate 8-2), 285 mg of the expected product melting at 179°–180° C.

IR Spectrum ($CHCl_3$);	
C=O	1800, 1780, 1746, 1699 cm^{-1}
C≡N	2235 cm^{-1}
Aromatics	1617, 1600, 1580, 1504 cm^{-1}

UV Spectrum (EtOH)	
max. 250 nm	ε = 28500
infl. 275 nm	ε = 6500
infl. 263 nm	ε = 3850

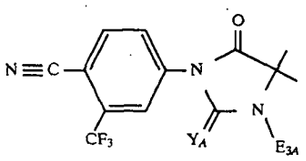
EXAMPLE 99

4-[3-[dimethyl (1,1-dimethylethyl) silyl] 4,4-dimethyl 2,5-dioxo 1-imidazolidinyl] 2-(trifluoromethyl) benzonitrle

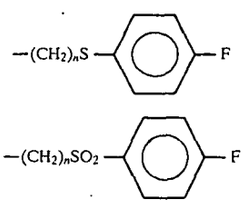
Using the procedure of Example 59, 450 mg of the product of Example 8—and 300 mg of dimethyl t-butylsilyl chloride in 2 ml of dimethylformamide were reacted to obtain after chromatography on silica (eluant: methylene chloride—acetone 99-1), 527 mg of the expected product melting at 147°–148° C.

IR Spectrum ($CHCl_3$);	
C≡N	2236 cm^{-1}
Aromatics	1615, 1579, 1505 cm^{-1}
UV Spectrum (EtOH)	
max. 258 nm	ε = 17000
infl. 275–285 nm	

In addition to the products described above, the following products are products which can be obtained within the scope of the present invention, namely the products of the formula:

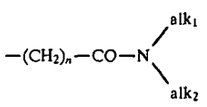


in which Y_A is oxygen or sulfur and R_{3A} has the following values:

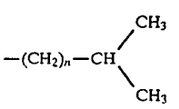


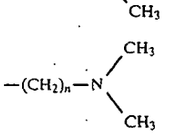
$(CH_2)_n-OH$

$(CH_2)_n-COO-alk$



$-(CH_2)_n-CO-alk$





$-(CH_2)_n-C\equiv N$

alk, alk_1 and alk_2 are alkyl of 1 to 4 carbon atoms and n is an integer between 1 and 4.

EXAMPLE 100

Tablets were prepared with a composition of 100 mg of 4-(5-oxo-2-thioxo-3,4,4-trimethyl 1-imidazolinyl)-2-trifluoromethyl-benzonitrile and sufficient excipient of lactose, starch, talc and magnesium stearate for a final tablet weight of 300 mg.

PHARMACOLOGICAL DATA

Study of the affinity of the products of the invention for the androgenic receptor.

1) Androgenic receptor

Male rats of the Sprague Dawley EOPS strain weighing 180 to 200 g, castrated 24 hours previously, were killed and the prostrate was removed, weighed and homogenized at 0° C. with a potter glass in a buffered solution (Tris 10 mM, saccharose 0.25 M, PMSF (phenyl methane sulfonyl fluoride) 0.1 mM, sodium molybdate 20 mM, HCl pH 7.4 into which was added extemporaneously 2 M of DTT (DL dithiothreitol) at a rate of 1 g of tissue per 8 ml of buffer solution. The homogenate was then ultracentrifuged at 0° C. for 45 minutes at 105,000 g and the aliquots of supernatant (=cytosol) were incubated for 30 minutes and 24 hours with a concentration (T) of tritiated testosterone and in the presence of increasing concentrations (0 to 2500.10^{-9}M) of cold testosterone or the test products. The concentration of bound tritiated Testostrone (B) was then measured for each incubate by adsorption method of carbon-dextran. The relative affinity of bonding (RBA) was calculated.

The following two curves were graphed: the percentage of the bound tritiated hormone B/T as a logarithm function of the concentration of the cold hormone and B/T as a logarithm function of the concentration of the tested cold product. The line of the equation

$$I_{50} = \frac{(B/T\max + B/T\min)}{2}$$

was determined. B/T max=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T). B/T min=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T) in the presence of a large excess of cold hormone (2,500× 10^{-9}M).

The intersections of the straight line I_{50} and the curves permit an evaluation of the concentrations of the cold reference hormones (CH) and the cold test product (CX) which inhibit by 50% the bonding of the tritiated hormone on the receptor. The RBA 9of the test product was determined by the equation

RBA=(CH)/(CX)

and the following results expressed in ARL were obtained with testosterone=100.

	Incubation 30 minutes	Incubation 24 hours
Product Example 1	27.5	3
Product Example 2	22	6
Product Example 4	21	5
Product Example 11	28	8
Product Example 12	128	92
Product Example 13	31	39
Product Example 14	27	7
Product Example 15	69	24

2) Study of the affinity of the products of the invention for the androgen receptor.

Male rats of the Sprague Dawley EOPS strain weighing 180 to 200 g, castrated 24 hours previously, were killed and the prostate was removed, weighed and homogenized at 0° C. with a potter glass in a buffered solution (Tris 10 mM, saccharose 0.25 M, PMSF (phenyl methane sulfonyl fluoride) 0.1 mM, sodium molybdate 20 mM, HCl pH 7.4 into which was added extemporaneously 2 mM of DTT (DL

dithiothreitol) at a rate of 1 g of tissue per 8 ml of buffer solution. The homogenate was then ultracentrifuged at 0° C. for 30 minutes at 209,000 g and the aliquots of supernatant (=cytosol) were incubated for 30 minutes and 24 hours with a concentration (T) of tritiated testosterone and in the presence of increasing concentrations (0 to 2500.10^{-9}M) of cold testosterone or the test products. The concentration of bound tritiated Testostrone (B) was then measured for each incubate by adsorption method of carbon-dextran. The relative affinity of bonding (RBA) was calculated.

The following two curves were graphed: the percentage of the bound tritiated hormone B/T as a logarithm function of the concentration of the cold hormone and B/T as a logarithm function of the concentration of the tested cold product. The line of the equation

$$I_{50} = \frac{(B/T\max + B/T\min)}{2}$$

was determined. B/T max=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T). B/T min=% of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T) in the presence of a large excess of cold hormone (2,500× 10^{-9}M).

The intersections of the straight line I_{50} and the curves permit an evaluation of the concentrations of the cold reference hormones (CH) and the cold test product (CX) which inhibit by 50% the bonding of the tritiated hormone on the receptor. The RBA of the test product was determined by the equation

RBA=100(CH)/(CX)

and the following results expressed in RBA were obtained with testosterone=100.

	Incubation 24 hours
Example 59	31
Example 71	163
Example 77	300
Example 79	81
Example 81	28

3) Determination of the androgen or anti-androgen activity by the dosage of ornithine carboxylase.

Six week old male Swiss mice castrated 24 hours receive oral does of the test products as a 0.5% suspension in methyl cellulose simultaneously with a subcutaneous injection of 3 mg/kg of testosterone propionate in solution in sesame oil containing 5% of benzyl alcohol to determine the anti-androgen activity. Active agonists were determined in the absence of testosterone propionate. The test compounds as well as testosterone were administered in a volume of 10 ml/kg. 16 hours after the treatments, the animals were killed, the kidneys were removed and then homogenized at 0° C. with a teflon-glass grinding apparatus in 10 volumes of buffer Tris-HCl 50 mM at a pH 7.4 containing 250 mM of pyridoxal phosphate, 0.1 mM EDTA and 5 mM of dithiothreitol. The homogenate was centrifuged at 105,000 g for 45 minutes.

At 37° C., renal ornithine decarboxylase transforms an isotropic mixture of cold ornithine and tritiated ornithine in cold putrescine and tritiated putrescine. The putrescine was then collected on selective ion-exchange papers. After drying, excess non-transformed cold and tritiated ornithine were eliminated by washing 3 times with 0.1 M ammonium hydroxide. The papers were dried and the radioactivity was determined after addition of an Aqualite sample. The results expressed in fmoles (10^{-15}M) of tritiated putrescine formed per hour mg of protein are reported in the following Table

PRODUCT OF EXAMPLE	ANTAGONISM IN MG/KG	PERCENT
11	3	83
12	0.1	12
	0.3	36
	1	68
	3	94
	10	99
12	(Agonism) 10	0
14	Antagonism 3	87
15	0.3	4
	1	82

4) Determination of the androgen or anti-androgen activity by the dosage of ornithine carboxylase.

Swiss six week old male mice castrated24 hours received oralor percutaneous doses of the test products as a 0.5% suspension in methyl cellulose or in ethanol simultaneously with a sub-cutaneous injection of 3 mg/kg of testosterone propionate in solution in corn oil to determine the anti-androgen activity. Active agonists were determined in the absence of testosterone propionate. The test compounds as well as testosterone were administered in a volume of 10 ml/kg. 20 hours after the treatments, the animals were killed, the kidneys were removed and then homogenized at 0° C. with a teflon-glass grinding apparatus in 10 volumes of buffer Tris-HCl 50 mM at a pH 7.4 containing 250 mM of pyridoxal phosphate, 0.1 mM EDTA and 5 mM of dithiothreitol. The homogenate was centrifuged at 209,000 g for 45 minutes.

Principle of dosage

At 37° C., renal ornithine decarboxylase transforms an isotopic mixture of cold ornithine and tritiated ornithine in cold putrescine and tritiated putrescine. The putrescine was then collected on selective ion-exchange papers. After drying, excess non-transformed cold and tritiated ornithine were eliminated by washing 3 times with 0.1 M ammonium hydroxide. The papers were dried and the radioactivity was determined after addition of an Aqualite sample. The results expressed in fmoles (10^{-15}M) of tritiated putrescine formed per hour/mg of protein are reported in the following Table.

The same test were repeated with the following changes:

Test A: the products were administered percutaneously at 1.5 mg/kg at a volume of 10 μl.

Test B: the products were administered orally at 1 mg/kg.

Test C: the products are administered orally at 3 mg/kg.

The results are in the following Table.

The results are expressed in % of inhibition of the ODL the samples receiving only the testosterone propionate:

Products of example	ODL Test A	Test B	Test C
58	40	36	
71	32		67
75	41		
78	78		
80	62		
81	35		
83	58		

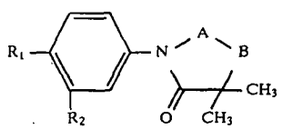
CONCLUSION

The tests show that the tested compounds of the invention possess a strong anti-androgen activity and do not have agonist activity.

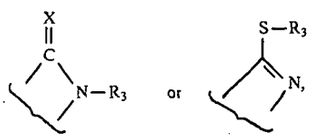
Various modifications of the compounds and method of the invention may be made without departing from the spirit or scope thereof and it is to be understood that the invention is intended to be limited only as defined in the appended claims.

We claim:

1. A compound selected from the group consisting of a compound of the formula



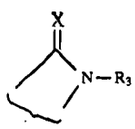
wherein R_1 is selected from the group consisting of —CN, —NO_2 and halogen, R_2 is —CF_3 or halogen, —A-B is



X is —O— or —S—, R_3 is selected from the group consisting of a) hydrogen, b) alkyl, alkenyl and alkynyl of up to 12 carbon atoms, [c)] phenyl and phenylalkyl unsubstituted or substituted with at least one member of the group consisting of —OH, halogen, —OCH_3, —CN and haloalkyl, [d)] acyl of an organic carboxylic acid of up to 7 carbon atoms, [e)] free or salified carboxy, carboxy esterified with alkyl and amidified carboxy, [f)] amino and mono and dialkylamino of 1 to 4 carbon atoms and [g)] —S—phenyl unsubstituted or substituted with at least one member of the group consisting of—CF_3 and alkyl, alkenyl, alkoxy, alkenyloxy, alkynyl and alkynyloxy of up to 12 carbon atoms with the sulfur unoxidized or oxidized to sulfone or sulfoxide, the alkyl, alkenyl and alkynyl being uninterrupted or interrupted with oxygen, sulfur or nitrogen and Y is —O—, —S— or —NH— with the provisos that when X is oxygen, R_3 is hydrogen and Y is —O— or —NH—, then R_1 is NO_2 or —CN and when X is sulfur and Y is —O— then at least one of the following conditions is satisfied, R_1 is —CN and R_2 is —CF_3 and their non-toxic, pharmaceutically acceptable acid addition salts.

2. A compound of claim 1 wherein Y is oxygen.

3. A compound of claim 1 wherein —A-B— is



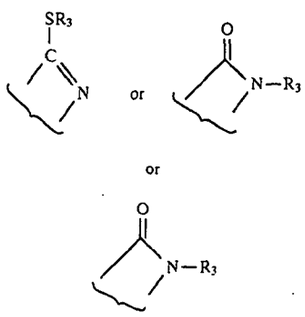
and X is sulfur.

4. A compound of claim 3 wherein R_3 is hydrogen or alkyl of 1 to 4 carbon atoms optionally substituted with a —OH or methoxy.

5. A compound of claim 1 wherein R_1 is —CN or halogen.

6. A compound of claim 1 wherein R_1 is chlorine.

7. A compound of claim 1 wherein —A-B— is



and R_3 is alkyl or alkenyl of up to 6 carbon atoms unsubstituted or substituted or uninterrupted or interrupted by oxygen or unoxidized or oxidized sulfur or unsubstituted or substituted aralkyl or acyl[or trialkylsilyl].

8. A compound of claim 7 wherein R_3 is alkyl of 1 to 6 carbon atoms unsubstituted or substituted by at least one member of the group consisting of halogen, —OH, —O acyl, carboxy, carboxy esterified with alkyl, a heterocycle, O-alkyl and unoxidized or oxidized S-aryl with the aryl unsubstituted or substituted with at least one member of the group consisting of halogen and alkoxy.

9. A compound of claim 8 wherein R_3 is alkyl of 2 to 4 carbon atoms substituted by a member selected from the group consisting of chlorine, ethoxycarbonyl[, tertbitoxy] *and tertbutoxy* carbonyl, [cyclopentyloxycarbonyl, unoxidized or oxidized 4-fluorophenylthio, morpholino, phenylmethoxy, triphenylmethoxy and methylsulfonyloxy].

10. A compound of claim 7 wherein R_3 is acetyl or benzoyl [or (1,1-dimethylethyl)dimethylsilyl].

11. A compound of claim 1 selected from the group consisting of 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl)-2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl-5-oxo-2-thioxo 1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile, 4-4,4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo-1-imidazolidinyl 2-(trifluoromethyl)-benzonitrile, 3-(3,4-dichlorophenyl)-2-thioxo-1,5,5-trimethyl-4-imidazolidinone, 1-(4-nitro-3-(trifluoromethyl) phenyl-3,4,4-trimethyl-2,5-imidazolidinedione, 4-4,5-dihydro4,4-dimethyl-5-oxo-2-(phenylmethyl) thio-1H-imidazol-1-yl-2-(trifluoromethyl) benzonitrile, 4 4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile, 3-(4-cyano 3-trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoic acid and 4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl benzonitrile.

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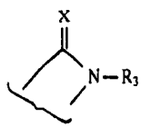
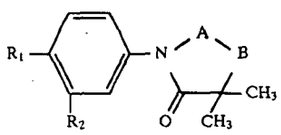
12. A compound of claim 1 wherein Y is —O— except the compounds wherein the —A-B— group is

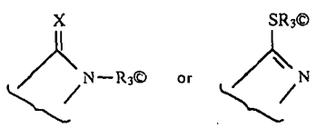


in which X is oxygen and R_3 is hydrogen, R_2 is halogen or trifluoromethyl and R_1 is nitro or halogen.

13. A compound of the formula



wherein R_1, R_2 and Y have the definitions of claim 1, —A—$_i$—B_1 is



Y is oxygen or sulfur and R'_3 is R_3 with any reactive functions protected.

14. An anti-androgenic composition comprising an anti-androgenically effective amount of at least one compound of claim 1 and an inert pharmaceutical carrier.

15. A composition of claim 14 wherein the active compound is selected from the group consisting of 4-(5-oxo-2-thioxo-3,4,4-trimethyl-1-imidazolidinyl) 2-(trifluoromethyl)-benzonitrile, 4-(4,4-dimethyl-5-oxo-2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl)-benzoitrile, 4-4.4-dimethyl-3-(2-hydroxyethyl)-5-oxo-2-thioxo 1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile, 3-(3,4-dichlorophenyl) 2-thioxo-1,5,5,-trimethyl-4-

imidazolidinone, 1-(4-nitro-3-(trifluoromethyl)-phenyl-3,4, 4-trimethyl-2.5-imidazolidinedione, 4-4,5-dihydro4,4-dimethyl-5-oxo-2-(phenylmethyl)thio-1H-imidazol 1-yl)2-(trifluoromethyl) benzonitrile-4,4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile, 4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile-3-(4-cyano 3-trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-dioxo 3-(4-hydroxybutyl) 1- imidazolidinyl) 2-(trifluoromethyl) benzonitrile.

16. A method of inducing anti-androgenic activity in warm-blooded animals comprising administering to warm-blooded animals an anti-androgenically effective amount of at least one compound of claim 1.

17. A method of claim 16 wherein Y is oxygen.

18. A method of claim 16 wherein R_1 is —CN or halogen.

19. A method of claim 16 wherein R_1 is chlorine.

20. A method of claim 14 wherein the active compound is selected from the group consisting of 4-(5-oxo-2-thioxo-3, 4,4-trimethyl-1-imidazolidinyl) 2-(trifluoromethyl)-benzonitrile, 4-(4,4-dimethyl-5-oxo-2-thioxo 1-imidazolidinyl)-2-(trifluoromethyl)-benzoitrile, 4-4,4-dimethyl-3-(2-hydroxyethyl) 5-oxo-2-thioxo-1-imidazolidinyl-2-(trifluoromethyl)-benzonitrile, 3-(3,4-dichlorophenyl)-2-thioxo-1,5,5-trimethyl-4-imidazolidinone, 1-(4-nitro-3-(trifluoromethyl)-phenyl-3,4, 4-trimethyl-2,5-imidazolidinedione, 4-4,5-dihydro4,4-dimethyl-5-oxo-2-(phenylmethyl)-thio-1H-imidazol-1-yl-2-(trifluoromethyl) benzonitrile-4,4,4-dimethyl 3-(2-hydroxyethyl) 5-oxo 2-thioxo 1-imidazolidinyl 2-(trifluoromethyl) benzonitrile, -4-(4,4-dimethyl 3-(4-hydroxybutyl) 5-oxo 2-thioxo 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile-3-(4-cyano 3-trifluoromethyl) phenyl) 5,5-dimethyl 2,4-dioxo 1-imidazolidinebutanoic and acid and 4-(4,4-dimethyl 2,5-dioxo 3-(4-hydroxybutyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile.

* * * * *

Annexure X

US005656651A

United States Patent [19]

Sovak et al.

[11] **Patent Number: 5,656,651**

[45] **Date of Patent: Aug. 12, 1997**

[54] **ANDROGENIC DIRECTED COMPOSITIONS**

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[73] Assignee: **Biophysica Inc.**, La Jolla, Calif.

[21] Appl. No.: **491,130**

[22] Filed: **Jun. 16, 1995**

[51] **Int. Cl.**[6] **A61K 31/415**; C07D 233/72; C07D 233/86; C07D 233/84; C07D 233/88; C07D 405/04

[52] **U.S. Cl.** **514/396**; 514/397; 514/398; 514/399; 514/400; 514/391; 548/320.1; 548/321.1

[58] **Field of Search** 514/396–400, 514/391; 548/320.1

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Primary Examiner—Floyd D. Higel

Attorney, Agent, or Firm—Flehr Hohbach Test Albritton & Herbert LLP

[57] **ABSTRACT**

Substituted phenylthiohydantoins are provided for use in detecting the presence of tumor cells having androgenic receptors and providing for cytostatic and cytotoxic activity toward such cells. The subject compounds provide for vehicles for specific targeting to the androgenic receptor containing cells of cytostatic and/or cytotoxic agents, heavy or light radioactive or radioopaque atoms, and the like for detection and treatment of cancer cells involving androgenic receptors or blocking androgenic receptors.

7 Claims, No Drawings

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ANDROGENIC DIRECTED COMPOSITIONS

INTRODUCTION

TECHNICAL FIELD

The field of this invention is diagnosis and treatment of androgenic related neoplasia and blockage of androgenic receptors.

BACKGROUND

The growth of prostate cancer (CaP) depends upon the presence of androgen (male) hormones, acting via androgen receptors contained in the cell's nucleus. The only effective, albeit temporary, therapy of prostate cancer is based upon interference of male hormone production or activity, using estrogenic steroids or non-steroidal substances to block the cancer cells' androgen receptors. There are a number of problems with these therapies. Steroidal estrogens had to be abandoned due to their high cardiovascular toxicity. The only steroidal compound clinically used today is cyproterone acetate. However, it also binds to the glucocorticoid and progestin receptors. Current, clinically-used non-steroidal anti-androgens such as Flutamide, Casodex or Anandron do not bind sufficiently to androgen receptors to achieve their complete blockage. None of the current anti-androgens provide permanent relief. It is suspected that the incomplete blockage of the receptors may be the reason why, with time, the therapy invariably becomes ineffective as the CaP cells mutate having proliferated metastatically. At that phase, the cells cannot be substantially influenced by any known chemotherapy or radiation.

There is the further consideration that the current armamentarium for the diagnostic staging of prostate cancer is extremely poor and yet essential in choosing the therapeutic mode. Proof of metastatic dissemination beyond the prostate excludes surgery and relegates these patients to systemic therapy. With improved diagnostic staging, unnecessary prostatectomies, a major and potentially mutilating surgery, could be avoided.

Only recently, an assay has become available for the detection of CaP cells circulating in the blood. However, that finding alone does not imply the existence of metastases. Typically, early metastases occur in the lymph nodes and the later ones develop in the bones. While ^{99}Tc scans can visualize bone defects, the lymph node metastases are extremely difficult to locate since typically, the infiltrated nodes are neither enlarged nor show changes on either magnetic resonance or x-ray computed tomography. Further, because of their low metabolic rate, the pathological nodes cannot be identified by positron emission spectrography using ^{18}F-deoxyglucose. Lymph node biopsy is possible only in the pelvic area. Early metastases in inaccessible paraaortic lymph nodes cannot be detected and consequently these patients are operated upon needlessly. Recently developed radiolabeled monoclonal antibodies against prostate cancer have only a limited use due to their low target specificity and long persistence in the blood pool, liver and spleen, which interferes with the imaging.

There have been a number of attempts to develop a CaP radionuclide scanning agent. Several radioiodinated androgen steroids were made, but they suffer from synthetic complexity. Steroidal androgens labeled with ^{18}F were synthesized as a potential PET imaging agent for prostate cancer, but their practicability is limited due to the complicated synthesis and need for specialized rare equipment (PET scanners) to detect positron emitting radionuclides. There is a further consideration that androgens promote CaP growth.

There is, therefore, substantial interest in developing novel compounds which can provide for the diagnosis and therapy of prostate cancer.

Relevant Literature

N-aryl substituted imidazolinediones have been reported in DE32 22 523; Offenlegungsschrift 26 49 925; WO88/03404; EP0 436426; EP0 494819; EP0 580459, and Teutsch, J. Steroid Biochem. Molec. Biol. (1994) 48:111–119. The activity of the trifluoromethyl, nitro- and trifluoromethyl, cyanophenyl derivatives as high-affinity ligands for the androgen receptor are reported in Teutsch, supra., as well as in many of the foregoing patents.

SUMMARY OF THE INVENTION

Specific N-substituted 3-trifluoromethyl-4-cyano phenylthio-4',4'-dimethylhydantoins, their amino and thione analogs are provided having substitution at the remaining annular atom. Substituents include cyclic and aliphatic groups. Of particular interest are groups which can be used for imaging and/or have enhanced therapeutic index.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

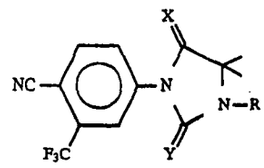
N-substituted arylthio-4',4'-dimethylhydantoins are provided, where when the 3-N-substituent comprises other than an iodoaryl group, the hydantoin is a monothiohydantoin, where the other sp^2 carbon atom is bonded to oxygen, or nitrogen (imino). The compounds find use for diagnosis and/or therapy associated with androgenic receptors. The subject compounds have high affinity for androgen receptors of a variety of cell types and are able to exert at least one of proliferation inhibition or cytotoxicity for therapy or preferential binding for use as a detection medium for cells and tissues comprising androgenic receptors or for other identification.

For the most part, the subject compositions can be divided into three categories as characterized by the N-substituent: A group of from two to eight, usually from two to six carbon atoms, more usually from two to four carbon atoms, particularly two to three carbon atoms, which may be aliphatic or heterocyclic, generally having from zero to three, more usually from zero to two heteroatoms, preferably from one to two heteroatoms, which may be derivatized, particularly alkylated or acylated, where the alkyl or acyl group will be of from one to ten, more usually one to eight, preferably of from one to six carbon atoms, where the acyl group will generally be of from two to six carbon atoms, where the non-oxo-carbonyl may be bonded to from zero to two oxygen and/or nitrogen atoms, and zero to one carbon atoms; where the heterocycle will be from five to six annular members, particularly five annular members, where the annular members will be oxygen and nitrogen, generally having from 1 to 3 annular heteroatoms; the second group will have an agent, frequently a cytotoxic agent and/or imaging agent bonded to the hydantoin, normally through a linking group of from one to six, usually one to four carbon atoms, preferably two to three carbon atoms and one heteroatom, where the linking group may include one or more functionalities, such as amino, oxy, and non-oxo-carbonyl, where amides and esters may be involved, e.g. urethanes; and the third group will involve carbocyclic aryl groups, particularly iodoaryl, which may be bonded to the nitrogen of the hydantoin through a linking group of from one to eight, usually two to six carbon atoms, preferably two to three carbon atoms, where the linking group may include an amino, oxy or non-oxo-carbonyl functionality, particu-

larly ester or amide, and the aryl group may be substituted with oxy, amino, non-oxo-carbonyl, and derivatives thereof. As the aryl group, phenyl is of particular interest.

Tissue comprising cells with androgen receptors include prostate tissue, ovary tissue, testes, etc. Hosts of interest include primates, e.g. humans, domestic animals and pets.

The first group of the compounds of the subject invention will have the following formula:



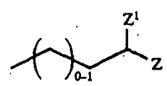
wherein:

X is oxygen or nitrogen, where the proviso that when R is iodoaryl, X may be sulfur;

Y is sulphur, with the proviso that when R is iodoaryl group, Y may be sulphur, oxygen or nitrogen, preferably X and Y are different;

R is an organic group, which may be aliphatic, alicyclic, aromatic, heterocyclic, or combinations thereof, to be further defined below.

The first group of compounds will comprise monothiohydantoins, where the other oxo group of the hydantoin will be oxygen or nitrogen. These groups will, for the most part, have R having the following formula



wherein:

Z is hydroxyl, amino, a substituted amino or a 4-diazolyl, particularly a 4-(1',3'-imidazolyl);

Z^1 is hydrogen, hydroxyl, or may be taken together with Z to provide for olefinic or acetylenic unsaturation, or a 2,2-dimethyldioxalane.

The substituents on amino nitrogen may be varied widely, depending upon the use of the compound. For cytotoxicity or antiproliferative activity, the amino group may be unsubstituted or substituted, particularly with the single acyl group, where the acyl group may serve to enhance the activity of the compound by changing its pharmacokinetic activities, by providing for a second cytotoxic or antiproliferative compound, by providing for a chelating agent for chelating a metal ion, particularly a radioactive metal or non-metallic on, for carrying a radioopaque atom, or the like. Radioactive elements include fluorine, iodine, gadolinium, technetium, etc.

Similarly, the hydroxyl, particularly the terminal hydroxyl, may be employed as a site for linking, forming ethers or esters, where the groups bound to oxygen will come within the above description.

In addition, iodoaryl groups may be employed which are linked to the nitrogen through an alkyl chain, where the alkyl chain may be of from 1 to 6, usually from 1 to 4, preferably from 2 to 4 carbon atoms. The iiodoaryl group may be linked directly to the carbon of the alkyl group or linked through a heteroatom, particularly nitrogen or oxygen, e.g. amide, secondary amine, ether, ester, etc. where the iodoaryl group may have a non-oxo-carbonyl or amino group linked to an annular carbon atom as part of the linking chain. The iodoaryl will generally have from 2 to 4, usually 2 to 3 iodine atoms, and may be further substituted with oxy, particularly hydroxy or alkoxy of from 1 to 3 carbon atoms, or amino, or a substituted amino (mono- or disubstituted), having alkyl substituents having a total of 1 to 6 carbon atoms, more usually 1 to 4 carbon atoms, and 0 to n-1 oxy groups, where n is the number of carbon atoms in the substituent. A variety of aminosubstituted symmetrically substituted triiodoisophthaldiamides and diaminosubstituted symmetrically substituted triiodobenzamides have been reported in the literature, where the nitrogen atoms are substituted with acyl groups, alkyl groups or oxyalkyl groups of 1 to 6, usually 1 to 4 carbon atoms and 0 to n-1 oxy groups. See, for example, U.S. Pat. Nos. 4,547,357; 4,021,481; 4,364,921 and 4,341,756 and references cited therein. The carboxyl group may be used to link the iodoaryl group to the thiohydantoin throgh the alkyl chain.

Illustrative R groups include: allyl, propynyl, aminoethyl, aminopropyl, 2-hydroxypropyl, 3-hydroxypropyl, 2-hydroxyethyl, 2,3-dihydroxypropyl, 2-hydroxy-3-acetoxypropyl, 4-benzamidobutyl, 4-fluorobutyl, 4-iodobut-3-enyl, 3-(4'-oxazolyl-1,3)propyl, 2-(4'-diazolyl)ethyl, 3-(propionamido)propyl, N-phenoxycarbonyl 2-aminoethyl, N-methoxycarbonyl 2-aminoethyl, 3-(3',5'-diiodo-4'-dimethylaminophenyl)propyl, 2-(3',4',5'-triiodophenyl) propyl, N-(cysteinyl, glycyl, glycyl) 2-aminoethyl, (3',6',9'-triazanonoxy)ethyl, p-hydroxyphenylpropyl, and the carboxamide of N-nitrilotriacetic acid and 2-aminoethyl.

Alternatively, various cytotoxic agents may be employed, which are joined to the subject hydantoins by any convenient linking group, which does not significantly diminish the cytotoxic or antiproliferative activity of the compound. Compounds of interest include methotrexate, taxol, 5-fluorouracil, adriamycin, bleomycin, and the like.

The subject compounds can be prepared in accordance with conventional ways, varying the particular procedure based on the particular side groups. The preparation of hydantoins conveniently involves the use of an isocyanate and a substituted α-aminoacetonitrile. By appropriate choice of the isocyanate and the α-aminoacetonitrile, one may arrive at the final product in a single step. Alternatively, by employing various protective groups, which may be subsequently removed, or providing for substituents which become involved in the formation of the hydantoin or may provide for sites for further derivatization. Various procedures are described in EPO Publication Numbers 0 494 819 and 0 580 459. Also, a significant number of examples may be found in the subject experimental section.

The subject compositions find a variety of uses associated with prophylactic and therapeutic opportunities. By providing for substituents which allow for detection by x-rays, molecular resonance imaging, radioactivity, or the like, regions of a mammalian host, particularly humans, can be investigated, where the regions are associated with an androgenic receptor. Thus, cells or tissues associated with the androgenic receptors may be visualized, so as to identify neoplasms, benign tumors, mobile cells, etc. Thus, by having substituents which have radioactive atoms, heavy metals, heavy atoms such as iodine, or the like, one can visualize physiological structures associated with androgenic receptors.

In addition, the subject compounds have proliferative inhibitory capability in inhibiting the proliferation of cells having androgenic receptors and dependent upon signal transduction associated with the androgenic receptors. The subject compounds are found to have a high affinity for the androgenic receptors, demonstrating enhanced activity as compared to prior substituted hydantoins.

In addition, the subject hydantoins can be used as vehicles for transporting other cytotoxic agents to the androgen

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receptor comprising cells. Thus, while at the same time inhibiting androgenic activation, other pathways which inhibit proliferation may also be addressed. Thus, one can greatly enhance the therapeutic index of a known chemotherapeutic agent by directing the chemotherapeutic agent to specific sites in the host.

The subject compositions may be formulated in accordance with conventional ways for use in vivo. The subject compounds are found to be stable in human plasma at physiological temperatures. The subject compounds are found to have substantially greater cytostatic and cytotoxic effects in inhibiting cell growth for neoplastic cells, as compared to normal cells, i.e. having a high therapeutic index. The subject compositions are readily formulated in conventional carriers, such as saline, phosphate buffered saline, vegetable oils, ethanol, or other physiologically acceptable carrier.

The concentrations used for the subject compounds in diagnosis and therapy will be varied widely, depending upon the purpose of the compound, the patient being treated, the stage of the disease, whether the subject compounds are being used by themselves or in a combination therapy, the manner of administration, the responsiveness of the cancer cells to the drug, and the like. The particular dosage can be determined empirically. Other components of the formulation may include buffers, stabilizers, excipients, or the like. Depending upon the particular compound and its formulation, administration may be oral or parenteral, including intravascular, subcutaneous, intratumoral, intraperitoneally, etc.

The subject compounds may also be used in competitive assays for evaluating other compounds as to their cytotoxic or cytostatic effect. Thus, specific cell lines may be employed where the effect of an agent on the cytotoxic level of a subject compound may be determined in relation to the survival rate of the target cells. Also, in mixtures of cells containing neoplastic androgenic receptor containing cells the subject compounds can be used to eliminate the neoplastic cells in the presence of normal cells. Thus, in a variety of cultures, where androgenic receptor containing cells may be susceptible to becoming or are tumorous, by maintaining a cytoxic level of the subject compounds in the medium, the cells may be selectively killed.

The following examples are offered by way of illustration and not by way of limitation.

EXPERIMENTAL

The following compounds were prepared according to the general method described by Teutsch et al., J. Steroid Biochem. Molec. Biol. 1994; 1:111–119.

EXAMPLE 1

4-[3-(2'-(N-t-butoxycarbonyl)-aminoethyl)-4,4-dimethyl-5-imino-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-136)

Crude 2-trifluoromethyl-4-isothiocyanato-benzonitrile (700 mg, 3.07 mmol) was dissolved in THF (6.0 mL). At room temperature, triethylamine (59 μL, 0.42 mmol) was added to the stirring solution followed by 2-(1',2'-ethyldiamino-N-t-butoxycarbonyl)-2-cyanopropane (682 mg, 3.00 mmol). The reaction was refluxed for 40 minutes under a N_2 atmosphere and then the solvent was removed under reduced pressure. The resulting brown residue was purified by silica gel chromatography (CH_2Cl_2; Acetone, gradient) and treated with activated carbon to yield 951 mg (68.1%) of light yellow powder.

mp:81° C.(dec); UV (MeOH):λ_{max}=234 nm (ε=18841) and 260 nm (ε=21454);

EXAMPLE 2

4-[4,4-dimethyl-3-(2',2'-dimethyl-1',3'-dioxolane-4'-methyl)-5-imino-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-163)

BP-163 was prepared as described in Example 1 using the appropriate cyanoamine. Yield=63.3%.

UV (MeOH):λ_{max}=230 nm (ε=23528), 244 nm (ε=22733), and 258 nm (ε=24590);

EXAMPLE 3

4-[4,4-dimethyl-5-imino-3-(2'-propenyl)-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-208)

BP-208 was prepared by the same method described in Example 1 using the appropriate cyanoamine. Yield=67.3%.

EXAMPLE 4

4-[5-imino-2-thioxo-3-(2'-propynyl)-4,4-dimethyl-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile (BP-211)

BP-211 was prepared as described in Example 1 using the appropriate cyanoanime. The compound was purified by chromatography (CH_2Cl_2/Acetone, 100%→50:50 gradient by 10% segments) and isolated as an orange oil. the product was not further characterized and dried as is in the subsequent hydrolysis step.

EXAMPLE 5

4-[4,4-dimethyl-3-(2'-{4"-imidazolyl}ethyl)-5-imino-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-210)

BP-210 is prepared as described in Example 1 using the appropriate cyanoamine. The compound is purified by column chromatography and isolated by removal of volatiles as a pale yellow oil in good yield. It is used in the subsequent hydrolysis without further purification.

EXAMPLE 6

4-[4,4-dimethyl-5-imino-3-(2'-p-hydroxyphenylethyl)-2-thioxo-1-imidazolidinyl]-2 trifluoromethyl-benzonitrile. (BP-2 12)

BP-212 is prepared as described in Example 1 using the appropriate cyanoamine. The crude product is then loaded into a silica gel column and is eluted with methylene chloride-acetone. The fractions containing products are combined and concentrated to dryness to give the product as a pale yellow solid. The product was used as is for further reactions.

EXAMPLE 7

4-[3-(2'-aminoethyl) 4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-138)

BP-136 (300 mg, 0.66 mmol) was dissolved in MeOH (3.5 m) and 2N HCI (0.65 mL, 1.30 mmol) with stirring at room temperature. The reaction mixture was refluxed for two hours, then the solvent was removed under reduced pressure, and the resulting solid was crystallized as the hydrochloride from isopropanol. Yield 204 mg (79.0%).

mp:>200° C.; UV (MeOH): λ_{max}=234 nm (18441) and 252 nm (ε=20891)

EXAMPLE 8

4-[3-(2',3'-dihydroxypropyl)-4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-135)

BP-135 was prepared in the manner as described in Example 7 using the appropriate imine. The product was isolated by pouring the reaction mixture over a mixture of ice and water. The product was extracted with EtOAc, dried over $MgSO_4$ and the solvent removed under reduced pressure. BP-135 was purified by silica gel chromatography [CH_2Cl_2:Acetone, gradient) then treated with activated carbon to yield a hygroscopic amorphous solid. Yield=68.1%.

UV(MeOH):λ_{max}=234(ε=17480) and 254(ε=19963);

EXAMPLE 9

4-[4,4-dimethyl-5-oxo-3-(2'-propenyl)-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-82)

BP-82 was prepared in the same manner as described in Example 7 using the appropriate imine. The product was isolated by pouring the reaction mixture over a mixture of ice and water. The product was extracted with EtOAc, dried over $MgSO_4$ and the solvent removed under reduced pressure. BP-82 was purified by treatment with activated carbon and crystallization from IPA. Yield=87.4%.

mp:146°–148° C.; UV (MeOH):λ_{max}=232 nm (ε=18022) and 254 nm (ε=21877)

EXAMPLE 10

4-[3-(2'-N-(t-butoxycarbonyl)-aminoethyl)-4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-137)

BP-137 was prepared in the same manner as described in Example 7 except the reaction was heated at 50° C. for eight hours. The resulting white crystalline precipitate was filtered off and washed with cold MeOH/H_2O (50:50). Yield (87.1%).

mp:173°–175° C.; UV(MeOH):λ_{max}=234 nm (ε=18573) and 256 nm (ε=21038);

EXAMPLE 11

4-[4,4-dimethyl-3-[2',2'-dimethyl-1',3'-dioxolane-4'-methyl)-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-134)

BP-134 was isolated as an impurity in the silica gel chromatographic purification of BP-163.

mp:50° C.(dec); UV (MeOH):λhd max=234 nm (ε=18765) and 254 (ε=21499)

EXAMPLE 12

4-[4,4-dimethyl-3-(2'-propynyl)-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-199)

BP-199 was prepared as described in Example 7. The product was isolated as colorless crystals from methylene chloride:hexane.

mp:120°–121° C.(dec);λ_{max}=206 nm (ε=17,328), 232 (ε=18,068), 252 (ε=22,003).

EXAMPLE 13

4-[4,4-dimethyl-3-(2'-{4'-imidazolyl}ethyl)-5-oxo-2-thioxo-1-imidazolidinyl-2-trifluoromethyl-benzonitrile. (BP-213)

BP-213 was prepared as described in Example 7. The crude product was purified by column chromatography and isolated as a colorless solid in high purity (≧96%, HPLC).

UV:λ_{max}=234 nm (ε=14,113.8), 254 (ε=16,047.9).

EXAMPLE 14

4-[4,4-dimethyl-5-oxo-3-(2'-p-hydroxyphenylethyl)-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-214)

BP-214 is prepared as described in Example 7. the crude product is crystallized form hexane/methylene chloride and isolated in good yield as colorless crystals.

EXAMPLE 15

4-[3-(2'-N-acetylaminoethyl)-4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-139)

The free amine of BP-138 (100 mg, 0.28 mmol) was dissolved in $(AcO)_2O$ (5.0 mL) and allowed to stir at room temperature for 30 minutes. The solvent was then removed under reduced pressure and the resulting off-white solid was purified by silica gel chromatography (CH_2Cl_2: Acetone, 95.5) to yield 102 mg (91.6%) of pure compound.

mp:77°–79° C.(dec);UV (MeOH):λ_{max}=234 (ε=18,694), 254 (21,499)

EXAMPLE 16

4-[3-(2'-aminoethyl-N-(glycyl-N'-(2"-(triphenylmethyl thioacetyl)-glycine)))-4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-197)

DCC (1.1 mg, 5.35×10^{-3} mmol) was added to a stirring solution of N-(2-triphenylmethylthioacetyl)-glycyl-glycine (2.0 mg, 4.46×10^{-3} mmol) in THF (200 mL) at room temperature. The reaction was heated at 35° C. for two hours and then purified by preparative HPLC without further work up. Yield=50.2%.

EXAMPLE 17

4-[4,4-dimethyl-3-(4'-oxybutyl-O-glycyl-N-(2-(triphenylmethylthioacetyl)-glycine)))-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-198)

To a stirred solution of 2-(triphenylmethylthioacetyl)-glycyl-glycine (2.0 mg, 4.46×10^3 mmol) in THF (200 mL) was added DCC (1.1 mg 5.35×10^3 mmol), 4-[4,4-dimethyl-3-(4'-hydroxybutyl)-5-oxo-2-thioxo-1-imidazolinyl]-2-trifluoromethyl-benzonitrile (2.1 mg, 5.35×10^3 mmol) [Synthesized as described by Teutsch et al., supra] and a crystal of DMAP at room temperature for 45 minutes. The reaction was purified by preparative HPLC without further work-up. Yield=56.8%

EXAMPLE 18

4-[3-(2-aminoethyl-N-(glycyl-N-'(2-thio)-glycine)))-4,4-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-207)

Bu_3SiH is added to a stirring solution of BP-198 in 10% TFA/CH_2Cl_2 and is purified by preparative HPLC without further workup. This product can now be used as a substrate for complexing with ^{99}Tc by standard methods.

EXAMPLE 19

4-[4,4-dimethyl-3-4(oxybutyl-O-glycyl-N-(2-(thio)-glycine)))-5-oxo- 2-thioxo-2-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-209)

Bu_3SiH is added to a stirring solution of BP-198 in 10% TFA/CH_2Cl_2 and is purified by preparative HPLC without further workup. This product can now be used as a substrate for complexing with ^{99}Tc by standard methods.

EXAMPLE 20

The Gd-DTTA-HP-$(NCO)_2$ (N^1, N^3, -(bis-[3'-hydroxy-6'-[2"-isocyanatoethyl]pyridyl-2']methyl) diethylenetriamine

triacetic acid (for a similar chelate see Tetrahedron 47, 357 (1991)) is taken up in DMF. In a separate flask BP-138 is dissolved in DMF. This solution is added to Gd-DTTA-HP-$(NCO)_2$ and stirred at 50° C. for 20 hours. The product is precipitated by Et_2O addition and purified by preparative HPLC. (BP-228)

EXAMPLE 21

The GdHDBHPI (tryptate) derivative is taken up in N-methyl pyrrolidone and BP-138 is added as a solid at once with stirring. The solution is stirred for 18 hours at ambient temperature. The product is isolated by precipitation in hexane and purified by preparative HPLC. (BP-229)

EXAMPLE 22

4-[4,4-dimethyl-3-(2'-propenyl-3'-iodo)-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-215)

BP-82 is dissolved in cold (95%) phosphoric acid, to which phosphorous pentoxide is added. KI is added and the reaction is stirred and warmed to room temperature. After 2 hours, the reaction is poured onto ice water and extracted with methylene chloride. The combined organic layers are dried over $MgSO_4$. The product is purified by column chromatography and isolated as a colorless solid.

EXAMPLE 23

4-[4,4-dimethyl-3-(2'-{4"-imidazolyl 1-[2-^{125}I]}ethyl)-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-216)

BP-216 is dissolved in methanol. Radioiodination is accomplished with chloramine-T and Na[^{125}I]I or Na[^{131}I]I or Na[^{123}I]I by known methods. [Hunter and Greenwood, Nature 1962; 194:495–496] TLC with autoradiography indicates 50–75% incorporation of the radionuclide.

EXAMPLE 24

4-[4,4-dimethyl-5-oxo-2-thioxo-3-(4'-trifluoromethanesulfonatylbutyl)-1-imidazolinyl]-2-trifluoromethyl-benzonitrile. (BP-217)

The substrate, compound RU-59063, described by Teutsch et al., supra, is dissolved in methylene chloride. Pyridine is added and the solution cooled to 0° C. Under nitrogen, triflic chloride is added slowly and the reaction warms to room temperature. The solution is cooled and pyridinium hydrochloride is filtered away. The product is isolated by removal of volatiles and stored under nitrogen at 0° C.

EXAMPLE 25

4-[4,4-dimethyl-3-(4'-^{18}Fluorobutyl)-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile. (BP-218)

a) Incorporation of ^{18}F on BP-217 is accomplished by any of the known methods practiced at PET scanners. For example, ^{18}F-CsF can be obtained from a neon target system. [Tewson and Welsh, J. Nuc. Med. 1978, 19:1339] Similarly the 2-^{18}F-ethyl can be prepared via the triflate derivative of RU-57073.

b) The ^{18}F-labeled compound, BP-218 is also prepared with a no-carrier-added ^{18}F using tetrabutyl ammonium (^{18}F) fluoride generated from [^{18}F]H_2O by the ^{18}F reaction as described by Kilbourn and co-workers. [Kilbourn et al., Int. J. Appl. Radiat. Isot. 1984; 35:599] The product is purified by preparative reverse phase HPLC. The decay-corrected radiochemical yields range from 30–50%.

c) Direct fluorination of alcohols can also be accomplished by using diethylaminosulfur trifluoride. [Tewson and Welch, J. Org. Chem. 1978, 43:1090] Thus, the hydroxybutyl, 4-[4,4-dimethyl-3-(4-hydroxybutyl)-5-oxo-2-thioxo-1-imidazolidinyl]-2-trifluoromethyl-benzonitrile, is treated with [^{18}F]Et_2NSF_3 (generated from a neon target) in THF at –78° C. After slowly warming to room temperature, the volatiles are removed and the product is purified by column chromatography.

EXAMPLE 26

7-{imidazolidinyl-5",5"-dimethyl-4"-oxo-3"-[4"'-cyano-3"'-trifluoromethylphenyl-imidazolidinyl]-2"-thioxo-1"-ethylcarbamoxy}paclitaxel. [BP-196]

A round bottom flask charged with paclitaxel (60 mg, 0.07 mmol), imidazole (90 mg, 1.32 mmol) and a magnetic stir bar was placed under a N_2 atmosphere. CH_2Cl_2 (1.5 mL) was added and the solution was stirred at room temperature. To the solution was added portionwise a solution of 1.0M $ClSiEt_3$ in THF (5×100 μL, 0.5 mmol). The progress of the reaction was monitored by HPLC. Upon completion, the 2'-(triethylsiloxy)paclitaxel was purified by preparative HPLC yielding 51.3 mg (75%). Purity by HPLC 97%. Proton NMR of the product matched values given in the literature [Chandhary et al., J. Org. Chem. 1993; 58(15) :3798–3799]

A round bottom flask charged with 2'-(triethylsiloxy paclitaxel (30 mg, 0.03 mmol) and p-nitrophenylchloroformate (310 mg, 1.50 mmol) and a magnetic stir bar was placed under a N_2 atmosphere. A solution of pyridine (200 μL, 0.247 mmol) in CH_3CN (1.0 mL) was added and the mixture stirred at room temperature for 30 minutes. The product 2'-(triethylsiloxy), 7-(p-nitrophenylcarbonoxy)paclitaxel was purified by preparative HPLC yielding 24.2 mg (69%). Purity by HPLC was 96%.

To a round bottom flask charged with 2'-(triethylsiloxy), 7-(p-nitrophenyl-carbonoxy)paclitaxel (28.0 mg, 0.014 mmol), 4-[3-(2-aminoethyl-4',4'-dimethyl-5-oxo-2-thioxo-1-imidazolidinyl]-2-(trifluoromethyl)-benzonitrile (2×8.0 mg, 0.44 mmol) and a magnetic stir bar was added CH_2Cl_2 (300 μL). The solution was stirred at room temperature for 4 hours and the product, 2'-(triethylsiloxy)-7-{5",5"-dimethyl-4"-oxo-3"-[4"'-cyano-3"'-(trifluoromethyl)phenyl-1-imidazolidinyl]-2-"thioxo-1"-ethylcarbamoxy}paclitaxel, was purified by preparative HPLC yielding 8.2 mg (85%). Purity by HPLC 97%.

To a round bottom flask charged with 2'-(triethylsiloxy)-7-{5",5"-dimethyl-4"-oxo-3"-[4"'-cyano-3"'-(trifluoromethyl)phenyl-1-imidazolidinyl]-2-"thioxo-1"-ethylcarbamoxy}paclitaxel (5.0 mg, 0.004 mmol) and equipped with a stir bar was added formic acid (250 mL). The solution as stirred at room temperature for 15 minutes and the volatiles removed under vacuum. 7-{5",5"-dimethyl-4"-oxo-3"-[4"'-cyano-3"'-(trifluoromethyl)phenyl-1-imidazolidinyl]-2-"thioxo-1"-ethylcarbamoxy}paclitaxel was purified by preparative HPLC yielding 4.6 mg (>99%). Purity by HPLC 99%.

Testing:

All compounds were tested for stability by incubation in human plasma at 38° C. for three hours and subsequent analysis by high pressure liquid chromatography. All compounds tested were found to be stable under these conditions.

All compounds were screened on a panel of normal and cancer human cell lines, including human prostate cancer cell lines, PC-3, DU-145, and LnCAP. The purpose of this experiment was to assess cell growth inhibition by measuring cytotoxicity and cytostatic effects.

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Cells (10^4/well) were plated on 96 well plates with the following controls: no cells and toxic control (1×10^{-3}M sodium dodecyl sulfate (SDS). The drug was diluted in ethanol and added directly to the wells. Plates were incubated at 37° C. under 5% carbon dioxide in sterile air. in a humidified incubator for 72 hours. A solution (50 µl of 2,3-bis-(methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino) carbonyl]-2H-tetrazolium hydroxide (XTT), 1 mg/mL) in phosphate buffered saline (PBS, 100 mM) was added to each well, In the presence of viable cells, this colorless clear solution is enzymatically transformed to give a pink coloration, read at 450 nm using a microplate reader (Molecular Devices Thermomax). The inhibition of cell growth was measured by hemocytometer, counting cell viability. (Table I)

The results of compounds hitherto investigated are shown in Tables I and II. While the cytostatic effect of BP-82 is demonstrated in PC-3 human cell line (Table II), the growth inhibition (which reflects primarily cytotoxicity and may obscure the cytostatic property) is shown for compounds BP-196 and BP-199.

It is not certain whether the cytoxicity of BP-196 can be ascribed to the taxol moiety. The toxicity of this compound vis-a-vis normal cells is also quite high.

On the other hand, it appears that such targeting does occur with BP-199 which is most cytotoxic in the human prostate cancer lines containing at least some androgen receptors, but has low cytotoxicity in a variety of other human transformed and normal cells.

The androgenic and anti-androgenic activity of the current and novel compounds was tested in a specific assay described by Fuhrman et al. [J. Steroid Biochem. Molec. Biol. 1992; 42: 787–793]. This assay uses CV-1 cells derived from monkeys transfected with human androgen receptors. (Table III and IV).

TABLE I

Inhibition of Cell Proliferation at 72 hours:
Cytotoxic Effects of the Selected Novel Anti-Androgens.

Cell Line	Tumor	IC_{50} [M] BP-82	BP-196	BP-199
DU-145	Human Prostate (receptor poor)	1.39×10^{-5}	8.67×10^{-7}	8.51×10^{-5}
Ln CAP	Human Prostate (with androgen receptors)	6.60×10^{-5}	1.31×10^{-7}	8.20×10^{-7}
PC-3	Human Prostate (few androgen receptors)	3.15×10^{-5}	3.72×10^{-8}	1.32×10^{-7}
MCF-7	Human Breast	5.00×10^{-5}	9.89×10^{-7}	1.00×10^{-4}
MCF-7/ ADR	Human Breast (adriamycin resistant)	1.51×10^{-5}	1.00×10^{-5}	1.00×10^{-5}
Ovcar 3	Human Ovary	9.65×10^{-5}	5.00×10^{-8}	$>10^{-4}$
Molt-4	Human T-cell Leukemia	4.88×10^{-5}	1.47×10^{-7}	$>10^{-4}$
L-1210	Mouse Leukemia	2.50×10^{-5}	9.70×10^{-7}	1.10×10^{-5}
	Normal			
NH DF	Dermal Fibroblast (human)	9.17×10^{-5}	1.07×10^{-7}	$>10^{-4}$
HLF-1	Normal Lung Diploid (human)	3.90×10^{-5}	8.06×10^{-6}	$>10^{-4}$
CHO	Chinese Hamster Ovary	3.45×10^{-5}	8.76×10^{-6}	1.28×10^{-5}

TABLE II

Relative Growth Inhibition*
Hydantoin Derivatives at 10^{-5} M after 6 days.

Compound	No. of cells remaining expressed as a % of control	Observation
BP-82	≈70%	growth reduction only
BP-196	≈100%	cytotoxic cell death
BP-199	≈50%	growth reduction only
BP-213	≈40%	some cytotoxicity and growth reduction
BP-231	≈30%	growth reduction only

*Cell density 10^4/well

TABLE III

Anti-androgenic potency (IC_{50}) of current and novel anti-androgens.
Transactivation assay in CV1-3.9.2 cells;
Stimulation with 0.1 nM testosterone)

COMPOUND	IC_{50}[nM]
Cyproterone Acetate	11
RU59063*	23
Hydroxyflutamide	35
Casodex	180
BP134	21
BP135	158
BP136	200
BP137	20
BP138	139
BP139	239
BP199	15
BP82	≈6.5
BP163	217

*Described by Teutsch, (Ref. 1)

TABLE IV

Androgen Activity of Anti-Androgens in CVI-3.9.2 Cells

Test Compounds*	CAT Activity [cpm]
EtOH+	2250
R1881 (0.1nM)+	5400
R1881 (1.0nM)+	5600
R1881 (10nM)+	6700
RU59063	2600
BP134	1600
BP135	1900
BP136	1800
BP137	2000
BP138	1600
BP139	1500
BP82	1300
BP163	2100

*(Except as indicated, all compounds were tested at 1 µM)
+Controls

It is evident from the above results, that the subject compounds provide for a variety of advantages in directing a variety of agents to androgenic receptors of cells. Substantial therapeutic index is available between tumor cells and normal cells. The compounds are stable and can be readily formulated in a variety of ways. In addition, the subject compounds can be used as vehicles for bringing to tumor cells having androgenic receptors, cytotoxic agents, contrast agents, radioactive atoms, and the like. In this way,

tumors having androgenic receptors may be visualized, as well as treated therapeutically.

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A compound selected from the group consisting of:

(a) 4-[3'-(2"-propenyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(b) 7{5",5"-dimethyl-4"-oxo-3"-[4'"-cyano-3'"-trifluoromethylphenyl-1'-imidazolidinyl]-2"-thioxo-1"-ethylcarbamoxy}paclitaxel;

(c) 4-[3'-(2"-propynyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(d) 4-[3'-(2"-{4'"-imidazolyl}ethyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(e) 4-[3'-{2"-N-(ρ-hydroxy phenethyl) amidoethyl}-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(f) 4-[3'-(2",2"-dimethyl-1",3"-dioxolane-4"-methyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(g) 4-[3'-(2",3"-dihydroxypropyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(h) 4-[3'-(2"-N-(t-butoxycarbonyl)-aminoethyl)-4',4'-dimethyl-5'-imino-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(i) 4-[3'-(2"-N-(t-butoxycarbonyl)-aminoethyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(j) 4-[3'-(2"-aminoethyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(k) 4-[3'-(2"-N-acetylaminoethyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(l) 4-[3'-(2",2"-dimethyl-1",3"-dioxolane-4"-methyl)-4',4'-dimethyl-5'-imino-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(m) 4- [3'-(4"-fluorobutyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(n) 4-[3'-trans-(2"-propenyl-3"-iodo)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(o) 4-[3'-gem-(2"-propenyl-2"-iodo)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(p) 4-[3'-cis-(2"-propenyl-3"-iodo)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(q) 4-[3'-methylcyclopropyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(r) 4-[3'-cis-(2"-propenyl-3"-bromo)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile;

(s) 4-[3'-trans-(2"-propenyl-3"-chloro)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile; and

(t) 4-[3'-trans-(propanyl-3"-carboranyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile.

2. A compound according to claim 1, wherein said 4-[3'-(4"-fluorobutyl)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile comprises ^{18}F or ^{19}F.

3. A compound according to claim 1 which is 4-[3'-trans-(2"-propenyl-3"-iodo)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile where iodo is radioactively labeled iodine.

4. A compound according to claim 1 which is 4-[3'-gem-(2"-propenyl-2"-iodo)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile where iodo is radioactively labeled iodine.

5. A compound according to claim 1 which is 4-[3'-cis-(2"-propenyl-3"-iodo)-4',4'-dimethyl-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile where iodo is radioactively labeled iodine.

6. In a method for specifically directing an agent to cells comprising an androgenic receptor by adding said agent to a mammalian host comprising said cells, the improvement which comprises:

said agent being a compound according to claim 1.

7. A method according to claim 6, wherein said compound comprises a radioactive atom or heavy atom.

* * * * *

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Annexure XI

The Patents Act, 1970 (As Amended in 2005)
(Section 15)

In the matter of Application no. 6087/DELNP/2005 filed in India on 27/12/2005 for Grant of Patent; Corresponding International Patent Application No. PCT/US2004/012472,dated 21/04/2004, Claiming Priority Date 03/05/2003, USA;
Applicants:- M/S GILEAD PHARMASSET, INC, USA
Applicants Attorneys: M/S K& S PARTNERS, GURGAON, INDIA
ATTORNEY'S PRESENT FOR ARGUMENT: MS PRATIBHA SINGH, MR. D.C.GABRIEL & MR AMRISH TIWARI
EXAMINER: DR SUNIL GAUTAM, EXAMINER, PATENT OFFICE, NEW DELHI, INDIA

Date of Hearing: 24/07/2014

DECISION

[A] An application titled as "A (2'R)-2'-DEOXY-2'FLUORO-2'-C-METHYL NUCLEOSIDE" was filed in the Patent office, New Delhi on 27/**12/2005**for Grant of the Patent. The details of the application are mentioned herein below:

S.NO	Detail of the application	Dates of activity
1	Application No 6087/DELNP/2005	filed on 27/12/2005
2	International application no PCT/US2004/012472	filed on 21/04/2004
3	Priority country USA	Date of priority 30/05/2003
4	publication U/S 11(A)	09/05/2008
5	Form 18 filing done by.....APPLICANT HIMSELF	26/05/2006
6	FER & Last Date for compliance of objection U/S 21(1)	06/04/2009 &06/04/2010
7	Date of reply to the FER	18/03/2010
8	SER	07/05/14 AND NOTICE OF HEARING U/S 14 07/05/14 WITH DOH 24/07/2014
9	Date of hearing U/S-14	24/07/2014

[B] The claims filed initially were 131 in nos. A FER was prepared and sent to the party with the following objections:-

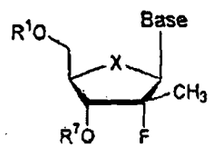
Serial Number	Objections
1	Distinguishing features as compared with prior art given is not clear and should be provided. The complete specification does not provide the advantages of the claimed invention vis a vis drawbacks of the compositions already known in the prior art.
2	Reference to foreign patent applications/patents should be replaced by Indian patent numbers
3	Claims 1-131 not clear in respect of the expression such as indicated therein.
4	Claims 1- 131 not clearly worded
5	Claims 1-131 do not sufficiently define the invention.
6	Title is not precise and does not sufficiently indicate the subject.
7	A Concise summary of the invention alongwith precise title should be filed in accordance to Rule 13(7) of PA, 1970, amendment 2005.
8	Subject matter of claims lack novelty and inventive step under section 2(1)(j) of Patents Act,1970,Amendment 2005 in view of all documents cited in ISR/IPRP and 1) BEERS M.H.; BERKOW R. (EDS.).: "MERCK MANUAL OF DIAGNOSIS AND THERAPY (17th ed.)" 1999 , MERCK RESEARCH

	LABORATORIES , WHITEHOUSE STATION N.J. XP002187299 236240 page 379, column 2, paragraph 2 -page 380, column 1, paragraph 1 2)MARCHAND, ARNAUD ET AL: "Stereospecific synthesis of unnatural.beta.-L-enantiomers of 2-chloroadenine pentofuranonucleoside derivatives" J. CHEM. SOC., PERKIN TRANS. 1 (1999), (16), 2249-2254 , XP001052612 3)VON JANTA-LIPINSKI, MARTIN ET AL: "Newly Synthesized L-Enantiomers of 3"-Fluoro-Modified ss-2"-Deoxyribonucleoside 5"-Triphosphates Inhibit Hepatitis B DNA Polymerases But Not the Five Cellular DNA Polymerases.alpha.,.beta.,.gamma.,.delta., and.epsilon. Nor HIV-1 Reverse Transcriptase" J. MED. CHEM. (1998), 41(12), 2040-2046 , XP001052614 4)VERRI, ANNALISA ET AL: "Relaxed enantioselectivity of human mitochondrial thymidine kinase and chemotherapeutic uses of L-nucleoside analogs" BIOCHEM. J. (1997), 328(1), 317-320 , XP001058113 5)LIN T-S ET AL: "Synthesis of Several Pyrimidine l-Nucleoside Analogues as Potential Antiviral Agents" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 51, no. 4, 23 January 1995 (1995-01-23), pages 1055-1068, XP004104973 ISSN: 0040-4020 6)LIN, TAI-SHUN ET AL: "Design and Synthesis of 2",3"-Dideoxy-2",3"-didehydro-.beta.-L- cytidine (.beta.-L-d4C) and 2",3"-Dideoxy-2",3"-didehydro-.beta.-L-5- fluorocytidine (.beta.-L-Fd4C), Two Exceptionally Potent Inhibitors of Human Hepatitis B Virus (HBV) and Potent Inhibitors of Human Immunodeficiency Virus (HIV) in " J. MED. CHEM. (1996), 39(9), 1757-9 , XP001052613 7)MANSOUR, T. S. ET AL: "Stereochemical aspects of the anti-HCMV activity of cytidine nucleoside analogs" ANTIVIRAL CHEM. CHEMOTHER. (1995), 6(3), 138-42 , XP001058115 8) WO 0009531:relates to a method for treating a host infected with hepatitis B comprising administering an effective amount of an anti-HBV biologically active 2"-deoxy-p-L-erythropentofuranonucleoside or a pharmaceutically acceptable salt or prodrug thereof, wherein the 2"-deoxy-p-L-erythro-pentofuranonucleoside has the formula : EMI50.1 BASE RO OH 0 wherein R is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, amino acid residue, mono, di, or triphosphate, or a phosphate derivative ; and BASE is a purine or pyrimidine base which may be optionally substituted. 9) WO 0191737 relates to A method for treating a host infected with hepatitis D virus comprising administering an effective treatment amount of 2"-deoxy-ss-L-erythro-pentofuranonucleoside of the formula: EMI60.1 or a pharmaceutically acceptable salt thereof, wherein RI is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, amino acid residue, mono, di, or triphosphate, or a phosphate derivative; and BASE is a purine or pyrimidine base that may optionally be substituted. 10) EP 0352248 L-ribofuranosyl nucleoside analogues of the formula <CHEM> wherein B is adenine, guanine, hypoxanthine, 2,6-diaminopurine or <CHEM> R<1> is H, F; R<3> is H, OH, F, N3, CN or R<1> and R<2> together constitute a chemical bond; R<3> is OH or <CHEM> wherein n is 0, 1 or 2; R<4> is OH, NH2; R<5> is H, CH3 or C2H5,with certain provisos, in the form of a mixture of alpha and beta anomers or in the form of an alpha or beta anomer for use in therapy in pharmaceutical compositions for therapeutic or prophylactic treatment of infections caused by HIV-viruses, hepatitis B virus or herpes viruses. 11)EP 0285884-relates to a novel process to produce 2",3"-dideoxynucleosides such as, for example, 2",3"-dideoxycytidine, in high yields. More particularly, the various stereoisomers of 2",3"-dideoxynucleosides are obtained. The alpha - and beta -(L)-2",3"-dideoxynucleosides and certain alpha -(D)-2",3"-dideoxynucleosides are obtained as stereochemically pure compounds not heretofore obtained. The compounds so produced are useful as antiviral and antibiotic agents. 12) WO 9613512-This invention relates to alpha and beta L-ribofuranosyl nucleosides, processes for their preparation, pharmaceutical compositions containing them, and methods of using them to treat various diseases in mammals. There are a lot of documents available, which relate to the claimed subject matter. The novel features of the invention in view of all the above cited documents need to be characterized in claim 1. The inventive feature of the invention in view of all the above cited documents needs to be defined in claim 1 to establish the inventive step.
9	Claims 1-131 fall(s) within the scope of such clause (d) of section 3 of Patents Act,1970,amendment 2005.There are many prior art citations(as mentioned above) which disclose compounds of the invention.In view of this the efficacy data (as to what is the improvement of the compounds of the invention in relation to prior art compounds) needs to be provided.

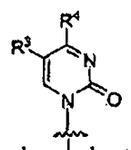
	Claims 16-30 fall(s) within the scope of such clause (e) of section 3 of Patents Act,1970,amendment 2005.Ratio of all the ingredients needs to be defined to establish synergism of the composition. **Claims 46-61 fall(s) within the scope of such clause (l) of section 3 of Patents Act,1970,amendment 2005.** **Claims 61-126 fall(s) within the scope of section 2(1)(j) of of Patents Act,1970,amendment 2005 since no process or product is defined.**
10	**Claims 1-131 appear to show multiplicity. Kindly note,the claim relates to compounds which are showing many subtituted groups,for ex. "X" in the claim relates to a number of varied groups(S,O or NH.....).It is not clear from the specification whether the inclusion of these groups would provide the same effect.**
11	**Application number should be given in form-3 & form-5.**
12	**Details regarding application for Patents which may be filed outside India from time to time for the same or substantially the same invention should be furnished within Six months from the date of filing of the said application under clause(b) of sub section(1) of secton 8 and rule 12(1) of Indian Patent Act.**
13	**Details regarding the search and/or examination report including claims of the application allowed, as referred to in Rule 12(3) of the Patent Rule, 2003, in respect of same or substantially the same invention filed in all the major Patent offices such as USPTO,EPO and JPO etc., along with appropriate translation where applicable, should be submitted within a period of Six months from the date of receipt of this communication as provided under section 8(2) of the Indian Patents Act.**
14	**Extraneous matter (marginal number, PCT application no etc.) should be deleted in specification.**
15	**Application No. should be given on drawing sheets.**
16	**Complete International preliminary examination report should be filed as only first page of PCT/IB/373 has been received.**
17	**Abstract should be filed with a title, concise summary of the invention and within 150 words according to Rule 13(7) of The Patents Rules, 2003.**

As a reply to the FER the applicants came up with the twenty claims. The same are reproduced herein below :

1. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D or P-L) or its pharmaceutically acceptable salt of the structure:



wherein the Base is a pyrimidine base represented by the following formula



X is 0; R^1 and R^7 are independently H, a monophosphate, a diphosphate, a triphosphate, a H-phosphonate, a Ct-Cto alkyl, a Ct-C\0 alkyt'sulfonyl, a phenyl Ct- C10 alkyl sulfonyl, a biphenyl Ct-C\0 alkyl sulfonyl, or a naphthyl C1-C10 alkyl sulfonyl; and R^3 isH and R^4 is NH2 or OH.

2. The (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (13-D or 13-L) as claimed in claim 1 or its pharmaceutically acceptable salt thereof, wherein R^7 is H and R^1 is a monophosphate, a

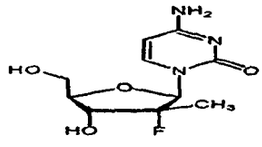
diphosphate, or a triphosphate.

3. The (2'R)-2'-deoxy-2'-fluoro-2'-C-metbyl nucleoside (13-D) as claimed in claim 1 or its pharmaceutically acceptable salt thereof, R^7 is H and R^1 is a diphosphate or a triphosphate.

4. The (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D or P-L) as claimed in claim 1 or its phannaceutically acceptable salt thereof wherein R^7 is H and R^1 is a triphosphate.

5. The (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D or P-L) as claimed in claim 1 or its phannaceutically acceptable salt thereof wherein R^1 and R^7 are H.

6. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (13-D) or its pharmaceutically acceptable salt thereof of the formula:



7. A pharmaceutical composition comprising about *50* mg to about 2000 mg or more of the nucleoside as claimed in claim **1** or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition comprising about *50* mg to about 2000 mg or more of the nucleoside as claimed in claim 2 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition comprising about *50* mg to about 2000 mg or more of the nucleoside as claimed in claim 3 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

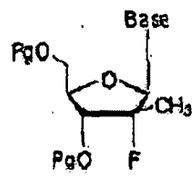
10. A pharmaceutical composition comprising about *50* mg to about 2000 mg or more of the nucleoside as claimed in claim 4 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim *5* or its p pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition comprising about *50* mg to about 2000 mg or more of the nucleoside as claimed in claim 6 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

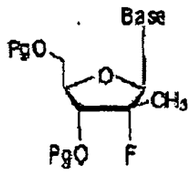
13. A method of synthesizing the nucleoside as claimed in claim **1,** which comprises

glycosylating the pyrimidine with a compound having the following structure:



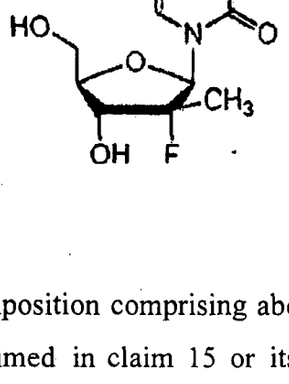
wherein R is C1-C4 lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-C,-CIO alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH_2-C_1-C_{10} alkyl, CH,-C,-CIO alkenyl, CH,-phenyl, CH,-biphenyl, CH,-naphthyl, $CH_2$0-C_1-C_{10} alkyl, CH,O-phenyl, CH,O-biphenyl, CH,O-naphthyl, 80_2-C,-CIO alkyl, 80_2-phenyl, 8 -biphenyl, 80_2-naphtyl, tert-butyldimethylsilyl, tert'butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

14. A method of synthesizing the nucleoside as claimed in claim 1, which comprises selectively deprotecting a 3'-0Pg or a 5'-0Pg of a compound having the following structure:



wherein, each_Pg is independently a protecting group selected from among C(O)-C 1- C" alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH,, CH,-C,-CIO alkyl, CH,-C 1- CIO alkenyl, CH,-phenyl, CH,-biphenyl, CH,-naphthyl, CH,O-C,-CIO alkyl, CH,O- phenyl, CH,O-biphenyl, CH,O-naphthyl, S -C,-CIO alkyl, 8 -phenyl, SO,- biphenyl, SO,- naphtyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

15. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D) or its phannaceutically acceptable salt thereof of the formula:



16. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 15 or its phannaceutically acceptable salt and optionally a pharmaceutically acceptable carrier.
17. A liposomal composition comprising liposomes comprising about 50 mg to about 2000 mg or more of the compound as claimed in claim 1 and optionally a pharmaceutically acceptable carrier.
18. A liposomal composition comprising liposomes comprising about 50 mg to about 2000 mg or more of the compound as claimed in claim 6 and optionally a phannaceutically acceptable carrier.
19. A liposomal composition comprising liposomes comprising about 50 mg to about 2000 mg or more of the compound as claimed in claim 15 and optionally a pharmaceutically acceptable carrier.
20. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D or P-L) or its phannaceutically acceptable salt substantially as herein described with reference to the accompanying drawings and as illustrated in the foregoing examples.

[C] The Ld. Examiner on re-examination (file note dated 07/05/2014) of the aforesaid amended claims , maintained objections as mentioned below:

Serial Number	Objections
1	**Subject matter of revised claims 1-20 lacks novelty and inventive step in view of documents;** **D1-WO2001/92282** **D2-WO0191737** **D3-WO2001/90121** **D4-WO2002/057425** **D5-EP0352248** **D6-WO1999/43691** **D7-WO2002/18404**

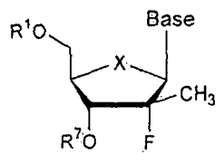
D8-WO2002/32920
D9-Perlman et al., J. Med. Chem., 1985, 28, pages 741-748
D10-Schinazi et al., Antimicrobial Agents and Chemotherapy, May 2002, pages 1394-1401

Document D1 discloses the structure in which a sugar attached to a nitrogenous base. Further D1 discloses the Markush Structure of formula XI, XVI, XVII and XVIII. All these formulas provide various options for substitutions and the substitutions discloses that the nitrogenous base may be a purine or a pyrimidine, further several options are provided for the substitution of RI, R6, R7, R9 and RI0. From these substitutions it is clear that D1 encompasses compounds similar to the compounds of the present application.
Document D2 discloses a method for treating a host infected with hepatitis D virus comprising administering an effective treatment amount of 2"-deoxy-ss-L-erythro-pentofuranonucleoside of the formula: EMI60.1 or a pharmaceutically acceptable salt thereof, wherein RI is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, amino acid residue, mono, di, or triphosphate, or a phosphate derivative; and BASE is a purine or pyrimidine base that may optionally be substituted.
Document D3 also discloses the molecule in which a sugar attached to a nitrogenous base. D3 at formula XI, XVI, XVII and XVIII provides various options for substitutions and the substitutions disclose that the base may be a purine or a pyrimidine, further several options are provided for the substitution of RI, R6, R7, R9 and R10. From these substitutions it is clear that D3 discloses the similar compounds as claimed in the present application. Document D4 discloses the compounds which falls within the scope of present application. The compounds of D4 also discloses a fluoro and an alkyl substitution in the 2" position and a hydroxyl group at 3" position of sugar molecule. The base is selected from the compounds represented by the general structure which appears to be the purine or pyrimidine derivatives.
Document D5 discloses the L-ribofuranosyl nucleoside analogues used for the treatment of infections caused by HIV virus, hepatitis B virus or herpes virus. Document D6 discloses the compounds nucleoside i.e. a nitrogenous base with sugar molecule. These compounds are chemically similar to the general structure of the present application.
Document D7 discloses the derivatives of nucleosides and comprises of a nitrogenous base with a sugar molecule.
Document D8 discloses modified nucleosides useful for the treatment of viral infections and abnormal cellular proliferation. Document D9 discloses the antiviral activity of 2" -fluoro-5-substituted pyrimidine nucleosides wherein, the 2"-position of sugar molecule is substituted with a fluoro group and 3 "-position is substituted with a hydroxyl group.
Document D10 also discloses such nucleoside analogs wherein the sugar molecules are attached at 2"-position with a fluoro group and 3 "-position with hydroxyl group and the said compounds are known for anti-HIV activity.

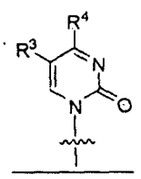
	The above said document teaches the same as claimed in the instant application and therefore considered prejudicial to the novelty and inventive step of the subject-matter of the said claims. In light of the above claims do not constitute an invention u/s 2(1)j of Indian Patent Act as amended.
2	**Revised claims 1-6 and 15 are not allowable under section 3(d) since same or similar compounds are already known in the art for similar properties. *Derivative* of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to known efficacy. There is no such data in the specification that demonstrates such therapeutic efficacy of the claimed compound over the prior art. Claims 13 and 14 are directed to a process for synthesis of the compounds as claimed in claim 1 and therefore these claims are drawn to a mere process without involving any new reactants or resultant products which is also not allowable u/s 3(d). Revised claims 7-12, 16-19 fall u/s 3(e) of the Patents (Amended) Act, 2005 as the said claim defines a mere admixture resulting only in the aggregation of the properties of the components thereof. It is not clear if the combined agents act together to provide a technical effect that is greater than just the sum of the two or more agents alone, or whether the combination is in fact a mere juxtaposition with no interaction of the agents.**
3	**Claim 20 is not allowable U/S 10(4)(c) of the Patent Act as the claim is unclear, vague and unsearchable.**

D] In view of the abovesaid final objection and nature of the objection the attorney were given an opportunity of being heard and to submit their arguments in favour of their application U/S 14. The date of hearing U/S 14 was fixed and DOH was 24/07/2014. **MS PRATIBHA SINGH, MR. D.C.GABRIEL & MR AMRISH TIWARI** appeared for hearing and submitted arguments in favour of their case. The finally revised claims (total Ten)were also given during the hearing by the applicants agent, the same are reproduced herein below:

1. A nucleoside or its pharmaceutically acceptable salt of the structure:



wherein the Base is a pyrimidine base represented by the following formula



493

X is O; R^1 and R^7 are independently H, a monophosphate, a diphosphate, or a triphosphate; and R^3 is H and R^4 is NH_2 or OH.

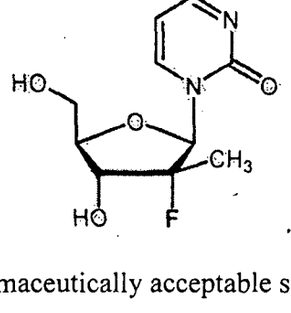
2. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, wherein R^7 is H and R^1 is a monophosphate, a diphosphate, or a triphosphate.

3. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, R^7 is H and R^1 is a diphosphate or a triphosphate.

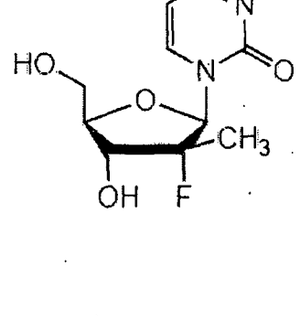
4. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R^7 is H and R^1 is a triphosphate.

5. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R^1 and R^7 are H.

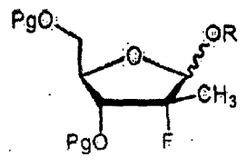
6. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:



7. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:



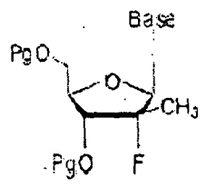
8. A method of synthesizing the nucleoside as claimed in claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure:



1-4

wherein R is C_1-C_4 lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-C_1-C_{10} alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH_2-C_1-C_{10} alkyl, CH_2-C_1-C_{10} alkenyl, CH_2-phenyl, CH_2-biphenyl, CH_2-naphthyl, CH_2O-C_1-C_{10} alkyl, CH_2O-phenyl, CH_2O-biphenyl, CH_2O-naphthyl, SO_2-C_1-C_{10} alkyl, SO_2-phenyl, SO_2-biphenyl, SO_2-naphtyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

9. A method of synthesizing the nucleoside as claimed in claim 1, which comprises selectively deprotecting a 3'-OPg or a 5'-OPg of a compound having the following structure:



wherein, each_Pg is independently a protecting group selected from among C(O)-C_1-C_{10} alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH_3, CH_2-C_1-C_{10} alkyl, CH_2-C_1-C_{10} alkenyl, CH_2-phenyl, CH_2-biphenyl, CH_2-naphthyl, CH_2O-C_1-C_{10} alkyl, CH_2O-phenyl, CH_2O-biphenyl, CH_2O-naphthyl, SO_2-C_1-C_{10} alkyl, SO_2-phenyl, SO_2-biphenyl, SO_2-naphtyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

10. A nucleoside as claimed in any of the Claims 1 to 7 as and when used for the preparation of a pharmaceutical composition or medicament.

[E] Pre grant oppositions: Two Pregrant Oppositions have been filed against the Grant of the Patent on this application.

(i) first pregrant opposition filed by : M/S Natco Pharma Ltd, Hyderabad through M/S Rajeshwari & Associates on 13/03/2014

Grounds of opposition:

- Section 25(l)(b)/(c): Lack of novelty
- Section 25(l)(e): Lack of inventive step
- Section 25(l)(t): Subject of claims 1 to 20 is not an invention within the

meaning of this Act or is not patentable under this Act

- Section 25(1)g: The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
- Section 25(l)h:The Applicant has failed to disclose to the Controller the information required under Section 8.

(ii) Second opposition filed by : Delhi Network of Positive People (DNP+), New Delhi, Initiative for Medicines, Access & Knowledge {1-MAK), lnc, USA throgh Fidus Law Chamber, New Delhi on 19/6/2014:

Grounds of the opposition:

a) 25{l)(b) - that the invention so far as claimed In any claim of the complete specification has been published before the priority date of the claim.

b) 25{1) (c) -that the Invention so far as claimed in any claim of the complete specification published on or after priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that for the applicant's claim

c) 25(1)(e) - that the invention so far as c)claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step having regard to the matter published as mentioned In clause {b) or having regard to what was used in India before the priority date of the applicant's claim .

d) 25{1){f) - that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act, in particular under sections 3(d).

e) 25{1){g) - that the complete specification does not sufficiently and clearly describe the Invention or the method by which it is performed;

f) 25(l)(h) - that the applicant has failed to disclose to the Controller the information required by S-8 or has furnished the information that in any material particular was false to his knowledge.

[F] ANALYSIS OF THE FINAL CLAIMS IN THE LIGHT OF THE OBJECTIONS MAITAINED, AND ATTORNEYS ARGUMENT:

It appears from the hearing letter that the following issues on unrevised 20 claims need to be resolved before the grant of the patent on this application:-

(i) The claims are not novel and inventive in view of the document cited and identified in the hearing letter as D1 to D9. It is noted that the citations D1 (is WO 200192282, priority date of 2001 is equivalent and family member to the cited doc as referred in FER as ISR citation no US 2003060400, Priority date 27/03/2003, hereinafter combidely D1), D2 (is WO 0191737 same as that of cited in the FER, hereinafter D2) and D5 (is EP0352248 same as that of cited in FER, hereinafter D5) are the same as raised in the

FER whereas D3, D4, D6 to D9 are freshly raised. Therefore D3, D4, D6, D7, D8 and D9 shall not be considered in the proceedings.

(ii) The Product and process claims fall u/s 3(d) and 3(e).

(iii) Unrevised claim 20 omnibus claim, is not allowed.

Since the above said three issues of the FER issued under the provisions of the Patent Act, were unresolved the applicant's attorney were given an opportunity of being heard u/s 14 for finalization of the application. Now let us discuss the above said issues in the light of amendments in the claim in the hearing and arguments placed before me by the applicants attorney in favor of their case.

Issue No 1, Novelty and Inventive step: The learned examiner in the subsequent eaxamination report cum hearing letter has raised the objection that the invention is not patentable u/s 2(1)(j).
ARGUMENTS OF THE APPLICANTS AGENT:

Applicants respectfully request the Controller to withdraw the novelty and Inventive Step rejections for at least the following reasons:

A. The cited references do not disclose or suggest the compounds of the present application;

B. Seemingly minor changes in substituents at the 2' position of the nucleoside result in large changes in activity and toxicity; and

C. Teachings of the prior art did not enable the synthesis of 2'-fluoro (down), 2'-methyl (up) nucleosides.

We now go into detail on these points.

<u>The Present Invention</u>

The present invention is directed towards pharmaceutical compounds useful in the treatment of Hepatitis C virus (HCV) infection. HCV infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be about 170 million worldwide and about 18 million in India. The present invention is directed to 2′-fluoro (down)-2′-methyl (up) nucleosides and their corresponding mono-, di-, and tri-phosphate forms. These compounds have high levels of activity against HCV, low toxicities, and other favorable characteristics largely because of this unique substitution pattern.

Presently, treatment of HCV infection with Interferons (IFNs) has been commercially available for

the treatment of chronic hepatitis for nearly a decade. Unfortunately, the effect of IFN is temporary and a sustained response occurs in only 8% - 9% of patients chronically infected with HCV (Gary L. Davis. Gastroenterology 18: S104-S114, 2000). Most patients, however, have difficulty tolerating interferon treatment, which causes severe flu-like symptoms, weight loss, and lack of energy and stamina. One more drug, Ribavirin (1- (3-D-ribofuranosyl-1-1, 2, 4-triazole-3-carboxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside analog sold under the trade name, Viriazole (The Merck Index, llth edition, Editor: Budavari, S., Merck & Co., Inc., Rahway, NJ, pl304, 1989). Ribavirin reduces serum amino transferase levels to normal in 40% of patients, but it does not lower serum levels of HCV-RNA (Gary L. Davis, 2000). Thus, ribavirin alone is not effective in reducing viral RNA levels. Additionally, ribavirin has significant toxicity and is known to induce anemia. Ribavirin is not approved for monotherapy against HCV. It has been approved in combination with interferon alpha-2a or interferon alpha-2b for the treatment of HCV. The current therapies using ribavirin and interferon require 48 weeks of treatment—nearly a whole year. Because of the severe side effects and long duration of therapy, many patients do not receive the complete course of therapy and are not cured of this disease.

In light of the fact that HCV infection has reached epidemic levels worldwide, and has tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat hepatitis C that have low toxicity to the host and that can shorten the duration of treatment.

A. The Cited References Do Not Disclose or Suggest Nucleoside Compounds Having a 2'-Fluoro (down), 2'-Methyl (up) Substitution Pattern.

References D1 – D10 fail to disclose or suggest the compounds of the present application, for at least the reasons given below.

D1-WO2001/92282

According to the Notice, "D1 encompasses compounds similar to the compounds of the present application."

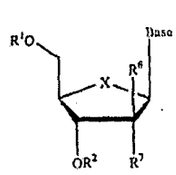
As a preliminary matter, an assertion that compounds in the prior art are "similar" to those in an application is not a proper rejection under a theory of novelty or inventive step. A novelty rejection requires that the exact compound be disclosed. None of the cited references

do so. An inventive step rejection requires a proper and reasoned showing that compounds in the prior art render compounds of the application obvious to a person of skill in the art. Any such argument is lacking in this examination report, and thus the report fails to make a *prima facie* case on inventive step. An "obviousness" argument can be established only by showing such references as may give a person skilled in the art a reason to cause the substitution. In the absence of such a reference, mere similarity in the compounds in a "general" manner does not establish obviousness.

Moreover, the Notice provides no description or bounds of what the term "similar" means. Therefore, the Applicants have no reference as to which compounds of D1 are being asserted against them.

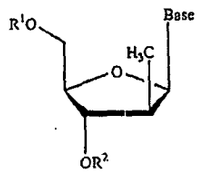
Thus, the mere assertion that compounds in the prior art are "similar" to those of the application is not a proper basis for a rejection under either a theory of novelty or inventive step. Further, as explained below, D1's compounds are not similar **to those of the present application.**

Regarding novelty, Applicants direct the Controller to Formula (XI), (XVI), (XVII), and (XVIII):



(XI)

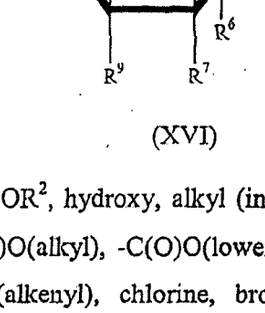
or



(XI)

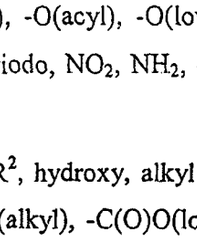
X is O, S, SO_2 or CH_2

R^7 is hydrogen, OR^3, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and



(XVI)

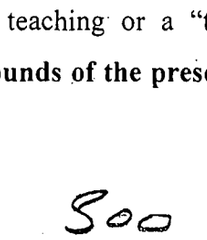
R^7 and R^9 are independently hydrogen, OR^2, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;



(XVII)

R^6 is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;

R^7 and R^9 are independently hydrogen, OR^2, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;



(XVIII)

R^8 is H, alkyl (including lower alkyl), chlorine, bromine or iodine;

alternatively, R^7 and R^9, or R^8 and R^9 can come together to form a pi bond;

The Controller may note that the R^7 substituent in these compounds does *not* include fluorine. Only chlorine, bromine and iodine were contemplated at this position, suggesting that fluorine was omitted purposefully, a negative teaching or a "teaching away". **As described in the Background section above, the compounds of the present invention have a 2'-fluoro (down) –**

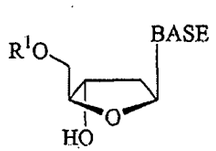
2'-methyl (up) substitution pattern. This substitution pattern is not disclosed in D1. **Further, D1 does not describe how to make a compound with a 2'-fluoro** (down) **– 2'-methyl** (up) **substitution pattern or provide any data indicating that such a compound has anti-*flaviviridae* activity, let alone anti-HCV activity.**

Regarding inventive step, the Applicants respectfully assert that no *prima facie* case has been advanced. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. A prior art reference teaches away when a person of ordinary skill in the art, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. Having explicitly excluded fluorine as an option for R7, it cannot be said that the person with ordinary skill in the art would have come up with the current solution for the technical problem given the disclosure of D1. As only chlorine, bromine and iodine were contemplated at R^7 position, suggesting that fluorine was omitted purposefully and it teaches away from the present invention.

The rejections over D1 should therefore be withdrawn.

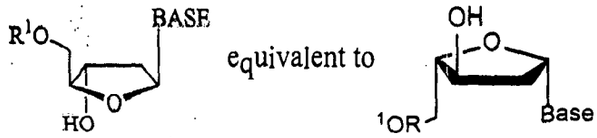
D2-WO0191737

A general structure of the compounds disclosed in the '737 publication is shown below.

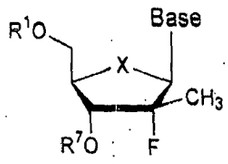


First, compounds of D2 have neither **a fluoro** nor **a methyl substituent on the ribose ring. In other words, compounds of D2 have** no substituents at the 2' position **of the ring. These compounds are therefore very different from those of the present application.**

Furthermore, the ribose ring of these compounds has a different three-dimensional orientation in relation to the base, -OH, and $-CH_2OR^1$ substituents than the compounds of the present application (the oxygen of the furanose ring is pointing towards the reader rather than away), as clearly shown here:



in contrast to compounds of the present application:

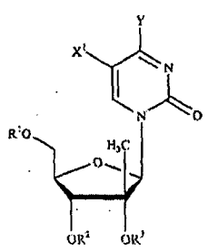


Finally, D2 is directed to methods of treating Hepatitis Delta virus, which is caused by a virus structurally unrelated to the Hepatitis C virus.

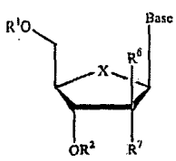
These compounds are therefore very different from, and do not disclose or suggest, the compounds of the present application. The rejection over this reference should be withdrawn for at least these reasons.

D3-WO2001/90121

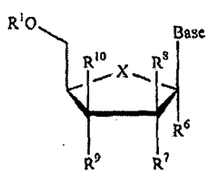
Compounds of D3 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern.



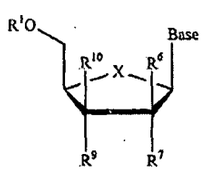
(V)



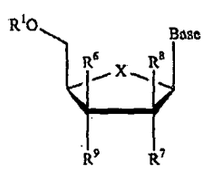
(XI)



(XVI)



(XVII)



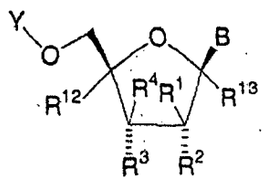
(XVIII)

In particular, the R^7 substituents do not include fluorine. Similar to the compounds of D1, in the compounds of D3 chlorine, bromine and iodine were contemplated at this position, suggesting that fluorine was omitted purposefully. **Further, D3 does not describe how to make a compound with a 2'-fluoro (down) – 2'-methyl (up) substitution pattern or provide any data indicating that such a compound has anti-*flaviviridae* activity, let alone anti-HCV activity.**

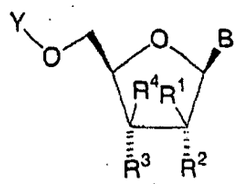
This reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

D4-WO2002/057425

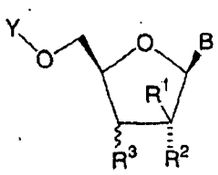
WO 2002/057425 discloses several general structures, shown here:



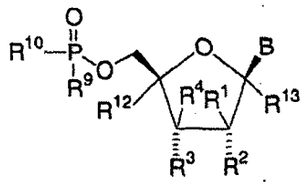
(I)



(II)



(III)



(IV)

The various R substituents can be chosen from a long list of possibilities. The possibilities are shown here, just for for R^1 and R^2:

R^1 is hydrogen, C_{2-4} alkenyl, C_{2-4} alkynyl, or C_{1-4} alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of R^2 and R^3 is hydroxy or C_{1-4} alkoxy and the other of R^2 and R^3 is selected from the group consisting of

hydrogen,
hydroxy,
halogen,
C_{1-4} alkyl, optionally substituted with 1 to 3 fluorine atoms,

C_{1-10} alkoxy, optionally substituted with C_{1-3} alkoxy or 1 to 3 fluorine atoms,
C_{2-6} alkenyloxy,
C_{1-4} alkylthio,
C_{1-8} alkylcarbonyloxy,
aryloxycarbonyl,
azido,
amino,
C_{1-4} alkylamino, and
di(C_{1-4} alkyl)amino; or

R^2 is hydrogen, C_{2-4} alkenyl, C_{2-4} alkynyl, or C_{1-4} alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of R^1 and R^3 is hydroxy or C_{1-4} alkoxy and the other of R^1 and R^3 is selected from the group consisting of

hydrogen,
hydroxy,
halogen,
C_{1-4} alkyl, optionally substituted with 1 to 3 fluorine atoms,
C_{1-10} alkoxy, optionally substituted with hydroxy, C_{1-3} alkoxy, carboxy, or 1 to 3 fluorine atoms,
C_{2-6} alkenyloxy,
C_{1-4} alkylthio,
C_{1-8} alkylcarbonyloxy,
aryloxycarbonyl,
azido,
amino,
C_{1-4} alkylamino, and
di(C_{1-4} alkyl)amino; or

R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated monocyclic ring system optionally containing a heteroatom selected from O, S, and NC_{0-4} alkyl;

D4 cannot be considered novelty destroying for the presently claimed compounds as it does not specifically point out the same substitution pattern of the instant invention. **It therefore fails to disclose this element of the invention. First, the R^1 substituent can be chosen from one of hydrogen, C_{2-4} alkeny, C_{2-4} alkynyl, or C_{1-4} alkyl, each of which may be substituted. There is** no specific disclosure **or calling out of a methyl group in this position. Second, the R^2 group may also be chosen from a long list of possibilities; there is** no specific disclosure **of a "halogen" wherein that halogen is fluorine. Further,** there is no preference **for any compounds having the same substitution pattern as that of the present invention, and there are no compounds in the Examples section which have the same substitution pattern of the instant invention. Still further,** the specification fails to provide any guidance or suggestion **as to compounds having the particular 2'-fluoro (down) – 2'-methyl (up) substitution pattern of the instant invention.**

Furthermore, reference D4 provides no guidance to persons of ordinary skill in the art concerning the synthesis **of nucleosides having a 2'-fluoro (down) – 2'-methyl (up) substitution pattern.**

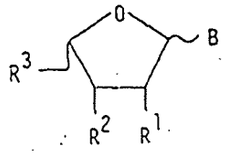
As discussed below, the successful synthesis of nucleosides having a 2'-fluoro (down) – 2'-methyl (up) substitution pattern was extraordinarily difficult.

This reference does not provide the basis for a novelty or inventive step rejection for at least these reasons, and therefore cannot be used to support a rejection on novelty or inventive step.

D4 fails to provide clear and unmistakable directions to the specific combinations

D5-EP0352248

Compounds of D5 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern:

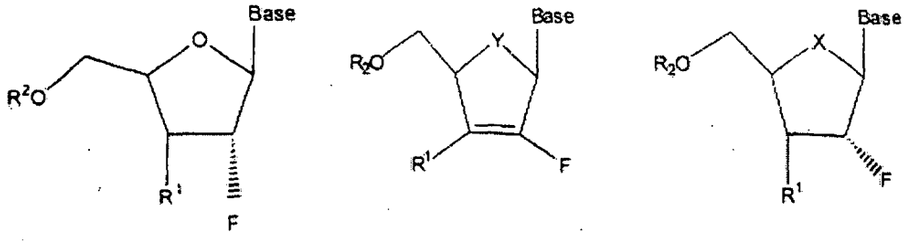


As clearly shown, these compounds are only mono-substituted at the 2' position.

This reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

D6-WO1999/43691

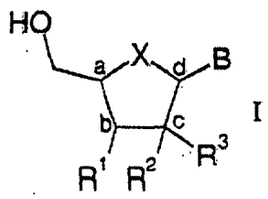
Compounds of D6 also do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern, as clearly seen from the structures.



This reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

D7-WO2002/18404

Compounds of D7 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern.



I

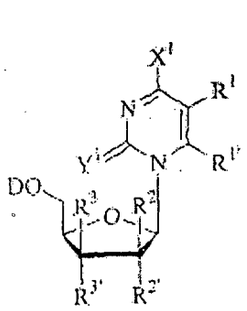
In formula I, (1) R^2 is hydrogen, hydroxyl, alkoxy, chlorine, bromine or iodine and R^3 is hydrogen; (2) R^2 and R^3 together represent $=CH_2$; or (3) R^2 and R^3 represent fluorine. These possibilities do not allow, and therefore do not include, **the 2' substitution pattern of the instant invention.**

Moreover, D7 provides over 250 preferred embodiments of formula I, the vast majority of which are mono-substituted at the 2' position (position "c") and have R^2 = -OH. Only three examples of di-substitutions at the 2' position are provided, and all of these are di-fluoro substitutions (Compounds 242, 243 and 245).

Thus, this reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

D8-WO2002/32920

Compounds of D8 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern.



[I-a]

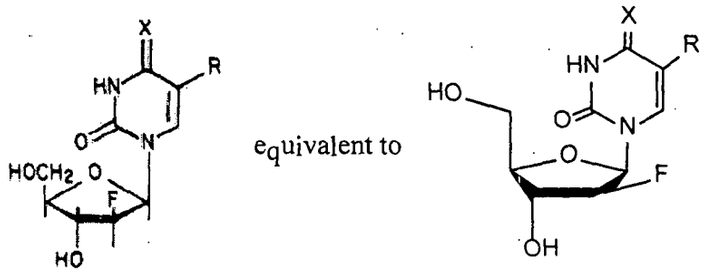
Specifically, the R^2 and $R^{2'}$ positions of formula [I-a] do not include methyl or any alkyl substituent:

each R^2 and $R^{2'}$ independently is hydrogen or halogen (F, Cl, Br or I), OH, SH, OCH_3, SCH_3, NH_2, $NHCH_3$, $CH=CH_2$, CN, CH_2NH_2, CH_2OH, CO_2H.

This reference therefore does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

<u>D9-Perlman et al., J. Med. Chem., 1985, 28, pages 741-748</u>

Compounds of D9 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern. First, the "stem" in the drawings of the furanose ring (the vertical lines on the ring where no substituent is specified) refer to hydrogen atoms and not to some other substituent. So at the 2' position for example, this is a 2'-fluoro (up) and 2'- hydrogen (down).



This observation is supported by the chemical name of the compounds. Also, the fluoro substituent at the 2' position is in the "up" position and not in the "down" position.

This reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

<u>D10-Schinazi et al., Antimicrobial Agents and Chemotherapy, May 2002, pages 1394-1401</u>

Compounds of D10 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern. First, this reference is primarily concerned with compound DPC 817, which does not have substituents at the 2' position and in fact has a double bond between the 2' and 3' carbon atoms.

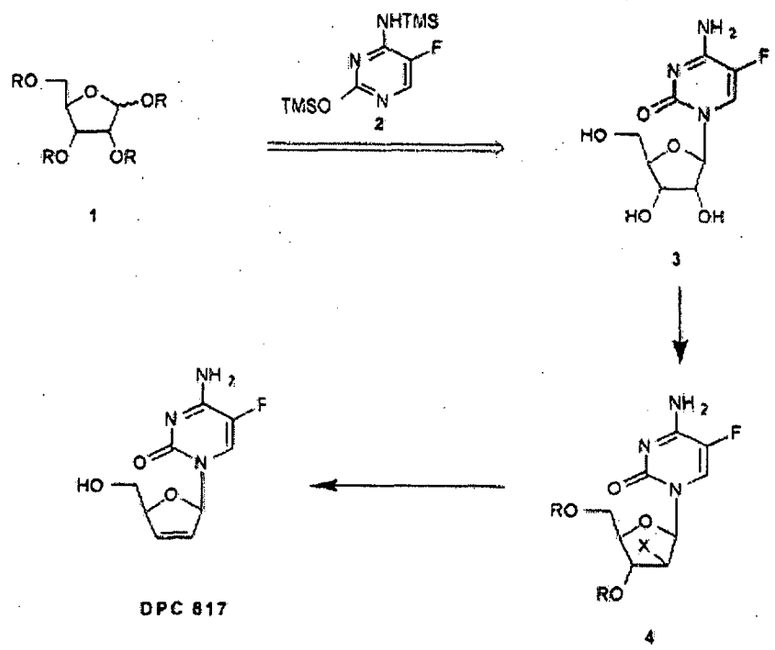


FIG. 1. Synthesis of DPC 817.

Second, the intermediate compounds used to make DPC 817 do not have the substitution pattern of the present application.

Also, this reference regards compounds having activity against the human immunodeficiency virus (HIV), which is a different target than HCV.

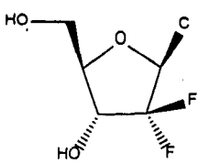
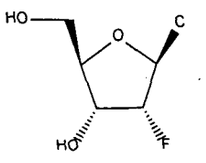
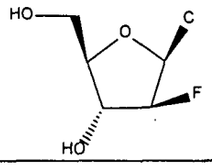
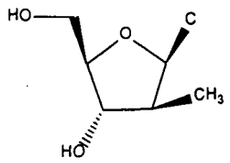
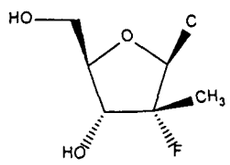
This reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above. In view of the above discussion, it is the Applicant's view that the present invention is in fact novel and the objection under section 2(l)(j) of the Patents Act should be withdrawn.

<u>B. Seemingly Minor Changes in Substituents at the 2' Position of Nucleosides Result in Large Changes in Activity or Toxicity.</u>

The particular substitution pattern of the claimed compounds is unique, and imparts unexpectedly high activity and low toxicity to them.

Applicant re-submits Table 1, which shows activity and cytotoxicity of various 2'-substituted nucleosides. The data for Compound 5 (present invention) is unexpectedly better than the comparator compounds.

Table 1. Activity and Cytotoxicity Comparison of 2'-Substituted Cytidine Analogs

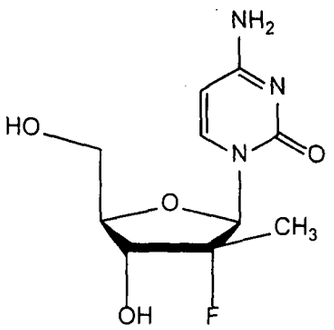
			Cytotoxicity			
No.	**Compound**	**HCV Activity EC_{90} (μM)**	**Clone A** CC_{50} (μM)	**Hep G2** CC_{50} (μM)	**BxPC3** CC_{50} (μM)	**CEM** CC_{50} (μM)
1		<1	<0.1	<1	<1	<1
2		5.66	>100	400	10	6
3		Cannot determine: Toxic to cells	<50	200	5	5
4		9.73	10.47	40	<1	<1
5		4.5	>100	>1000	>1000	>1000

"C" represents cytosine.

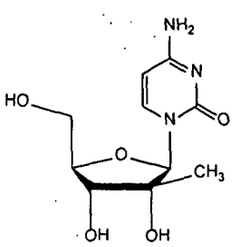
For example, the 2'-fluoro (down) – 2'-hydrogen (up) compound (Compound 2) shows good HCV activity but is also toxic in certain cell lines. The 2'-fluoro (up) – 2'-hydrogen (down) compound (Compound 3) is too toxic to test. The 2'-di-fluoro compound (Compound 1) is very active but also very toxic. Finally, the 2'-methyl (up) – 2'-hydrogen (down) compound (Compound 4) has activity but is also toxic against certain cell lines.

These data show the high degree of unpredictability of these compounds. Compound 5, therefore, has a very unexpected and surprising activity and toxicity profile.

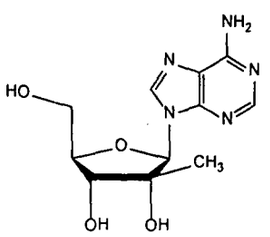
In addition, the learned Controller may refer to the experimental data already disclosed in the specification which clearly indicates that 2'-fluoro (down)-2'-methyl (up) substitution pattern on the nucleoside are non-toxic and bioactive as compared to other nucleoside compounds. Particularly, Tables 1 to 9 of the present application compare activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (compound 5) with 2'-C-methylcytidine and 2'-C-methyladenosine.



(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine **(compound 5)**



2'-C-methylcytidine



2'-C-methyladenosine

The unexpected properties of Compound 5 cannot be predicted and, thus, could not have been obvious **from the other comparator compounds.**

As such, Applicants assert that from the data presented above, it is clear that the 2'-fluoro (down)-2'-methyl (up) substitution pattern present in the nucleosides of the present application unexpectedly imparts therapeutic activity against HCV while at the same time exhibiting no toxicity to the host.

In view of above, the compounds of instant invention are novel and not obvious to one skilled in the art. Hence the Applicant respectfully requests the Controller to waive this objection.

C. The Prior Art Did Not Enable the Synthesis of 2'-Fluoro (down), 2'-Methyl (up) Nucleosides.

None of the cited references describe how to make the compounds of the present application.

The current applicant, Gilead Pharmasset LLC ("Gilead"), has successfully defended challenges to corresponding applications in other countries—in particular Norway and the United States—by Idenix Pharmaceuticals, Inc. ("Idenix"). One issue central in these challenges was whether Idenix made 2'-fluoro (down), 2'-methyl (up) nucleosides before the inventor of the Gilead applications did.

Both, the court in Norway and the Patent Trial and Appeal Board (PTAB) of the United States Patent and Trademark Office (USPTO) decided that they did not, and that Gilead was the first to do so.

The Oslo District Court issued a decision on March 21, 2014 (Annex A) **which, in part, discussed how difficult it was to make 2'-fluoro (down), 2'-methyl (up) nucleosides. The Oslo District Court wrote**

> "*... the skilled person will be faced with a number of choices that have to be made in order to be able to produce or synthesise* [a 2'-fluoro-2'-methyl nucleoside]. *Firstly, a choice needs to be made between the sugar route and the nucleoside route. Thereafter, starting materials need to be chosen. Many alternatives will be available in respect of both route alternatives, and the choices will not be perceived as obvious. Moreover, a fluorination reagent needs to be selected. This also involves numerous alternatives. Even if one starts out from the most precise and restrictive part of the description, as well as the alternative claims, there are several options. One may for example choose both natural and synthetic bases. Finally, one needs to select reaction conditions and solvents, etc., for the various reactions. The Court notes that minor variations in chemical processes may have a major impact and be decisive in terms of whether or not one succeeds in bringing about the desired compound.*" *(emphasis added)*
>
> ***Oslo District Court, Case No. 12-155575TVI-OTIR/01 and 13-170456TVI-OTIR/01, 21 March 2014, page 32.***

The Court then gave its judgment on whether Idenix made any 2'-fluoro-2'-methyl nucleosides before the priority date of the present application:

"...the skilled person will, in order to carry out the invention, have to find an overall solution that will depend on the sum total of a number of partial solutions. The Court is of the view that the skilled person would not be able to carry out the invention without a considerable amount of trial and error. This conclusion is also supported by the fact that Idenix itself would not appear to have been able to produce the compound until at a much later date."

***Id.*, p. 33.**

The Oslo District Court found the Clark patent to be valid and the Idenix patent to be invalid.

The PTAB of the USPTO reached a similar conclusion: Clark was the first to invent 2'-fluoro (down), 2'-methyl (up) nucleosides.

Testimony by Dr. Victor E. Marquez on this point was important to the decisions of both the Oslo District Court and the PTAB (USPTO). In his testimony for the Norway trial (Annex B), **Dr. Marquez described, based on his review of Idenix's internal documents, that Idenix employed** a team of Ph.D. chemists and consultants specializing in fluorination chemistry, all of whom were unable to make the 2'-fluoro (down), 2'-methyl (up) nucleosides for a period of over three years. **Dr. Marquez noted that these chemists tried at least** seven potential chemical routes and 16 different reagents **in attempts to make a 2'-fluoro (down), 2'-methyl (up) nucleosides.** All of these attempts failed. **It was only after the publication of the Clark patent application (corresponding to 6087/DELNP/2005) when researchers at Idenix were finally able to synthesize compounds of this type.**

In summary, the applicants request the Controller to withdraw the novelty and inventive step rejections because (A) none of the cited references describe or suggest the same compounds, (B) the compounds have unexpectedly high activity and low toxicity not suggested by the prior art, and (C) prior art did not teach how to make the claimed compounds, as illustrated by Idenix's difficulties.

Thus, it is Applicant's position that (2'R)-2'-deoxy-2'fluoro-2'-c-methyl nucleoside of the present invention remain novel and inventive in view of the cited reference. As such, Applicant respectfully submits that the Examiner's rejection for lack of novelty and inventiveness is improper and should be withdrawn.

D. Corresponding Applications in Many Other Countries Have Been Granted.

The Controller may note that claims similar to those presented here in 6087/DELNP/2005 have been granted in numerous countries (see Form 3 details):

Country	Patent No.
Australia	2004253860
Canada	2527657
China	200480019148.4
Colombia	1214
Indonesia	P0028288
Israel	172259
Israel (Divisional)	210367
Japan	4958158
Japan (Divisional)	5266357
Korea	200883703
Mexico	275935
Malaysia	138477
Norway	0333700
New Zealand	543867
Philippines	1-2005-502136
Russia	2358979
Singapore	117252
South Africa	2005-09521
United States	7429572
United States (Continuation)	8415322

Exemplary claim sets from some of these countries are included in **Annex 3**.

In view of these arguments, the claimed compounds of the instant application are novel and not obvious to one skilled in the art. Hence the Applicant respectfully requests the Examiner to waive these objections.

OBSERVATION:- In respect of novelty & Inventive Step of the present claims 1 to 10 the arguments of the Ld Attorney is agreeable. It has been noticed that learned examiner has raised citation from D1 to D9 in the hearing letter wherein D1, D2 and D5 were similar to the citation raised in the FER for examination of Novelty and inventive step. Therefore only Matching citations of hearing letter and FER are being considered for finalization of this application w.r.t. novelty and inventive step of the invention. The D1 is the closest prior art to this claimed invention. On comparing the finally revised claims from 1 to 10 with citation given in the FER and hearing letter primafacie does not appear to affect the novelty and inventive step of the present set of the claims. This has further been confirmed by grant of patent with similar set of claims in various jurisdictions namely JPO (Patent No. 4958158 and 5266357), US (Patent No 7429572 and 8415322). Therefore I have no hesitation to acknowledge Novelty and Inventive step of the present set of claims.

Issue No 2, Application of Section 3 (d): Ld Exr has raised the non Patentability objection U/S 3(d) in FER & Hearing letter On the basis of cited documents D1, D2 & D5. The arguments of the applicants agent in this regard are reproduced herein below:

ARGUMENTS OF THE APPLICANTS AGENT:

Arguments of the applicants Attorney has been reproduced herein below:

Applicants respectfully ask the Controller to withdraw the rejection over Section 3(d) for at least the following reasons.

A. A Rejection Based on Section 3(d) is Not Applicable

There is a fundamental error in the application of Section 3(d) to the present case. The submissions of the Applicant are as under:

a. Section 3(d) does NOT apply to all pharmaceutical and chemical inventions;

b. The provision clarifies its application viz., "**new forms of known substances**" – meaning thereby – there has to be a "known substance". In the absence of a "known substance" there cannot be a "new form"

c. The section further clarifies that even "new forms of known substances" are patentable – if significant therapeutic efficacy is shown.

Thus,

(i) there has to be a known substance;

(ii) the application has to be for a new form of that substance;

(iii) that new form in order to be patentable has to demonstrate therapeutic efficacy.

(iv) Therapeutic efficacy has to be established by means of filing comparative data.

In order for Section 3(d) to have application the first two conditions have to be satisfied. The testing of a product for therapeutic efficacy is only after the first two conditions are found applicable.

The Applicant respectfully submits that Section 3(d) only bars a new form of a known substance which does not result in the enhancement of known efficacy of that substance or a new property or

new use for known substance or new use of a known process. It is submitted that Section 3(d) was designed to make a higher bar of innovation for patentability of new salts, esters, and other derivatives (second generation compounds) of known substances (e.g. pharmaceuticals) unless they differ significantly in properties in regard to efficacy to avoid alterations being made to the FORM of such substances and thus extending market exclusivity of known substances. It is NOT meant to create a higher bar for new substances by deeming all new compounds to be merely derivatives of known compounds.

As discussed earlier in detail that presently claimed compounds are novel and inventive and do not exist in the prior art. The claimed compounds are NOT new forms of known compounds. Thus, it must be concluded that the presently claimed compounds are not salts, esters, ethers, polymorphs, pure forms, particle sizes, isomers, mixtures of isomers, complexes, combinations or other similar simple derivative forms of the reference compounds, thereby, making them totally new compounds with unpredictable properties absent Applicant's invention. As such, these new compounds do not fall within the ambit of Section 3(d). The present improper use of 3(d) attempts to define every new compound as merely a derivative of some known structural chemical core thereby barring patentability, despite the compound's novelty and inventiveness in the unpredictable chemical arts.

The Controller may also refer to Judgment given by Delhi High Court in ROCHE *V.* CIPLA (Erlotinib Hydrochloride) case, wherein impugned Roche Patent was held valid and Erlotinib was not considered as a mere derivative or new form of known substance Gefitinib (Erlotinb differs from Gefitinb with respect to the substitution of a methyl group with ethynyl at the third meta (3') position). Following were some key findings by the Delhi High Court w.r.t. Section 3(d) and known substance:

"Cipla's challenge to the validity of the impugned patent on it being attracted by section 3(d) did not find favour with the court on account of Cipla failing to meet the positive evidence onus to sustain that challenge. The court observed that Cipla had to prove that IN '774 is the 'new form of an old substance' (the 'old substance' being EP '226) and that Example 51 of EP '226, through further reaction, can result in IN '774 is insufficient to establish 'new form of an old substance' unless proven to be contrary, which none of their witnesses deposed."

In light of the above, the Applicants submit that the claimed compounds are completely novel and inventive and are not merely new forms (salt, ester, derivative, etc.) of *"known substances"*. Thus, Section 3(d) cannot be applied to the claims of the instant application.

Without prejudice to the submission that Section 3(d) is not applicable, it is submitted that as discussed above, and with respect to Table 1, compounds of the present application have a unique and novel 2'-fluoro (down) – 2'-methyl (up) substitution pattern. This substitution pattern, among other aspects of the compound, imparts both high potency and low toxicity to the compounds. Compounds which differ in the substitution pattern at this same position do not possess the same potency vs. toxicity profile.

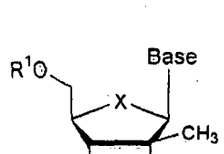
The Controller may note that the Table 1 discloses activity and cytotoxicity data of various 2'-substituted nucleosides. The data presented for the biological profile of Compound 5 (present invention), includes both the intrinsic potency against HCV and cytotoxicity, which exhibits better and unexpected activity over the structurally closest compound. This unexpected activity cannot be predicted based on the structure-activity relationship of related compounds. Further, it is unexpected that appending both a methyl substituent and a fluoro substituent to the 2'-position of a 2'-deoxycytidine nucleoside wherein the methyl substituent is in the β-position (up) and the fluoro substituent is in the α-position (down) would produce a compound (Compound 5) that is both a potent inhibitor of HCV replication in cell culture and lacks cytotoxicity. It is clear that compounds containing either a single fluorine atom in either the 2'-β-position (Compound 3) or the 2'-α-position (Compound 2) or containing di-fluoro substitution at the 2'-position (Compound 1) demonstrate activity against HCV but also show significant cytotoxicity in one or more cell lines tested. In addition, the 2'-deoxycytidine analog (Compound 4) with only a 2'-β-methyl substituent shows substantial cytotoxicity against all cell lines.

In the light of the above, the Applicants submit that the claimed compounds are completely novel and inventive. Thus, Section 3(d) cannot be applied to the claims of the instant application. Hence the Applicants respectfully request the Controller to waive this objection.

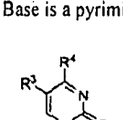
OBSERVATION:- As discussed earlier the citation D1, D2 and D5 cited in the hearing letter are similar to the FER and the closest prior art being D1 as herein before described which discloses the similar compound with changes of orientation of FLUORINE in sugar moiety of the claimed compound(cf comound XI of D1). The change in the orientation of the fluorine downwards in the sugar moiety of claimed compound changes the properties such as lowering of cytotoxicity. This kind of variation of orientation of the groups can make the compound novel and Inventive however, in the eyes of section 3(d) this novel and inventive substance is " considered to be the same substance, unless they differ significantly in properties with regard to efficacy". According to the hon'ble SC decision in Novartis AG vs GOI, CA No. 2706-2726/2013 para 180-192, the efficacy means the therapeutic efficay. Therapeutic effcacy may be proved by showing clinical trials so as to prove significant difference in the properties with regard to efficacy. Therefore the compound XI as discosed in D1 is the closest prior art as being structurally closed to the presently claimed compound and therefore is the same compound to D1 in the eyes of the section 3(d). Furthermore the compound as disclosed in D1 and in the presently claimed compound are having the same use in the treatment of HCV infection and flavivirus infection . In such circumstances the applicants must

have shown the therapeutic efficacy data to show the significant difference in the properties with regard to efficacy by providing the clinical trials etc. The applicants showed the cytotoxcity data to prove the difference in properties which is insufficient to proove significant increase in the therapeutic efficacy. The data does not show any clinical trials to prove the improvement in the terapeutic efficacy.

The formula of the claimed compound of this application:

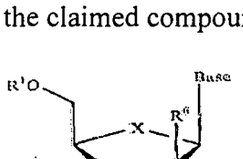


wherein the Base is a pyrimidine base represented by the following formula



X is O; R^1 and R^7 are independently H, a monophosphate, a diphosphate, or a triphosphate; and R^3 is H and R^4 is NH_2 or OH

The formula of the claimed compound no (XI) of citation D1:



(XI)

R^7 is hydrogen, OR^3, hydroxy, alkyl (includin
Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl),
alkyl), -O(alkenyl), chlorine, bromine, iodin
N(lower alkyl)$_2$, -N(acyl)$_2$; and R6 is H,OH, R, Azido, Cino, alkenyl, alkyne.....Chloro, Bromo, Fluoro, Iodo, NO2

The applicants submission that for application of sec 3(d) there should be the known substance is not acceptable as the intention of the law comes out from the words "...salts, esters....shall be considered the same substance, unless they differ...". These words clearly shows that the claimed compound may have passed the test of novelty on minor changes in the molecule but to qualify sec 3 (d) which this compound does not show the properties with regard to the therapeutic efficacy". In other words we can say that a molecule with minor changes in addition to the novelty must show significantly enhanced therapeutic efficacy as compared to the nearest prior art molecule which is structurally and functionally close. Similar is the case here, the molecule as claimed in the present application is structurally and functionally similar to the molecule of Document D-1 (XIth compound may be novel due to the different orientation (stereo isomerism) of the fluoro group in the sugar moiety of the nucleoside but to qualify the requiement of section 3 (d) such novelty must result in significant enhancement of the therapeutic efficacy as compared to the cited molecule D1 compound XI therapeutic properties. The data provided in Table 1 cannot be considered sufficient and appropriate to show the enhancement of the therapeutic efficacy. The judgement of Honourable Delhi court in case of Roche vs Cipla does not apply on this case as

erlotinib and Gefitinib were different in groups by substitution of a methyl group with ethnyl group at the third meta position whereas in the present case the difference lies only in the orientation of fluoro group of compound XI of D1.

In view of all this the claimed compound appears to fall U/S 3(d) of the Patent Act.

The claims 8 & 9 relates to synthesis of the compound as claimed in claim 1 which is in the definition of novelty u/s 2(1)(j) read with section 3(d) has been considered as the same substance to the closest prior art compound of D1. Furthermore, the reactants and reaction conditions are almost similar for the preparation of the compounds of present invention and the closest prior art. Hence the claim numbers 8 & 9 are also not patentable u/s 3(d) as it amounts to mere use of known process which doesn't result in a new product or doesn't employ any new reactant.

The objection u/s 3(e) of the learned examiner maintained in the FER as well as in the hearing letter is considered complied with as in the revised claims 1-10, the composition claims have been deleted.

The objection of non allowance of omnibus claim is complied with as the said claim was deleted by the applicant.

In view of the above discussion herein above the application under consideration with claims 1-10 is not patentable u/s 3(d) of the patent act and liable to be refused .

The applicants plea that the hearing u/s 25(1) should have been appointed inviting both the parties (Opponents and Applicants) in the hearing to decide simultaneously the issues pending in the FER, hearing letter and the issues raised in both the oppositions is not agreeable for the following reason.

Arguments of the applicant:-

Firstly the arguments of the applicant's in this regard must be seen:-

"we would like to submit that whenever there are oppositions filed during the prosecution in an Indian Patent Application, it is practice and precedent that the examination (u/s 14 hearing) and the pre-grant opposition (u/s 25(1) hearing) coincide once all the formalities are fulfilled/over relating to the opposition.

The examination and pre-grant opposition is co-terminus as per the Indian Patent practice and precedent. In UCB Farchim Vs. Cipla, it was held that "*.....This court finds merit in the contention that the pre-grant opposition is in fact "in aid of the examination" of the present application by the Controller.*"

The same had reiterated in Snehlata Gupte Vs. Union of India as below:

".....The language of Rule 55 (6) leaves no manner of doubt that these two actions i.e. the consideration of the representation and the final decision on the application of Grant of Patent take place simultaneously."

Further, same has been practiced in many applications where pre-grant opposition has been filed during the prosecution. The various Courts and the Patent office in India held that whenever there are pre-grant Oppositions filed during the prosecution of an Indian Application, both the proceedings i.e. prosecution and Opposition ought to be heard at the same time and order could be passed to conclude the proceedings. Thereafter the Applicant can go to IPAB by way of an Appeal if it so desires. On the other hand, if the pre-grant Opponent is not satisfied with Controller's order they can file post-grant Opposition within one year from the date of grant. The above process involves only one single hearing before the Controller and thereafter the other remedies are open to the Parties as mentioned above. However, if the prosecution hearing is held while a pre-grant opposition is pending, the Controller of Patents cannot grant the Patent since the pre-grant Oppositions is pending and on the other hand, if Controller rejects the Application during prosecution, the Applicant will have to go to IPAB for restoring the application and get the case restored at IPAB and again come before the same Controller for re-opening the case for the Oppositions. Now, the Controller will have to re-open the case as well as pre-grant opposition and follow all the due process of Oppositions and once again hear the matter. By the time, even entire term of the Patent could expire.

The issue is why the Controller should pass two separate orders which may be same or different when the grounds of prosecution and pre-grant Oppositions are more or less same. Hence, coinciding the hearing of prosecution (u/s 14), opposition (u/s 25(1)) saves a lot of time and efforts not only on the part of Controller, but also for all other interested parties.

Further, term of Patent is just twenty years and unlike many other Patent office practices, there is no Patent term extension is available to the Indian Patents Applicants. Filing an Appeal on the Controller's rejection on Opposition during prosecution and getting the case restored and again undergo the pre-grant proceedings before the Controller will be harassment to the Applicant and unduly delay and rob the Applicant's valuable term of the Patent. Furthermore, even one of the opponents is also of the view that prosecution and opposition ought to be co-terminus (see attached letter from Fidus Law Chambers).

OBSERVATION:-

The said application was under the procedure of examination under section 12 & 13 and the objection of the Ld. Examiner was still pending for finalization. To finalise the said pending issues of the FER the Ld. Examiner has recommended hearing u/s 14 to hear the applicant to decide the

grant of Patent. Since the pregrant opposition was filed later to the last date for compliance of all the objection as mentioned in section 21(1) therefore, the process to consider the pregrant opposition was pending till the completion of the procedure of section 12 & 13. For the consideration of pending objections a hearing letter was issued and applicant was heard and wherein decision on this application is the refusal. Pending objections shown in the hearing letter were similar to the objection of the FER and accordingly only the applicant was heard u/s 14. As per rule Opponents could not be involved in the examination procedure, so not heard. Opponents will be involved only on the inception of proceedings under section 25(1). The pregrant opposition effect is infructuous by refusal of this application. However, if procedure of 25(1) read with rule 55 is initiated later, the opponents need to be heard and decision to be issued u/s 25(1) read with section 15. The referred judgement of honourable court in UCB Franchim vs Cipla is not applicable here as it was about the maintaining of appeal in High court or IPAB in respect of decision issued u/s 25(1). Further in this case it has been held "that pregrant opposition is in fact in aid of examination" is true however, this has not barred to work upon the home procedure first. Pre grant opposition filed here is treated as disposed off in favour of Opponent with the refusal of patent application at this point of time.

Second judgement of honourable court in Snehlata Gupte Vs. Union of India quoted by the applicant that the language of Rule 55(6) leaves no manner of doubt that these two actions i.e. the consideration of the representation and the final decision on the application of grant of patent take place simultaneously.

This judgement of honourable court is also not applicable in this case as application of procedure of rule 55 has not been initiated yet. Therefore, the contention of the applicant that hearing u/s 25(1) read with section 14 should have been taken together cannot be accepted.

[E] In view of the above mentioned observations I refuse to proceed for grant of patent on this application.

The documents filed by the opponents as mentioned above will be sent to the applicants alongwith this decision on 14/01/2015 for further processing as per the requirement of the Patent Rules.

The oppositions filed u/s 25(1) by the opponents as mentioned above at present is infructuous with this rejection of the application U/S 15 for further processing of the Patent Grant.

DATED: 13/01/2015

(HARDEV KARAR)
DEPUTY CONTROLLER OF PATENTS & DESIGNS
PATENT OFFICE, NEW Delhi

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