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FEBRUARY 1, 2024

THE CONTROLLER OF PATENT
THE PATENT OFFICE
DELHI, MUMBAI, KOLKATA, CHENNAI

RE: OPPOSITION U/S 25(2) OF THE PATENT ACT – BY LOW COST STANDARD THERAPEUTICS AGAINST INDIAN PATENT NO. 419253 (FORMERLY PATENT APPLICATION NUMBER 9313/DELNP/2011) DATED 28/11/2011
APPLICANT: GILEAD SCIENCES, INC.

Respected Sir,

We are filing this representation by way of Post-Grant Opposition along with annexures u/s 25 (2) of the Patents Act, 1970 and Rule 55 of the Patent Rules, 2003 in Form 7.

The Learned Controller is requested to take said opposition along with annexures on record and proceed further in the matter and keep the Opponent advised of each and every step taken in the matter.

We crave the leave of the Learned Controller to submit additional documents and/or evidence to support any of the averments in the representation as may be necessitated during the future proceeding.

Lastly, we request the Learned Controller to grant an opportunity of being heard before the present Opposition is finally decided.

Thanking you,

Yours faithfully,

PRAGYA SINGH THAKUR (IN /PA – 3329)
FOR RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

Encl.: As stated

C.C.: K&S PARTNERS
Email: ipo@knspartners.com;

BEFORE THE CONTROLLER OF PATENTS, NEW DELHI

IN THE MATTER OF:

The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005, and The Patents Rules, 2003, as amended by The Patents (Amendment) Rules, 2006

AND

IN THE MATTER of Post-Grant Opposition under Section 25(2)

AND

IN THE MATTER of Indian Patent No. 419253

(Formerly Indian Patent Application No. 9313/DELNP/2011)

IN THE MATTER OF:

LOW COST STANDARD THERAPEUTICS **.....**OPPONENT

VS.

GILEAD SCIENCES, INC. ....APPLICANT/ PATENTEE

POST-GRANT OPPOSITION BY LOWCOST STANDARD THERAPEUTICS

INDEX

8.	**Annexure – 6:** Copy of Article Bohm et al., "Fluorine in Medicinal Chemistry"; ChemBioChem, Volume 5, Issue 5, Special Issue: Fluorine in the Life Sciences, published 28 April 2004	1757-1763
9.	**Annexure – 7:** Copy of WO2007121125 (WO'125) published 25 October 2007	1764-1884
10.	**Annexure – 8:** Copy of Article Nettles et al. "*BMS-790052 is a First-in-class Potent Hepatitis C Virus (HCV) NS5A Inhibitor for Patients with Chronic HCV Infection: Results from a Proof-of-concept Study*"; 59th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Oct 31-Nov 1 2008, San Francisco, CA	1885-1891
11.	**Annexure – 9:** Copy of Article Gao et al. "*New BMS HCV NS5A Inhibitor: From Screen Hit to Clinic; Presented at the 15th International Symposium on Hepatitis C Virus & Related Viruses*", Oct 5-9, 2008,San Antonio, Texas	1892-1901
12.	**Annexure – 10:** Copy of Article Pol et al., "*Safety and Efficacy of the Combination Daclatasvir-Sofosbuvir in HCV Genotype 1-Mono-Infected Patients From the French Observational Cohort ANRS CO22 HEPATHER*"; Gastroenterology and Hepatology, Volume 11, Issue 6, Supplement 3, published June 2015	1902-1914
13.	**Annexure – 11:** Copy of duly notarized expert affidavit of Dr. Debkumar Nandi	1915-1930
14.	**Annexure – 12:** Copy of CV of Dr. Debkumar Nandi	1931-1938
15.	Copy of duly stamped Power of Attorney	Will follow

Dated this 01st day of February, 2024

PRAGYA SINGH THAKUR (IN /PA – 3329)
FOR RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, NEW DELHI

FORM 7

THE PATENTS ACT, 1970

(39 OF 1970)

AND

THE PATENTS RULES, 2003

NOTICE OF OPPOSITION

[See Section 25(2) and rule 55A]

We, **LOW COST STANDARD THERAPEUTICS**, having its registered office at I Floor, Premananda Sahitya Bhavan, Opposite Lakadipul, Dandia Bazar, Vadodara, 390001, Gujarat, India, hereby give Notice of opposition to the grant of patent in respect of Indian Patent No. 419253 (formerly patent application number 9313/DELNP/2011) dated 28/11/2011 made by **GILEAD SCIENCES, INC.** on the grounds:

(a) Section 25(2)(e): Lack of inventive step

(b) Section 25(2)(f): Invention is not patentable under section 3(d) and 3(e)

(c) Section 25(2)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

(d) Section 25(2)(h): Failure to disclose the information required by section 8 of the Patents Act.

(Detailed grounds are set out in the Opposition)

Our address for service in India is:

RAJESHWARI & ASSOCIATES, S – 357, FIRST FLOOR, NEAR HDFC BANK, PANCHSHEEL PARK, NEW DELHI – 110017, INDIA, Tel: + 91-11-41038911, Mobile No. 8368982401, Email: pragya@ralegal.co.in;

Dated this 01st day of February, 2024

PRAGYA SINGH THAKUR (IN /PA – 3329)
FOR RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, NEW DELHI

BEFORE THE CONTROLER OF PATENTS, THE PATENT OFFICE, NEW DELHI

In the matter of Section 25(2) of The Patents Act, 1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of Rule 55 of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

And

In the matter of Indian Patent number 419253 (formerly patent application number 9313/DELNP/2011) dated 28/11/2011, in the name of **GILEAD SCIENCES, INC.**

REPRESENTATION BY:

LOWCOST STANDARD THERAPEUTICS .....OPPONENT

VS.

GILEAD SCIENCES, INC. .....APPLICANT/ PATENTEE

REPRESENTATION BY WAY OF PRE-GRANT OPPOSITION UNDER SECTION 25(2) OF THE PATENTS ACT, 1970

We, Low Cost Standard Therapeutics**,** an Indian Company of I Floor, Premananda Sahitya Bhavan, Opposite Lakadipul, Dandia Bazar, Vadodara, 390 001, Gujarat, India, hereby submit our representation by way of opposition to the patent 419253 (formerly patent application number 9313/DELNP/2011) dated 28/11/2011 in the name of GILEAD SCIENCES INC. titled “Antiviral Compounds”.

STATEMENT OF CASE OF OPPONENT

The Opponent herein respectfully submits as under:

1. A Post-grant opposition under Section 25(2) of the Patents Act, 1970, is being submitted by the Opponent against Indian Patent No. 419253 (hereinafter referred to as the "impugned patent") which has been granted in favour of GILEAD SCIENCES INC. (Hereinafter referred to as the "Applicant/Patentee").

LOCUS

2. LowCost Standard Therapeutics (hereinafter LOCOST) is a not-for profit organisation having its office at I Floor, Premananda Sahitya Bhavan, Opposite Lakadipul, Dandia Bazar, Vadodara, 390 001, Gujarat, India. LOCOST was established to make essential medicines of quality at reduced costs by eliminating the margins shared with prescribers, distributers and related market costs. LOCOST makes essential medicines for those working with urban and rural poor in India. The goal of LOCOST is to provide good quality medicines at affordable prices for those working in remote areas.

3. Registered as Low-Cost Standard Therapeutics in 1983, it is a public charitable trust that is concerned with public health aspects of medicines: their genesis, costs, clinical trials, licensing, patenting, production, distribution and consumption till it reaches the end users, namely patients. LOCOST is also concerned about the long-term impact of medicines – their use, misuse and overuse, adverse reactions and side effects - and the public regulation of all related issues.

4. LOCOST has its own well-equipped production facility in Vadodara where it produces more than 100 essential and rational medicines. The establishment makes more than 60 essential medicines in 80 formulations (liquids, capsules, tablets).LOC LOCOST is also active in pharmaceutical policy advocacy at regional and national levels. LOCOST products are preferred by many not for profit health institutions across India The sales are directed at institutions and individuals that work on a not-for profit basis or cater to the poorest of people.

5. Manufacturing at LOCOST conforms to the highest standards of production set by the Government of India. LOCOST's production facilities have Schedule M certification of the Government of India and anytime now it is expected to have WHO-GMP certification too. LOCOST's management practises ethical business norms that further assure our long-standing clients that no corners are cut on quality standards.

6. LOCOST realizes that mere production of essential medicines is not enough. LOCOST also engages in educating prescribers as well as users. Its education cell focuses on issues related to education and training for rational use of medicines. LOCOST publishes a monthly in Gujarati, namely *Apnu Swasthya*, and other publications for the general public including but not limited to the Gujarati version of classics such as *Where there is no Doctor* and *A Lay Person's Guide to Medicine* (a guide on the use and political economy of medicines).

7. The Opponent is also engaged in the manufacture and sale of various antiviral compounds. Additionally, the Opponent has been conducting research in respect of antiviral compounds. The existence of the impugned patent is against public interest and research in respect of anti-viral compounds. Thus, the Opponent is a person interested having direct and tangible interest in filing the present opposition.

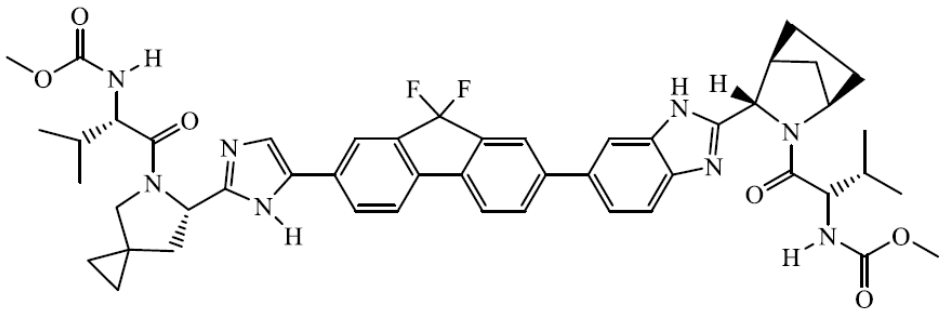
8. The present opposition is against Indian patent no. 419253 which was originally filed as Indian Patent Application No. 9313/DELNP/2011 on 28/11/2011. The said application was granted on 25/01/2023 with patent number 419253 (hereinafter referred as the Impugned Patent). The Impugned patent is titled "ANTIVIRAL COMPOUNDS". The priority date of the impugned patent is 13/05/2009. The impugned patent was published in the official journal of the patent office on 03/02/2023. The Impugned Patent is the national phase application of PCT/US2010/034600 and draws its priority from US application 61/177,972 dated 13 May 2009, US application 61/224,745 dated 10 July 2009 and US application 61/238,760 dated 01 Sep 2009.

9. The Impugned Patent is entitled "Antiviral Compounds"

10. The Opponent by way of this present post-grant opposition submits that the claims granted and on record are not patentable under the provisions provided in this Act. The

claims as filed and currently on record are annexed herewith as **Annexure-1** and reproduced herein below for ready reference:

1. A compound of formula:



or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

9. **PRIOR ARTS:** The opponent wishes to rely on the following prior arts as evidence in support of the grounds of opposition.

i. US20080096875 (US'875) published 24 April 2008 (**Annexed herewith as Annexure 2**)

ii. WO2008021927 (WO'927) published 21 February 2008 (**Annexed herewith as Annexure 3**)

iii. US20090068140 (US'140) published 12 March 2009 (**Annexed herewith as Annexure 4**)

iv. WO2007033175 (WO'175) published 22 March 2007 (**Annexed herewith as Annexure 5**)

v. Bohm et al., "Fluorine in Medicinal Chemistry"; ChemBioChem, Volume 5, Issue 5, Special Issue: Fluorine in the Life Sciences, published 28 April 2004 (**Annexed herewith as Annexure 6**)

vi. WO2007121125 (WO'125) published 25 October 2007 (**Annexed herewith as Annexure 7**)

vii. Nettles et al. "*BMS-790052 is a First-in-class Potent Hepatitis C Virus (HCV) NS5A Inhibitor for Patients with Chronic HCV Infection: Results from a Proof-of-concept Study*"; 59th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Oct 31-Nov 1 2008, San Francisco, CA; (**Annexed herewith as Annexure 8**)

viii. Gao et al. "*New BMS HCV NS5A Inhibitor: From Screen Hit to Clinic; Presented at the 15th International Symposium on Hepatitis C Virus & Related Viruses*", Oct 5-9, 2008,San Antonio, Texas (**Annexed herewith as Annexure 9**)

ix. Pol et al., "*Safety and Efficacy of the Combination Daclatasvir-Sofosbuvir in HCV Genotype 1-Mono-Infected Patients From the French Observational Cohort ANRS CO22 HEPATHER*"; Gastroenterology and Hepatology, Volume 11, Issue 6, Supplement 3, published June 2015 (**Annexed herewith as Annexure 10**)

10. It is submitted that the claims of impugned patent application are liable to be refused on following grounds as below, which are without prejudice to each other:
    (a) Section 25(2)(e): Lack of inventive step
    (b) Section 25(2)(f): Invention is not patentable under section 3(d) and 3(e)
    (c) Section 25(2)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
    (d) Section 25(2)(h): Failure to disclose the information required by section 8 of the Patents Act.

GROUND 1: Section 25(2)(e) Lack of Inventive Step

7. It is submitted that the invention as claimed is obvious and does not involve any inventive step in view of the disclosures published prior to the earliest priority date of the impugned patent i.e. prior to 13/05/2009.

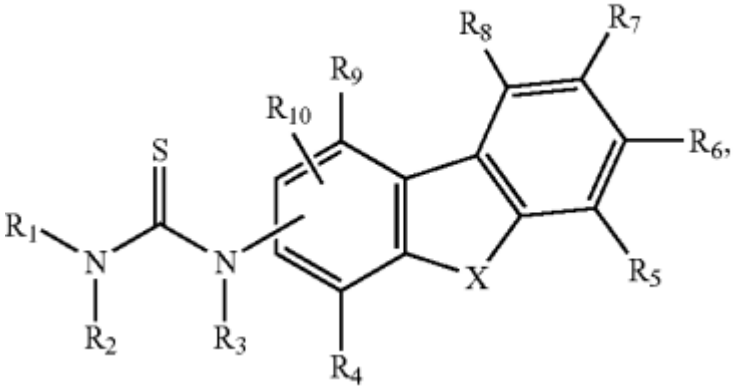
8. It is submitted that claims 1-30 of the impugned application lack inventive step and are obvious in view of common general knowledge in art and combined with teachings of the following-

- US20080096875 (US'875) published 24 April 2008 (Annexure 2)
- WO2008021927 (WO'927) published 21 February 2008 (Annexure 3)
- US20090068140 (US'140) published 12 March 2009 (Annexure 4)
- WO2007033175 (WO'175) published 22 March 2007 (Annexure 5)
- Bohm et al., "Fluorine in Medicinal Chemistry"; ChemBioChem, Volume 5, Issue 5, Special Issue: Fluorine in the Life Sciences, published 28 April 2004 (Annexure 6)
- WO2007121125 (WO'125) published 25 October 2007 (Annexure 7)

- Nettles et al. "*BMS-790052 is a First-in-class Potent Hepatitis C Virus (HCV) NS5A Inhibitor for Patients with Chronic HCV Infection: Results from a Proof-of-concept Study*"; 59th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Oct 31-Nov 1 2008, San Francisco, CA; (Annexure 8)
- Gao et al. "*New BMS HCV NS5A Inhibitor: From Screen Hit to Clinic; Presented at the 15th International Symposium on Hepatitis C Virus & Related Viruses*", Oct 5-9, 2008,San Antonio, Texas (Annexure 9)

9. It is submitted that US'875 discloses compounds that are effective in treating hepatitis C virus infection (para [0004], internal page 1). The general structure of one of the compounds is as shown below (internal page 49-50):

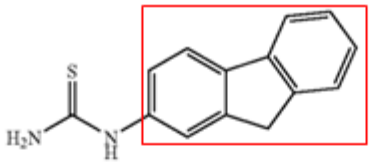
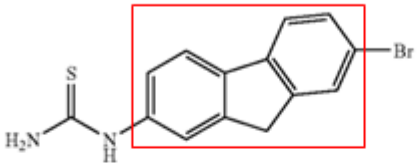
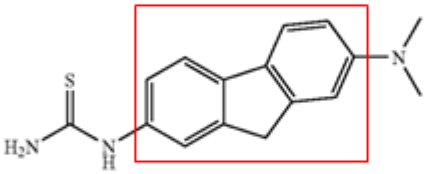
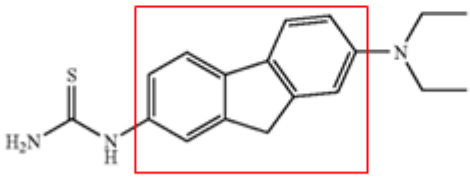
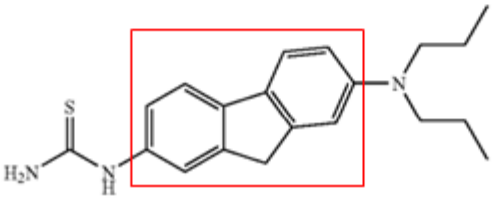
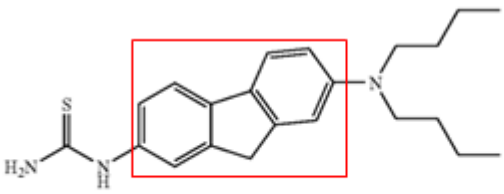
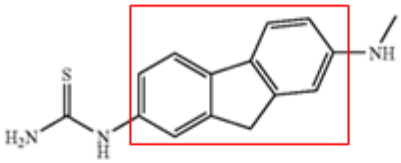
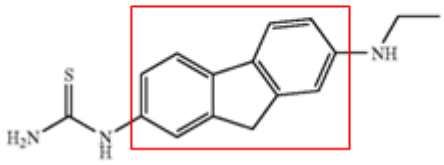
(II)

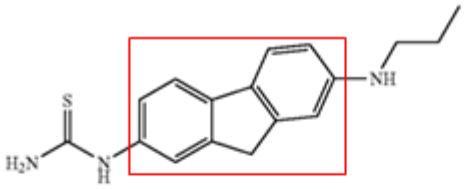
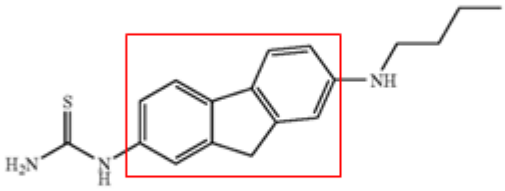
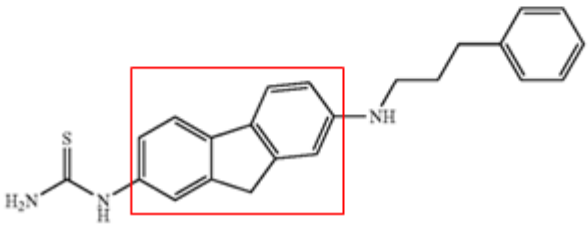
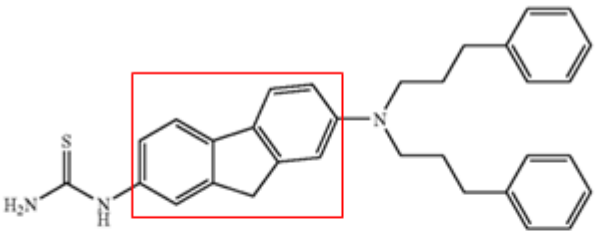
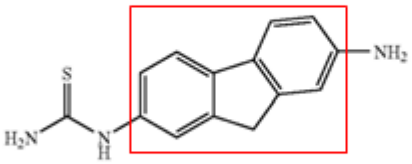
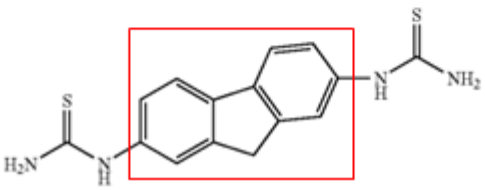


wherein X can be $C(R_aR_b)$, in which R_a, R_b are independently, H atom (internal page 50)

10. Thus, the compounds above, which are effective in treating hepatitis C virus infection possess a fluorene moiety as part of structure.

11. US'875 discloses several compounds active against HCV as shown below:

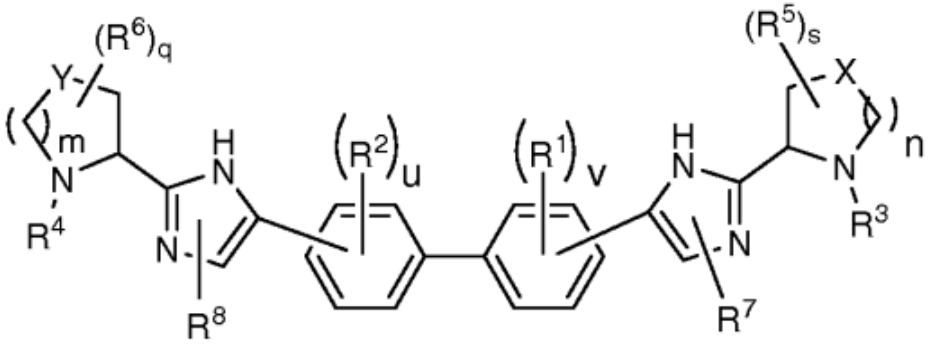
37		(9H-Fluoren-2-yl)-thiourea
38		(7-Bromo-9H-fluoren-2-yl)-thiourea
39		(7-Dimethylamino-9H-fluoren-2-yl)-thiourea
40		(7-Diethylamino-9H-fluoren-2-yl)-thiourea
41		(7-Dipropylamino-9H-fluoren-2-yl)-thiourea
42		(7-Dibutylamino-9H-fluoren-2-yl)-thiourea
43		(7-Methylamino-9H-fluoren-2-yl)-thiourea
44		(7-Ethylamino-9H-fluoren-2-yl)-thiourea

45		(7-Propylamino-9H-fluoren-2-yl)-thiourea
46		(7-Butylamino-9H-fluoren-2-yl)-thiourea
47		[7-(3-Phenyl-propylamino)-9H-fluoren-2-yl]-thiourea
48		{7-[Bis-(3-phenyl-propyl)-amino]-9H-fluoren-2-yl}-thiourea
49		(7-Amino-9H-fluoren-2-yl)-thiourea
50		(7-Thioureido-9H-fluoren-2-yl)-thiourea

12. From the above, it is clear that several compounds active against HCV possess the fluorene moiety as essential part of the structure. Thus, a person of skill in the art would be motivated to consider developing compounds possessing such a moiety for activity against hepatitis C.

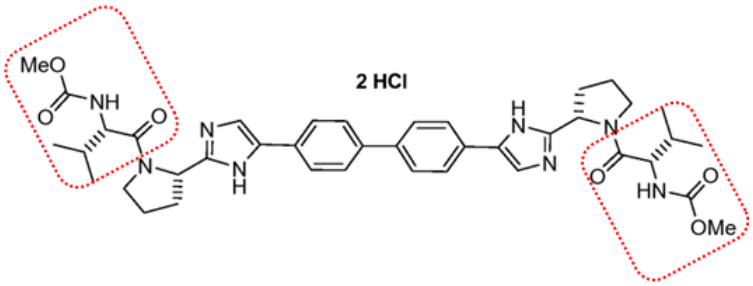
13. WO'927 discloses compounds that can inhibit the function of the NS5A protein encoded by the hepatitis C virus (HCV) as well as compositions comprising such compounds (lines 8-10, internal page 1)

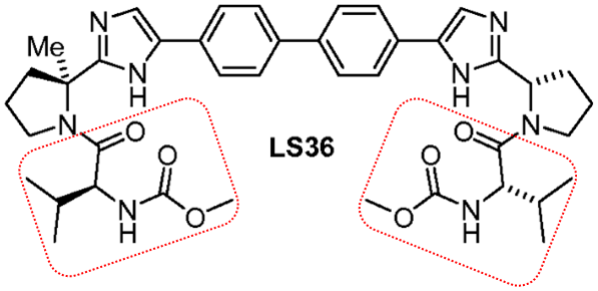
14. The compounds disclosed in WO'927 are represented by the following structure (lines 25-30, internal page 2):



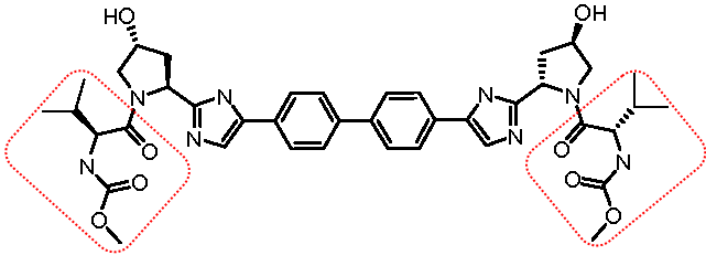
15. WO'927 discloses several compounds falling within the above Markush structure as shown below, that have identical moieties (encircled) attached at the end:

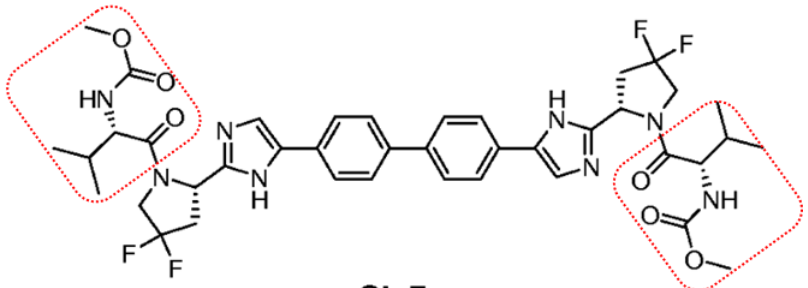
Example 24-23





JG-5





OL-7

16. The above moiety is referred to as “cap” in the disclosure of WO’927 (lines 13-18, internal page 13)

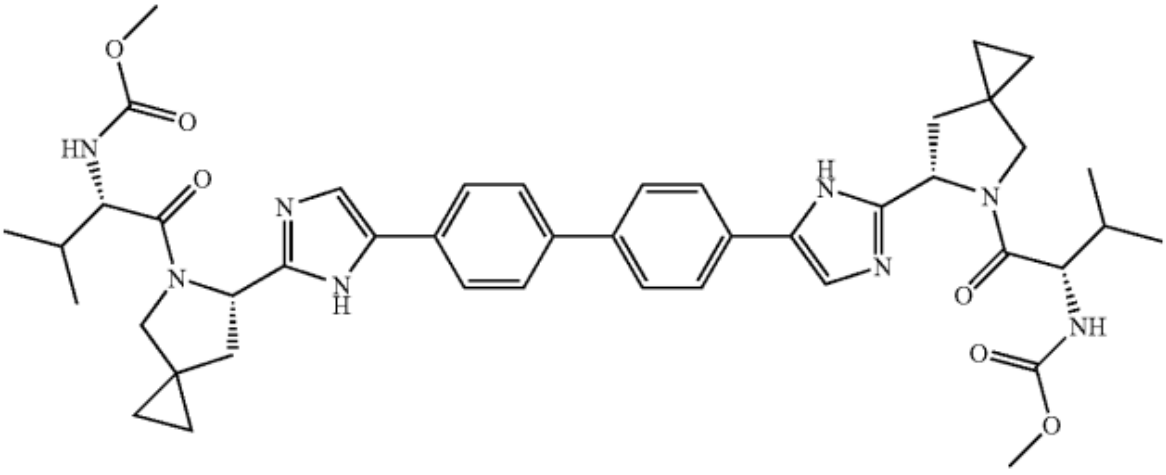
17. Further, it can be seen that in all of the above compounds (as well as several others disclosed in WO’927), the caps are attached to pyrrolidine rings.

18. The above-mentioned pyrrolidine moieties are themselves attached to imidazole rings on the molecules.

19. Thus, it can be seen that WO’927 discloses molecules that are active against NS5A protein of HCV virus. These molecules have a biphenyl central portion and symmetric or asymmetric portions attached to it including caps.

20. US’140 discloses antiviral compounds which can inhibit the function of the NS5A protein encoded by Hepatitis C virus (HCV), as well as compositions comprising such compounds (para [0002], internal page 1).

21. One of the compounds disclosed in US’140 is compound M145, the structure of which is shown below

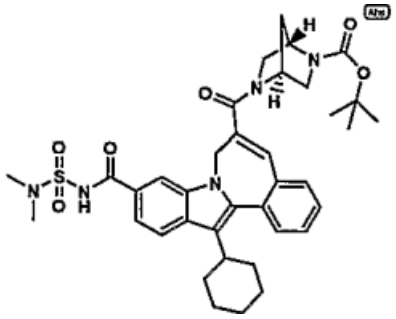


22. It can be seen that the aforementioned compound possesses an azaspiro moiety attached to the imidazole and end cap.

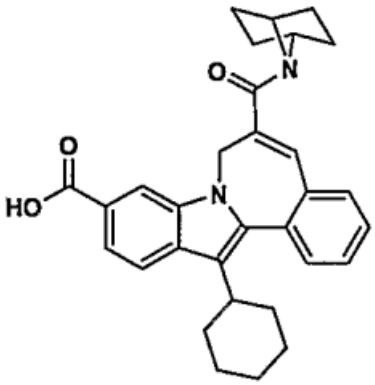
23. It is evident that a person skilled in the art would be motivated to consider substitution of above azaspiro moiety in between the imidazole ring and the cap.

24. WO'175 discloses compounds that are active against NS5B protein of the hepatitis C virus and can be useful in treating HCV and HCV infection (lines 4-5, internal page 117).

25. Some of the compounds disclosed in WO'175 are shown below:



(Internal page 51)



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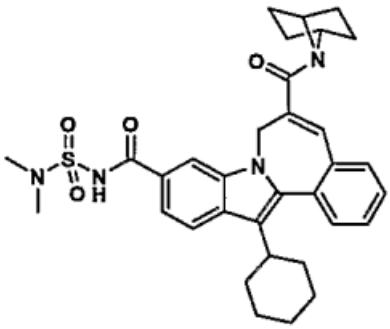

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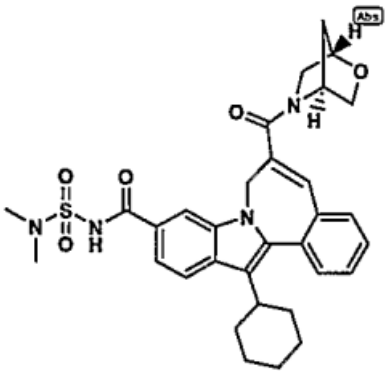


(Internal page 52)

26. It can also be seen that the above compounds possess a bicyclic ring which, as can be seen, is a heterocyclic ring in every case bearing a nitrogen on the ring. Further, these compounds also possess good activity in terms of IC_{50}, as all these compounds demonstrate an IC_{50} of B. As disclosed in WO'175, the value B represents a value of IC_{50} in the range of 0.01 µM - 1 µM, while the IC_{50} for the other are as follows A > 1 µM, C >10 µM, D 1 µM - 10 µM, E 1.0 µM – 0.07 µM.

27. Thus, a person skilled in the art would be motivated to explore and incorportae the motif of a bicyclic ring (with heterocyclic nitrogen) for developing compounds active against HCV non-structural protein.

28. Bohm et al. discloses how fluorine substitution is used in contemporary medicinal chemistry (Introduction, internal page 637).

29. Bohm et al. discloses the following in relation to fluorine (internal page 637 & page 638):

    1) Metabolic stability is one of the key factors in determining the bioavailability of a compound. Rapid oxidative metabolism by the liver enzymes, in particular the P450 cytochromes, is often found to limit bioavailability. A frequently employed strategy to circumvent this problem is to block the reactive site by the introduction of a fluorine atom. There are many examples [10±14] illustrating that the replacement of an oxidizable C_H group by a C_F group increases metabolic stability of the molecule.

    2) Fluorine can change the basicity of a compound. Highly basic groups can have a limiting effect on the bioavailability. A fluorine atom introduced close to a basic group reduces its basicity; this results in better membrane permeation of a compound and thus improved bioavailability.

3) Increasingly, fluorine substituents are introduced to increase the binding affinity of a compound. For example, most of the NK1 antagonists currently in clinical development contain a 3,5-di(trifluoromethyl)phenyl group to increase binding affinity.[15] In a recent review on the use of QSAR and computer-aided design methods, Wermuth described the 3,5-di(trifluoromethyl)phenyl group as™magic∫[16] because it is found in many published NK1 antagonists and classical QSAR does not account for this strong effect of fluorine.
Internal page 638

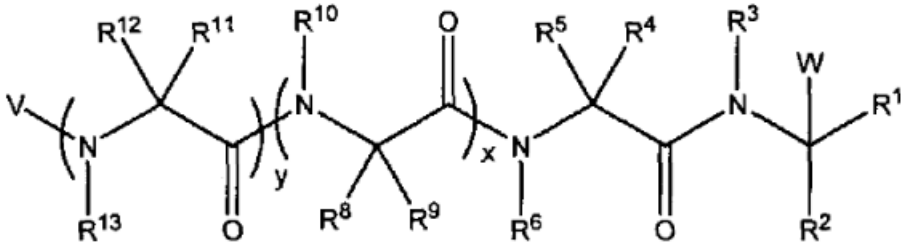
Depending on the position of the fluorine substituent relative to the acidic or basic group in the molecule, a pKa shift of several log units can be observed. For example, the pKa's of acetic acid and it's a fluorinated analogues are 4.76 (CH3COOH), 2.59 (CH2FCOOH), 1.24 (CHF2COOH), and 0.23 (CF3COOH).

30. It is submitted that Bohm et al teaches that favourable bioavailability of a compound can be obtained by substitution of fluorine. For example, the replacement, in CH_3COOH an allylic carbon would be in CH_3 moiety with fluorine atoms (CHF_2COOH) leads to its pKa value being significantly changed leading to enhancement of the pharmacokinetic properties and bioavailability of the molecule.

31. Thus, a person skilled in the art, seeking to favourably modify the bioavailability and pharmacokinetic properties of a molecule would seek to introduce fluorine on the molecule. Thus, for already known antiviral compounds, with structure as disclosed in US'819 could be favourable modified by making a substitution of fluorine on carbon atom of fluorene ring.

32. WO'125 discloses compounds that treat, inhibit or prevent the activity of HCV by inhibition of NS5a protein (Claim 50 & claim 55).

33. The general structure of the compounds disclosed in WO'125 is shown below:

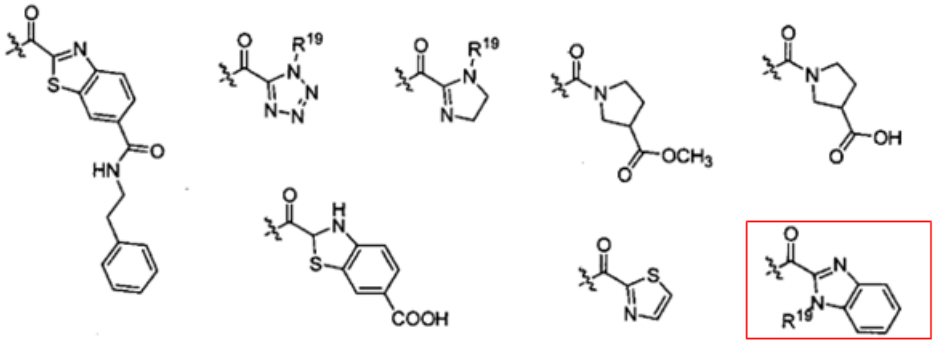


34. It is disclosed that, in one embodiment, the substituent W in the above structure can be among the following (internal page 14):

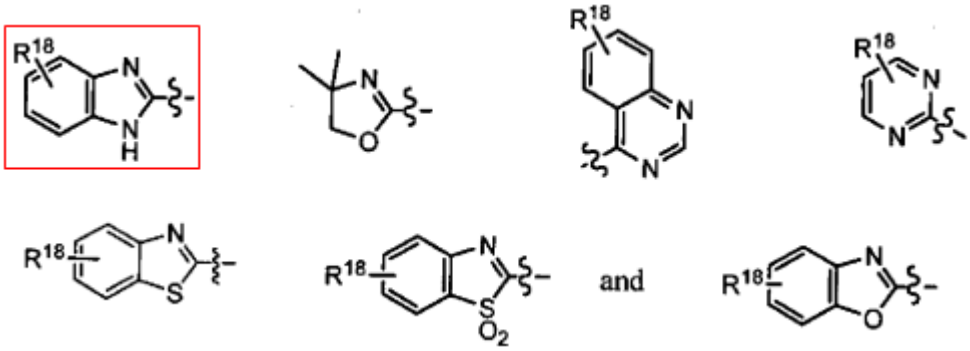
> halogen atom or C_{1-4}-alkyl. In yet another embodiment, W is selected from the group consisting of C(O)-C(O)NH_2, C(O)-C(O)N(H)-cyclopropyl, C(O)-benzothiazole, C(O)-benzoimidazole, C(O)-oxazole, C(O)-imidazole, and C(O)-oxadiazole, wherein the benzothiazole, benzoimidazole, oxazole and oxadiazole groups may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, C_{3-6}-cycloalkylC_{0-4}alkyl or C_{1-4}-alkyl.

35. Further, it is disclosed that W is selected from the following (internal page 14):

In another embodiment of the compounds of the invention, W is selected from the group consisting of



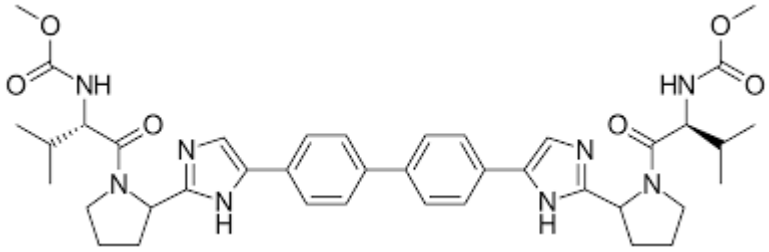
36. The substituent V is disclosed to be C(O)-R^{20} wherein R^{20} is selected from the group consisting of (internal page 15):



37. Thus, it can be seen that the benzimidazole moiety is a common motif in the compounds disclosed WO'125. These compounds inhibit the activity of NS5a protein of HCV and thus, a person skilled in ten art would be motivated to consider attachment of said moiety in compounds meant for activity against HCV.

Lack of technical advancement

38. It is submitted that the compound 23-24, which is disclosed in WO'927, and which is shown below, represents structurally close compound to the claimed compound in the impugned patent. This particular compound (which is known by the INN daclatasvir and also the code BMS-790052), was taken forward in clinical development and is now an approved medication for the treatment of hepatitis C. It is submitted that even before final approval, data for the immense potential of this compound was present much before the priority date of impugned patent. The claimed compound can be regarded as a derivative of the same, as will be apparent. The structure of daclatasvir is shown below, and the prior art (Annexure 8; Nettles et al. and Annexure 9; Gao et al.) are discussed below:



Lack of technical advancement in view of Nettles et al. (Annexure 8)

39. Nettles et al. discloses the results of a double-blind, placebo-controlled, single ascending dose study conducted on the molecule BMS-790052 (now known by the INN daclatasvir) to assess the safety and tolerability of a single oral dose of 1, 10 and 100 mg of BMS-790052 in patients with chronic genotype 1 HCV infection, as well as to assess the single-dose pharmacokinetics of BMS-790052 and to assess the effect of a single dose of BMS-790052 on plasma HCV RNA dynamics (internal page 3/7)

40. It is disclosed that BMS-790052 is a potent NS5A inhibitor that was safe and well tolerated in single doses up to 100 mg, has a PK profile that potentially supports once-daily dosing, produced a robust decline in HCV RNA (-3.6 logs after 48 hours from a single 100 mg) dose following a single dose in patients chronically infected with HCV genotype 1 (internal page 2/7).

41. It is also disclosed that BMS-790052 is a first-in-class, highly selective, oral HCV NS5A inhibitor that has broad genotype coverage and exhibits picomolar in vitro potency against

genotypes 1aand 1b. It is also disclosed that BMS-790052 has additive to synergistic effects in combination with interferon and other HCV inhibitors in-vitro.

42. Thus, it is clear that daclatasvir (BMS-790052) was already known to be potent highly selective NS5A inhibitor with favourable pharmacokinetic profile, much before the priority date of the impugned patent. Therefore, it was incumbent upon the patentee/applicant to demonstrate enhanced and superior activity of the claimed compound in comparison to daclatasvir (BMS-790052). The Patentee has failed to demonstrate said activity and thus, the invention, as represented by the claimed compound, completely lacks technical advancement.

Lack of Technical Advancement in view of Gao et al. (Annexure 9)

43. Gao et al. (Annexure 9) discloses the identification of BMS- 790052 (known now by the INN daclatasvir), which is reported to be a first-in-class molecule that was the most potent anti-HCV agent reported at the date of reporting with an EC_{50} of 50 pM and 9 pM against genotype 1a and 1b replicons, respectively. It is also reported that said molecule is equally potent against infectious HCV genotype 2a virus (JFH strain) and demonstrates broad genotype coverage withEC50s ranging from pM to the low nM range for genotypes 2a, 3a, 4a and 5a. Further, it is disclosed that BMS-790052 exhibited an additive to synergistic effect when combined with IFN-α, NS3 protease or NS5B polymerase inhibitors. (internal page 2/10).

44. Significantly, it is also disclosed that in proof-of-concept human trials, the in vitro potency of BMS-790052 translated to in vivo efficacy.

45. The study explored various aspects of the activity of BMS-790052 on the protein NS5A, which revealed that BMS-790052 potency is independent of adaptive mutations (internal page 8/10). Further, the combination of BMS-790052 with other compounds such as Interferon, NS5B, NS3 and nuclear analog revealed that such combinations are additive/synergistic (internal page 6/10). It is disclosed that the EC_{50} values for all resistant variants for BMS-790052 is less than 4 nM (internal page 5/10).

46. Thus, it is clear that BMS-790052 (daclatasvir) was already known to be extremely effective against various HCV genotypes before the priority date of the impugned patent. Thus, in conjunction with Nettles et al (Annexure 8, also available before priority date of

the impugned patent), it is evident that the patentee ought to have provided data in the specification establishing superior activity in comparison to daclatasvir. In the absence of such data, the invention, as represented by the claimed compound, completely lacks technical advancement.

47. Thus, to summarize the teachings of Annexures 2-9, it is apparent that a fluorene ring, as disclosed in the compounds of US'875 is present in compounds that are active against hepatitis C virus i.e. HCV can be considered as a basis for the development of further improved anti-HCV compounds. Further, it can be seen that compounds disclosed in WO'927 target NS5A protein of HCV virus. These compounds bear a structure that has a biphenyl ring system with rings on both sides of the central biphenyl ring and cap structure at the ends. This biphenyl ring can be modified by substitution of fluorine, as taught by Bohm et al. for the favourable bioavailability and pharmacokinetic properties. WO'927 also teaches that molecules active against HCV NS5A have a "cap" moiety at both ends of the structure (attached to pyrrolidine rings). The pyrrolidine rings are attached to imidazole moieties. Further, WO'125 discloses that benzimidazole based compounds are active against HCV viruses, thus motivating a person of skill in the art to consider substituting the imidazole in compounds disclosed in WO'927 with benzimidazole. Further, US'140 discloses compounds active against HCV, targeting NS5A protein that have an azaspiro moiety between the "cap" structure and the imidazole ring, which would motivate a person skilled in the art to substitute an azaspiro between the cap and the imidazole ring. Considering all of the above, a person skilled in the art arrives at the compound claimed in the present impugned patent. Further, as disclosed in Nettles et al. and Gao et al. above, compound 23-24 disclosed in WO'927 (now known by the INN daclatasvir) was already known to be extremely potent and effective against a number of HCV genotypes. This compound represents the closest compounds (as disclosed WO'927) to the claimed compound, and acting on the same target. The Patentee should have provided data establishing superior activity of the claimed compound in comparison to daclatasvir in the specification, considering that Nettles et al. and Gao et al. were in the public domain much before the priority of the impugned patent. The Patentee has clearly not done so. Thus, at the priority date of the patent, the invention can be seen to have lacked technical advancement. Thus, the invention, as represented by the claimed compound (and composition thereof) is clearly obvious and lacks inventive step in view of the Annexures 2-9.

48. Thus, the subject matter claimed in impugned patent, in view of the above submissions, is clearly obvious and lacks inventive step. The impugned patent, therefore, ought to be rejected on this ground alone.

GROUND 2: Claims not patentable under Section 25(2)(f)

The claimed subject matter in not patentable under Section 3(d) of the Act

49. It is submitted that the impugned patent application falls within the purview of section 3(d) of the Patents Act, 1970 which states that *"the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

    Explanation -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy."

50. It is humbly submitted that the compound claimed in the present impugned patent is a mere derivative of the compounds disclosed in WO'927, which also target the NS5A protein of HCV virus.

51. The Applicant/Patentee has not provided any comparative data against the compounds disclosed in WO'927, which are the closest both in terms of structure and in terms of the target. Therefore, no enhanced therapeutic efficacy or technical advancement has been demonstrated for the compound claimed in the impugned patent.

52. It is submitted that, as already elaborated in the preceding paragraphs under lack of technical advancement, the prior art Nettles et al. (Annexure 8) and Gao et al.(Annexure 9) reveal that the compound daclatasvir (compound 23-24 disclosed in WO'927), known also by the code BMS-790052, was already known to be extremely potent against HCV target protein NS5A (several genotypes of HCV) and had favourable pharmacokinetic properties. It was therefore incumbent upon the patentee to demonstrate enhanced therapeutic efficacy of the claimed compound against daclatasvir, considering that the

claimed compound is a derivative of said compound. The patentee has failed to demonstrate the same, and hence, in the absence of enhanced therapeutic efficacy, the claimed invention falls within the purview of section 3(d).

53. Further, Annexure 10 - Pol et al. (internal pages 17-18) discloses the results of Safety and Efficacy of the Combination Daclatasvir/Sofosbuvir in HCV Genotype 1-Mono-Infected Patients From the French Observational Cohort ANRS CO22 HEPATHER. The study was conducted to assess treatment of decompensated HCV cirrhosis in patients in diverse genotypes, for which Sofosbuvir and NS5A Inhibitors With/Without Ribavirin was administered to patients for HCV genotypes 1 and 3. The drugs sofosbuvir plus either daclatasvir or ledipasvir, with or without ribavirin, as selected by the physician were administered (Abstract summary, internal page 18)

54. It was found that **the combination of sofosbuvir and daclatasvir, with or without ribavirin, was superior to sofosbuvir and ledipasvir, with or without ribavirin (P<0.05) among genotype 3 patients** (Abstract summary, third column, internal page 18).

55. The above clearly demonstrates that the prior art molecule daclatasvir is more efficacious as compared to the claimed compound (now known by the INN ledipasvir), and that ledipasvir is infact inferior to daclatasvir. Thus, no enhanced therapeutic efficacy of claimed compound ledipasvir exists, as compared to daclatasvir. Therefore the claimed compound does not clear the bar of section 3(d).

56. Therefore, the impugned patent falls squarely within the purview of section 3(d) of the Patents Act 1970 and ought to be rejected on this ground alone.

The claimed subject matter in not patentable under Section 3(e) of the Act

57. It is submitted that the impugned patent falls within the purview of section 3(e) of the Patents Act, 1970 which states that "*a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance*".

58. It is submitted that claim 2 of the impugned patent is directed to a pharmaceutical composition comprising the compound of claim 1 (claimed compound) and a

pharmaceutically acceptable carrier. The specification of the impugned patent, however, shows no example of such a composition. No unexpected effect of the claimed composition is demonstrated anywhere in the specification. Thus, no synergistic effect of the claimed composition has been shown

59. The Applicant/Patentee, in its written submission pursuant to hearing under section 14, (dated January 21, 2023) contended that "*claim 2 relates to a pharmaceutical composition comprising a compound as claimed in claim 1 as an active ingredient, together with pharmaceutically acceptable carrier, wherein, the claimed composition derives its novelty and inventive step from the novel and inventive compound of the invention and the unexpected effect is achieved due to the unexpected effects from the claimed compound.*" Opponent submits that, if the unexpected effect of the composition is achieved due to unexpected effects of from the claimed compounds, there is no material difference between what is claimed in claim 1 and claim 2. In light of the above statement, claim 2 is redundant with respect to claim 1.

60. Further, the Patentee has made the contention that section 3(e) is not applicable where at least one component is novel (para 3, page 26 of 28). The Patentee has provided no basis for the aforementioned statement. No reference to any case law or other pertinent reference for above statement has been given.

61. Thus, claim 2 of the impugned patent does not

62. Thus the impugned application falls within the purview of section 3(e) of the Patents Act, 1970 and should be refused on the said ground.

GROUND 3: INSUFFICIENCY OF DISCLOSURE [section 25(2)(g)]

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

64. It is submitted that it is a well settled law that the specification should clearly and fairly describe the invention and disclose the best mode of working the invention so that the person skilled in the art could perform the invention without any undue efforts. Further, it is submitted that claims of impugned application are not fairly based on the

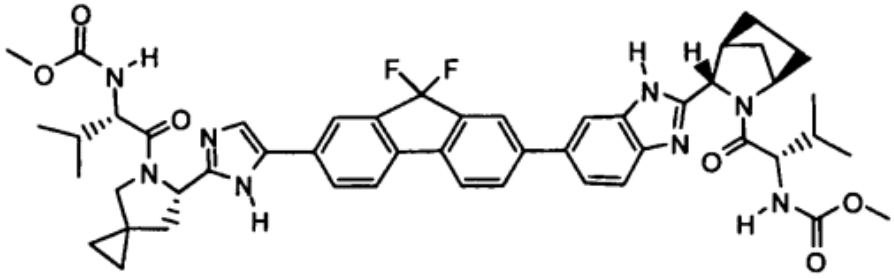
specification and the complete specification does not fairly describe the invention and the method by which it is to be performed.

65. The synthesis of claimed compound in the complete specification is shown (internal page 671-674) in a series of steps. It is submitted that the claim 1 is also directed towards the pharmaceutically acceptable salts of claimed compound. However, the specification does not show the synthesis of even a single species of salt, even though the patentee has claimed a very large number of pharmaceutically acceptable salts.

66. Claim 2 is directed towards a pharmaceutical composition comprising the claimed compound and a pharmaceutically acceptable carrier. However, there is no example of any composition shown in the specification, even though the claim encompasses a large number of all possible compositions of the claimed compound.

67. It is submitted that there is no indication of the particular ratio(s) of the claimed compound to the pharmaceutically acceptable carrier, as the same has not been provided in the specification or specified in the claims. Thus, it is not clear how much of the claimed compound vis-a-vis pharmaceutically acceptable carrier ought to be considered for making the composition. As such, the claim is directed to a very huge range of both entities, in the absence of limiting ratios.

68. The purported antiviral potency of the compounds is disclosed in the specification (including that of the claimed compound) on internal pages 919-974. The activity of the claimed compound is demonstrated on internal page 947. It is submitted that the complete specification discloses that the compounds of the invention are active against multiple HCV genotypes selected from 1a, 1b, 2a, 2b, 3a, 4a, and 5a. However, the biological data demonstrated in the specification is disclosed as being performed using a Renilla luciferase (RLuc)-based HCV replicon reporter assay - HCV 1b RLuc) for representative compounds of the invention. Thus, it appears that activity is demonstrated only with respect to one strain (1b) and not for the other strains that the specification discloses the compounds are active against. The activity of the claimed compound against 1a, 2a, 2b, 3a, 4a, and 5a has not been demonstrated and there is thus no indication that the compound is active against the above strains.



0.0045

69. It is submitted the activity of the claimed compound in animals or humans infected with the HCV virus has not been demonstrated by the Applicant/Patentee. Since myriad factors may affect the activity of a compound in a whole organism as compared to anti-HCV activity in just cells, the activity in whole organisms is vital to demonstrate actual effect against HCV virus, which has not been demonstrated in the specification.

70. Thus, the specification does not sufficiently and clearly describe the invention or the method by which it is to be performed and is liable to be rejected on said ground.

GROUND 4: INFORMATION RELATING TO CORRESPONDING APPLICATIONS UNDER SECTION 8 [SECTION 25(2)(H)]

71. The Applicant has failed to disclose to the Patent Office the information required under Section 8. The Applicant is required to provide all the information regarding the prosecution of the equivalent applications till the grant of the Indian application to the Patent Office in writing from time to time and also within the prescribed time.

72. It is observed that Applicant has not provided information about updated the status of corresponding application in the Form-3 which information has not been provided to the learned Controller.

73. Therefore, the applicant has failed to comply with the requirements of the section 8 of the act and the opponent demands rejection on this ground also.

74. It is submitted that the Applicant has failed to disclose the details of corresponding foreign applications and impugned patent application to be refused.

75. The opponents crave leave to file further submissions and evidence with respect to this ground.

CONCLUSION

76. In view of the above, the claims are not inventive and not patentable and insufficient. The post-grant opposition as filed may be allowed and the subject patent may be refused.

HEARING REQUESTED

77. The Opponent hereby requests a hearing under section 25(2) of the Patents Act, 1970 (hereinafter referred to as "the Patents Act") and Rule 55 of the Patents Rules (hereinafter referred to as "the Rules").

P R A Y E R

In the fact and circumstances of the case, the Opponent prays as follows:

i. that the Controller take the present Opposition on record; that the Indian Patent number 419253 (formerly patent application number 9313/DELNP/2011), be rejected under Section 25(2) of the Patents (Amendment) Act, 2005;

ii. that the Opponent may be allowed to file further documents and evidence if necessary to support their averments;

iii. that the Opponent may be allowed to file further prior art or other publications (such as those cited in ISR or IPER) if necessary to support their averments;

iv. that the Opponent may be allowed to file rejoinder and affidavit if necessary to support their averments;

v. that the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;

vi. that the Opponent may be allowed to make further submissions in case the Patentee makes any amendments in the claims;

vii. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this day of 01st day of February 2024

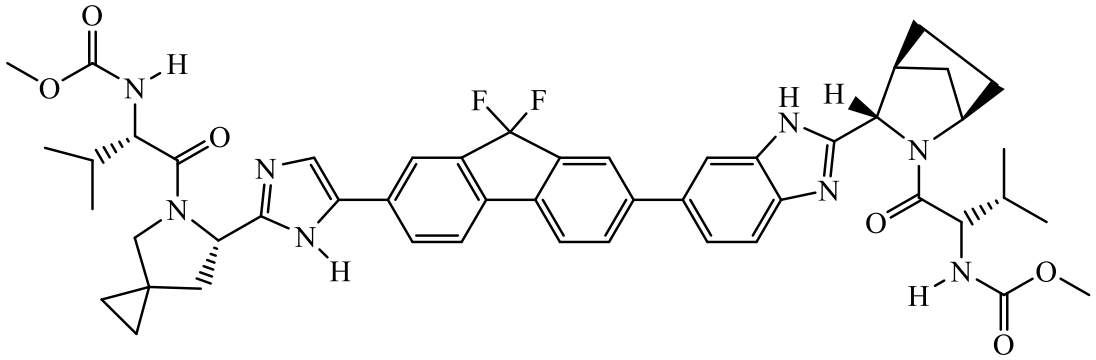
PRAGYA SINGH THAKUR (IN /PA – 3329)
FOR RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, NEW DELHI

Annexure - 1

We Claim:

1. A compound of formula:



or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

Dated this 28th day of November, 2011

Dr Jyoti Choithani Ramani
IN/PA/2450
OF K&S PARTNERS
ATTORNEY FOR THE APPLICANT

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(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2008/0096875 A1**

Chern et al. (43) **Pub. Date: Apr. 24, 2008**

(54) **THIOUREA COMPOUNDS**

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(21) Appl. No.: **11/839,346**

(22) Filed: **Aug. 15, 2007**

Related U.S. Application Data

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Publication Classification

(51) **Int. Cl.**

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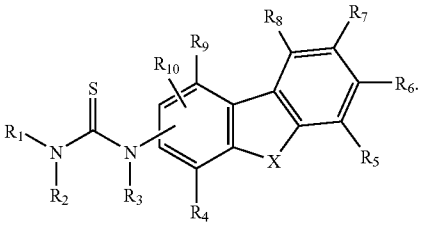
A61K 31/27		(2006.01)
A61K 31/343		(2006.01)
A61K 31/403		(2006.01)
A61K 31/4164		(2006.01)
A61K 31/44		(2006.01)
A61K 31/445		(2006.01)
A61K 31/47		(2006.01)
A61K 31/472		(2006.01)
A61K 31/495		(2006.01)
A61K 31/5375		(2006.01)
A61K 31/54		(2006.01)
A61P 31/12		(2006.01)
C07C 271/30		(2006.01)
C07C 335/02		(2006.01)
C07D 209/88		(2006.01)
C07D 213/72		(2006.01)
C07D 215/02		(2006.01)
C07D 217/00		(2006.01)
C07D 233/02		(2006.01)
C07D 241/04		(2006.01)
C07D 279/12		(2006.01)
C07D 295/14		(2006.01)
C07D 295/155		(2006.01)
C07D 307/91		(2006.01)

(52) **U.S. Cl.** **514/227.5**; 514/237.8; 514/255.03; 514/307; 514/311; 514/331; 514/353; 514/392; 514/411; 514/468; 514/480; 514/587; 544/160; 544/395; 544/58.1; 546/139; 546/152; 546/231; 546/305; 548/323.5; 548/444; 549/461; 560/28; 564/26; 564/27; 564/29

(57) **ABSTRACT**

This invention relates to thiourea compounds of formula (II) shown below:

(II)



Each variable in formula (I) is defined in the specification. These compounds can be used to treat hepatitis C virus infection.

THIOUREA COMPOUNDS

CROSS REFERENCE

[0001] Pursuant to 35 U.S.C. § 119(e), this application claims priority to U.S. Provisional Application 60/837,782, filed on Aug. 15, 2006. The contents of the provisional application are incorporated by reference.

BACKGROUND

[0002] Hepatitis C virus (HCV) infection is estimated to affect 170 million individuals worldwide. This disease is primarily transmitted through contaminated blood products. Although its spread has been slowed as a result of improvement in blood screening in many countries, it remains the leading cause of liver disease-related deaths in the world. For example, it causes about 10,000 deaths annually in the U.S. alone. In the absence of effective therapies, the death rate is expected to triple over the next 2 decades.

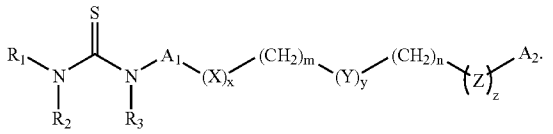
[0003] Current treatments based on interferon-alpha have low success rates, particularly for genotype-1 infections predominant in Europe, Japan, and the U.S. Also, they are expensive and poorly received by patients. Thus, there is a need to develop better therapeutic agents for treating HCV infection.

SUMMARY

[0004] This invention is based on the discovery that certain thiourea compounds are effective in treating hepatitis C virus infection.

[0005] In one aspect, this invention relates to thiourea compounds of formula (I):

(I)



In this formula, each of R_1, R_2, and R_3, independently, is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, aryl, or heteroaryl; or R_1 and R_2, together with the nitrogen atom to which they are bonded, are C_3-C_{20} heterocycloalkyl; or R_2 and R_3, together with the two nitrogen atoms to which they are bonded and the carbon atom bonded to both of the two nitrogen atoms, are C_3-C_{20} heterocycloalkyl; each of A_1 and A_2, independently, is aryl or heteroaryl: each of X, Y, and Z, independently, is O, S, S(O), $S(O)_2$, $N(R_a)$, $C(R_aR_b)$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl, in which each of R_a and R_b, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; each of m and n, independently, is 1, 2, 3, 4, or 5; and each of x, y, and z, independently, is 0 or 1.

[0006] Referring to formula (I), a subset of the thiourea compounds described above are those in which x is 1, y is 0, and z is 0. In these compounds, X can be O or NH, A_1 can be phenylene, A_2 can be phenyl, and each of R_1, R_2, and R_3, independently, can be H or C_1-C_{10} alkyl optionally substituted with aryl.

[0007] Another subset of the thiourea compounds described above are those in which x is 1, y is 0, and z is 1. In these compounds, X and Z can both be O, each of R_1, R_2, and R_3 can be H, or R_1 and R_2, together with the nitrogen atom to which they are bonded, can be C_3-C_{20} heterocycloalkyl, A_1 can be phenylene, and A_2 can be heteroaryl, or aryl optionally substituted with halo, aryl, heteroaryl, CN, OR, COOR, or NRR', in which each of R and R' independently, is H, C_1-C_{10} alkyl, or aryl. Referring to formula (I), another subset of the thiourea compounds described above are those in which x is 1, y is 1, and z is 1. In these compounds, X and Z can both be O, Y can be $C(R_aR_b)$ (in which each of R_a and R_b, independently, can be C_1-C_{10} alkyl), A_1 can be phenylene, A_2 can be phenyl optionally substituted with aryl, and each of R_1, R_2, and R_3 can be H.

[0008] The term "alkyl" refers to a saturated, linear or branched hydrocarbon moiety, such as —CH_3, —$CH(CH_3)_2$, or —CH_2—. The term "alkenyl" refers to a linear or branched hydrocarbon moiety that contains at least one double bond, such as —CH═CH—CH_3 or —CH═CH—CH_2—. The term "alkynyl" refers to a linear or branched hydrocarbon moiety that contains at least one triple bond, such as —O═C—CH_3 or —O═C—CH_2—. The term "cycloalkyl" refers to a saturated, cyclic hydrocarbon moiety, such as cyclohexyl or cyclohexylene. The term "cycloalkenyl" refers to a non-aromatic, cyclic hydrocarbon moiety that contains at least one double bond, such as cyclohexenyl. The term "heterocycloalkyl" refers to a saturated, cyclic moiety having at least one ring heteroatom (e.g., N, O, or S), such as 4-tetrahydropyranyl or 4-tetrahydropyranylene. The term "heterocycloalkenyl" refers to a non-aromatic, cyclic moiety having at least one ring heteroatom (e.g., N, O, or S) and at least one double bond, such as pyranyl. The term "aryl" refers to a hydrocarbon, moiety having one or more aromatic rings. Examples of aryl moieties include phenyl (Ph), phenylene, naphthyl, naphthylene, pyrenyl, anthryl, and phenanthryl. The term "heteroaryl" refers to a moiety having one or more aromatic rings that contain at least one heteroatom (e.g., N, O, or S). Examples of heteroaryl moieties include furyl, furylene, fluorenyl, pyrrolyl, thienyl, oxazolyl, imidazolyl, thiazolyl, pyridyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl and indolyl.

[0009] Alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl mentioned herein include both substituted and unsubstituted moieties, unless specified otherwise. Possible substituents on cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl include, but are not limited to, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, C_1-C_{10} alkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, amino, C_1-C_{10} alkylamino, C_1-C_{20} dialkylamino, arylamino, diarylamino, hydroxyl, halo, thio, C_1-C_{10} alkylthio, arylthio, C_1-C_{10} alkylsulfonyl, arylsulfonyl, acylamino, aminoacyl, aminothioacyl, amidino, guanidine, ureido, cyano, nitro, acyl, thioacyl, acyloxy, carboxyl, and carboxylic ester. On the other hand, possible substituents on alkyl, alkenyl, or alkynyl include all of the above-recited substituents except C_1-C_{10} alkyl. Cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl can also be fused with each other.

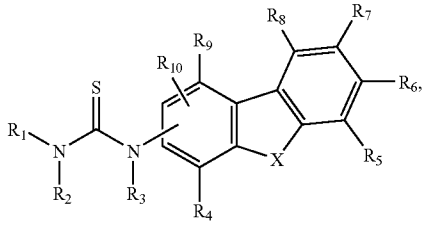
[0010] In another aspect, this invention features thiourea compounds of formula (I), in which R_1 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, aryl, or heteroaryl; each of R_2 and R_3, indepen-

dently, is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, aryl, or heteroaryl; or R_2 and R_3, together with the two nitrogen atoms to which they are bonded and the carbon atom bonded to both of the two nitrogen atoms, are C_3-C_{20} heterocycloalkyl: each of A_1 and A_2, independently, is aryl or heteroaryl; each of X, Y, and Z, independently, is O, S, S(O), $S(O)_2$, $N(R_a)$, $C(R_aR_b)$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl, in which each of R_a and R_b, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; each of m and n, independently, is 0, 1, 2, 3, 4, or 5; and each of x, y, and z, independently, is 0 or 1.

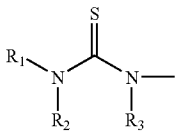
[0011] Referring to formula (I), a subset of the thiourea compounds described above are those in which x is 1, y is 0, and z is 0. In these compounds, X can be O, A_1 can be phenylene, A_2 can be phenyl, R_1 can be H or C_1-C_{10} alkyl optionally substituted with aryl, and R_2 and R_3, together with the two nitrogen atoms to which they are bonded and the carbon atom bonded to both of the two nitrogen atoms, can be C_3-C_{20} heterocycloalkyl;

[0012] In another aspect, this invention relates to thiourea compounds of formula (II):

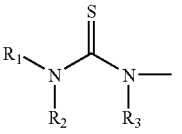
(II)



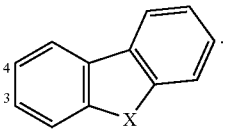
wherein X is O, $N(R_a)$, $C(R_aR_b)$, or C(O); each of R_1, R_2, and R_3, independently, is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, aryl, or heteroaryl; or R_2 and R_3, together with the two nitrogen atoms to which they are bonded and the carbon atom bonded to both of the two nitrogen atoms, are C_3-C_{20} heterocycloalkyl; and each of R_4, R_5, R_6, R_7, R_8, R_9, and R_{10}, independently, is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, aryl, heteroaryl halo, $N(R_cR_d)$, $N(R_c)$—C(S)—$N(R_dR_e)$; $N(R_c)$—$C(O)R_d$, or $N(R_c)$—C(O)O—R_d; in which each of R_a, R_b, R_c, R_d, and R_e, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl; provided that if R_{10} is at the 3-position, then



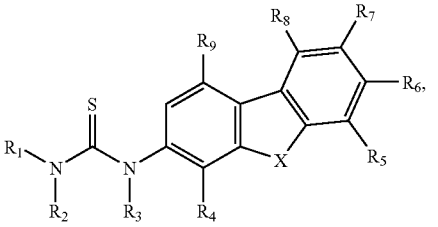
is at the 4-position, and; if R_{10} is at the 4-position, then



is at the 3-position. The 3- and 4-positions of the above formula are delineated below:



[0013] An embodiment of the just-described compounds features the following formula:



wherein X, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are as just defined.

[0014] Referring the above formula, a subset of the thiourea compounds described above are those in which each of R_1, R_2, and R_3, independently, is H, aryl optionally substituted with C_1-C_{20} heterocycloalkyl, heteroaryl, or C_1-C_{10} alkyl optionally substituted with C_1-C_{10} alkoxy, aryl, N(RR'), in which each of R and R independently, is H or C_1-C_{10} alkyl. In these compounds, each of R_4, R_5, R_6, R_7, R_8, and R_9, independently, can be H, halo, $N(R_cR_d)$, $N(R_c)$—C(S)—$N(R_dR_e)$; $N(R_c)$—$C(O)R_d$, or $N(R_c)$—C(O)O—R_d. For example, each of R_4, R_5, R_7, R_8, and R_9 can be H and R_6 can be H, halo, $N(R_cR_d)$, $N(R_c)$—C(S)—$N(R_dR_e)$, $N(R_c)$—$C(O)R_d$, or $N(R_c)$—C(O)O—R_d.

[0015] Another subset of the thiourea compounds described above are those in which each of R_1, R_2, and R_3 is H; or R_4 is $(CH_2)_nCH_3$, in which n is 1, 2, 3, 4, 5, or 6, and each of R_2 and R_3 is H.

[0016] In still another aspect, this invention features a method for treating hepatitis C virus infection. The method includes administering to a subject in need thereof an effective amount of one or more thiourea compounds of formula (I) or (II) shown above. The term "treating" or "treatment" refers to administering one or more thiourea compounds to a subject, who has an above-described infection, a symptom of such an infection, or a predisposition, toward such an infection, with the purpose to confer a therapeutic effect, e.g., to cure, relieve, alter, affect, ameliorate, or prevent the above-described infection, the symptom, of it, or the predisposition toward it.

[0017] In addition, this invention encompasses a pharmaceutical composition that contains an effective amount of at least one of the above-mentioned thiourea compounds and a pharmaceutically acceptable carrier.

[0018] The thiourea compounds described above include the compounds themselves, as well as their salts, prodrugs,

and solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a thiourea compound. Suitable anions include chloride, bromide, iodide, sulfate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, acetate, malate, tosylate, tartrate, fumurate, glutamate, glucuronate, lactate, glutarate, and maleate. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a thiourea compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ton, and an ammonium cation such as tetramethylammonium ion. The thiourea compounds also include those salts containing quaternary nitrogen atoms. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing active thiourea compounds. A solvate refers to a complex formed between, an active thiourea compound and a pharmaceutically acceptable solvent. Examples of pharmaceutically acceptable solvents include water, ethanol, isopropanol, ethyl acetate, acetic acid, and ethanolamine.

[0019] Also within the scope of this invention is a pharmaceutical composition containing one or more of the above-described thiourea compounds for use in treating HCV infection, as well as this therapeutic use and use of the compounds for the manufacture of a medicament for treating HCV infection.

[0020] The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

[0021] The table below show 183 exemplary compounds of this invention:

TABLE 1

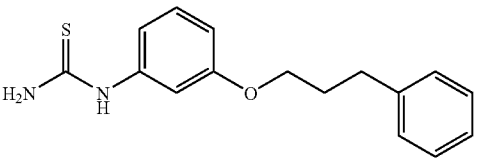
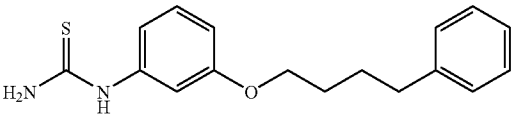
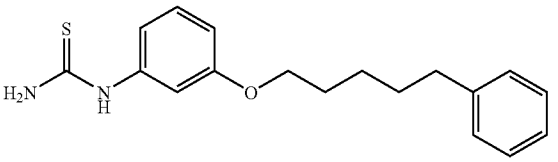
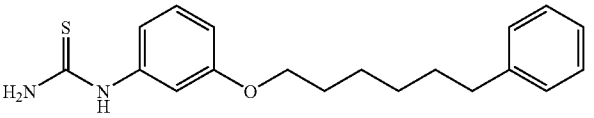
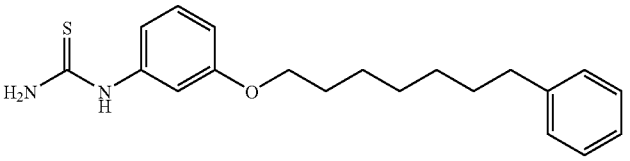
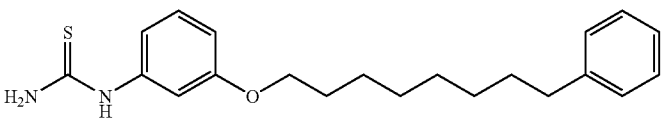
Compound No.	Structure	Name	Molecular Weight (M + 1)
1		[3-(3-Phenyl-propoxy)-phenyl]-thiourea	287
2		[3-(4-Phenyl-butoxy)-phenyl]-thiourea	301
3		[3-(5-Phenyl-pentyloxy)-phenyl]-thiourea	315
4		[3-(6-Pehnyl-hexyloxy)-phenyl]-thiourea	329
5		[3-(7-Phenyl-heptyloxy)-phenyl]-thiourea	343
6		[3-(8-Pehnyl-octyloxy)-phenyl]-thiourea	357

TABLE 1-continued

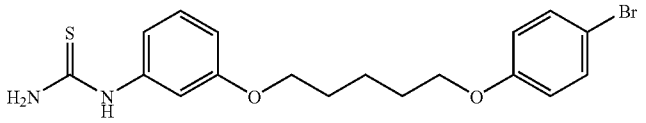
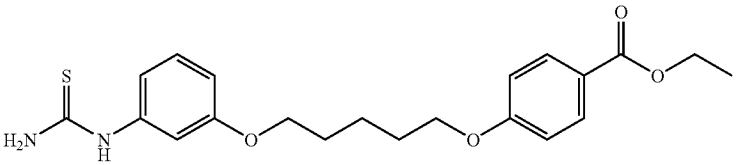
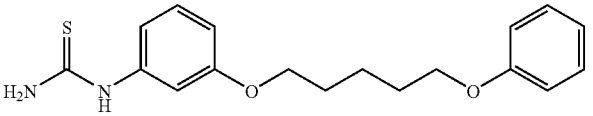
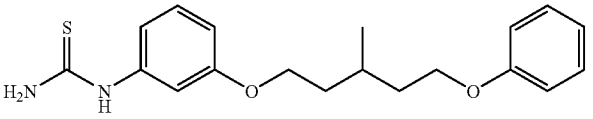
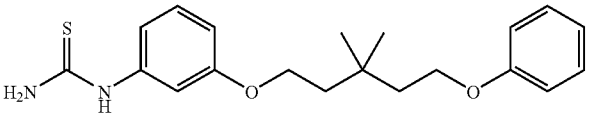
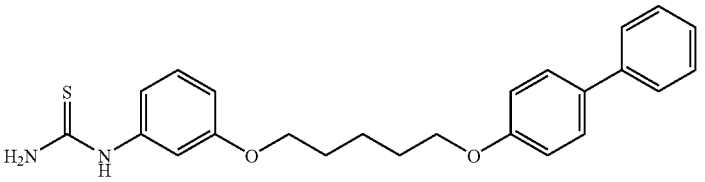
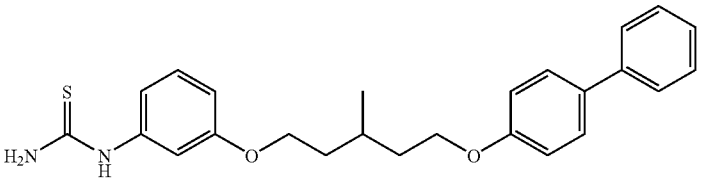
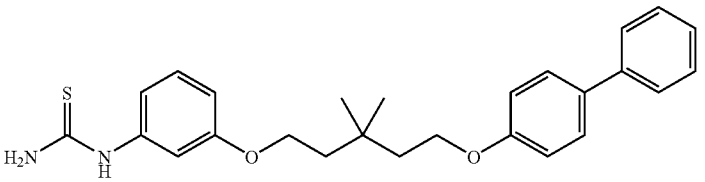
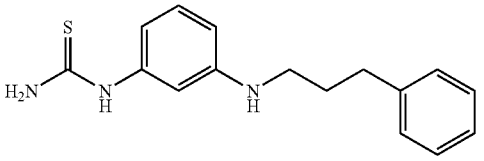
Compound No.	Structure	Name	Molecular Weight (M + 1)
7		{3-[5-(4-Bromo-phenoxy)-pentyloxy]-phenyl}-thiourea	409 411
8		4-[5-(3-Thioureido-phenoxy)-pentyloxy]-benzoic acid ethyl ester	403
9		[3-(5-Phenoxy-pentyloxy)-phenyl]-thiourea	331
10		[3-(3-Methyl-5-phenoxy-pentyloxy)-phenyl]-thiourea	345
11		[3-(3,3-Dimethyl-5-phenoxy-pentyloxy)-phenyl]-thiourea	359
12		{3-[5-(Biphenyl-4-yloxy)-pentyloxy]-phenyl}-thiourea	407
13		{3-[5-(Biphenyl-4-yloxy)-3-methyl-pentyloxy]-phenyl}-thiourea	421
14		{3-[5-(Biphenyl-4-yloxy)-3,3-dimethyl-pentyloxy]-phenyl}-thiourea	435
15		[3-(3-Phenyl-propylamino)-phenyl]-thiourea	286

TABLE 1-continued

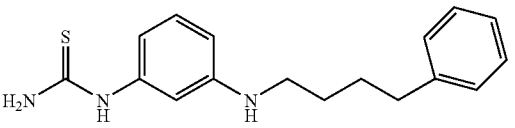
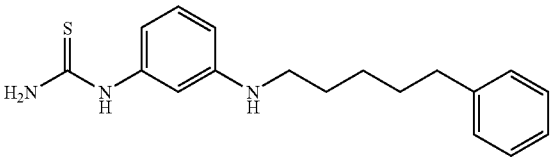
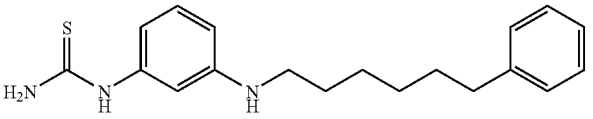
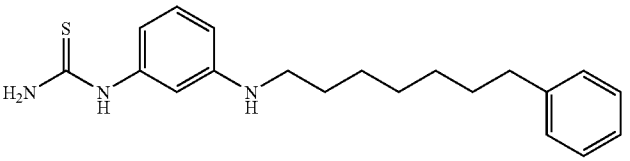
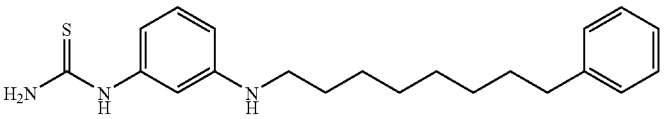
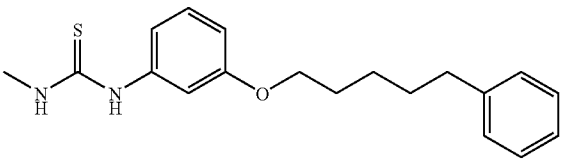
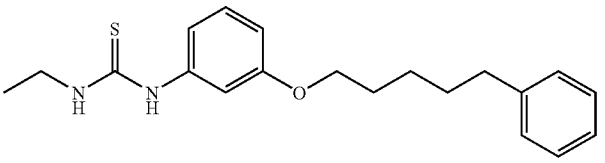
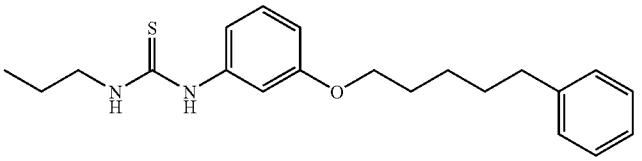
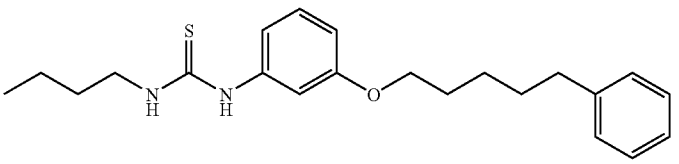
Compound No.	Structure	Name	Molecular Weight (M + 1)
16		[3-(4-Phenyl-butylamino)-phenyl]-thiourea	300
17		[3-(5-Phenyl-pentylamino)-phenyl]-thiourea	314
18		[3-(6-Phenyl-hexylamino)-phenyl]-thiourea	328
19		[3-(7-Phenyl-heptylamino)-phenyl]-thiourea	342
20		[3-(8-Phenyl-octylamino)-phenyl]-thiourea	356
21		1-Methyl-3-[3-(5-phenyl-pentyloxy)-phenyl]-thiourea	329
22		1-Ethyl-3-[3-(5-phenyl-pentyloxy)-phenyl]-thiourea	343
23		1-[3-(5-Phenyl-pentyloxy)-phenyl]-3-propyl-thiourea	357
24		1-Butyl-3-[3-(5-phenyl-pentyloxy)-phenyl]-thiourea	371

TABLE 1-continued

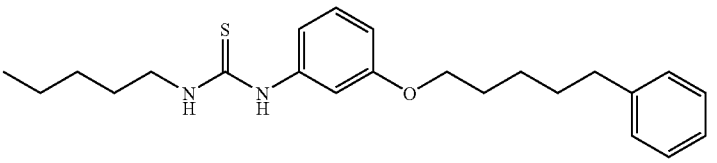
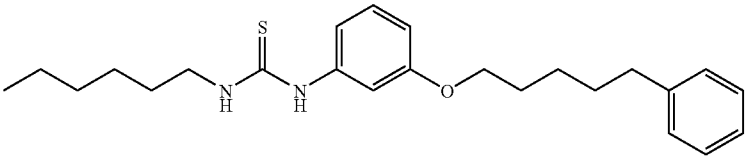
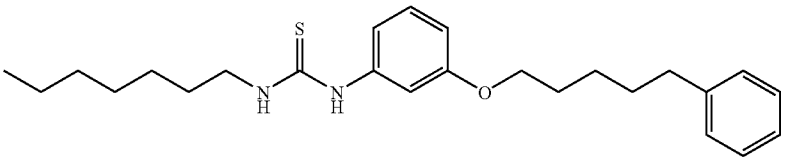
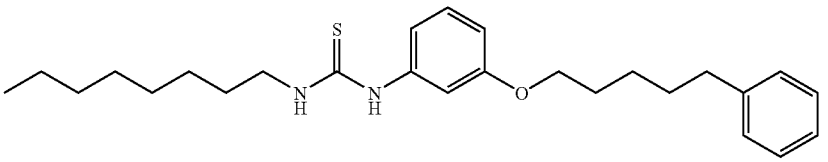
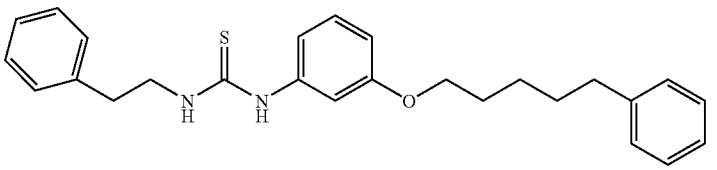
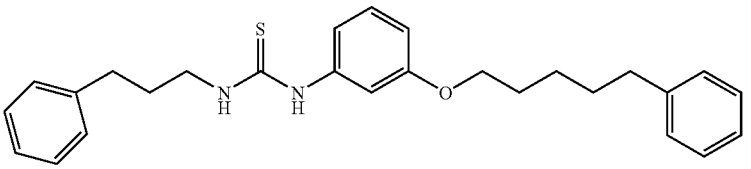
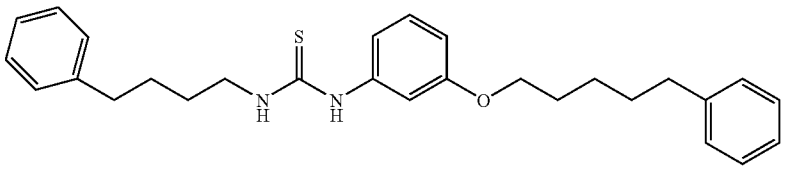
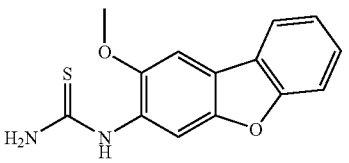
Compound No.	Structure	Name	Molecular Weight (M + 1)
25		1-Pentyl-3-[3-(5-phenyl-pentyloxy)-phenyl]-thiourea	385
26		1-Hexyl-3-[3-(5-phenyl-pentyloxy)-phenyl]-thiourea	399
27		1-Heptyl-3-[3-(5-phenyl-pentyloxy)-phenyl]-thiourea	413
28		1-Octyl-3-[3-(5-phenyl-pentyloxy)-phenyl]-thiourea	427
29		1-Phenethyl-3-[3-(5-phenyl-pentyloxy)-phenyl]-thiourea	419
30		1-[3-(5-Phenyl-pentyloxy)-phenyl]-3-(3-phenyl-propyl)-thiourea	433
31		1-(4-Phenyl-butyl)-3-[3-(5-phenyl-pentyloxy)-phenyl]-thiourea	447
32		(2-Methoxy-dibenzofuran-3-yl)-thiourea	273

TABLE 1-continued

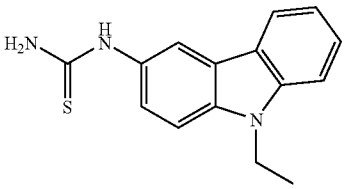
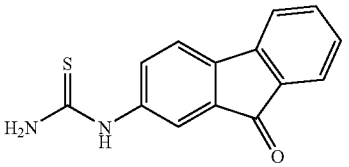
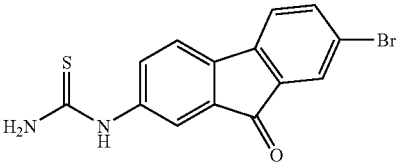
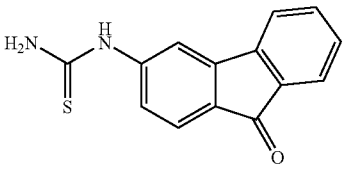
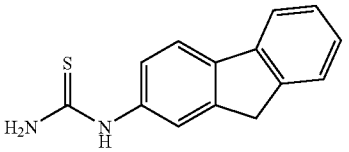
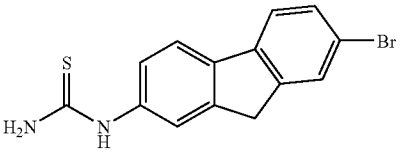
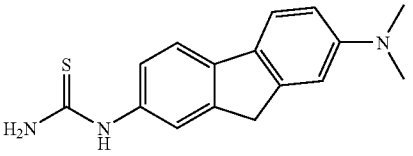
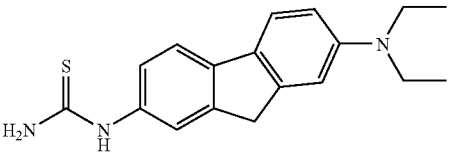
Compound No.	Structure	Name	Molecular Weight (M + 1)
33		(9-Ethyl-9H-carbazol-3-yl)-thiourea	270
34		(9-Oxo-9H-fluoren-2-yl)-thiourea	255
35		(7-Bromo-9-oxo-9H-fluoren-2-yl)-thiourea	332 334
36		(9-Oxo-9H-fluoren-3-yl)-thiourea	255
37		(9H-Fluoren-2-yl)-thiourea	241
38		(7-Bromo-9H-fluoren-2-yl)-thiourea	320
39		(7-Dimethylamino-9H-fluoren-2-yl)-thiourea	284
40		(7-Diethylamino-9H-fluoren-2-yl)-thiourea	312

TABLE 1-continued

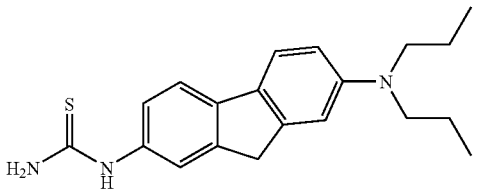
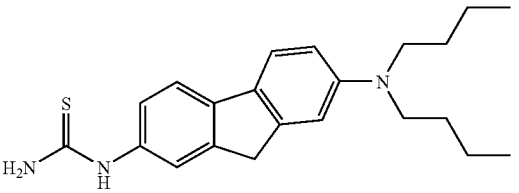
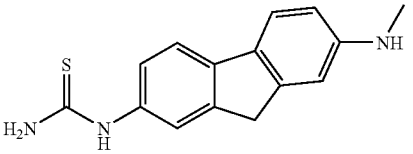
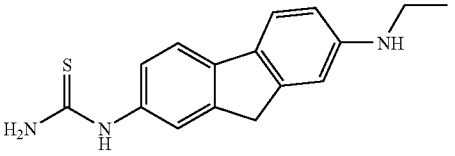
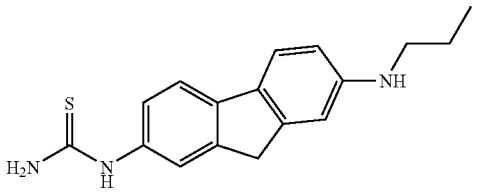
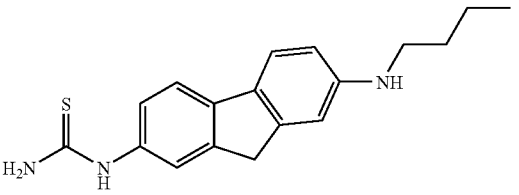
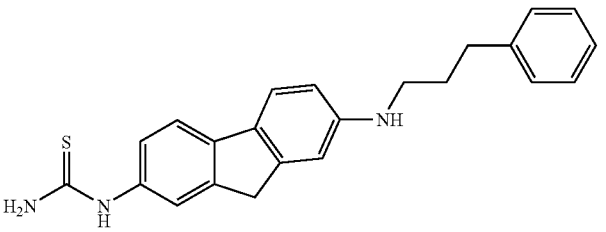
Compound No.	Structure	Name	Molecular Weight (M + 1)
41		(7-Dipropylamino-9H-fluoren-2-yl)-thiourea	340
42		(7-Dibutylamino-9H-fluoren-2-yl)-thiourea	368
43		(7-Methylamino-9H-fluoren-2-yl)-thiourea	270
44		(7-Ethylamino-9H-fluoren-2-yl)-thiourea	284
45		(7-Propylamino-9H-fluoren-2-yl)-thiourea	298
46		(7-Butylamino-9H-fluoren-2-yl)-thiourea	312
47		[7-(3-Phenyl-propylamino)-9H-fluoren-2-yl]-thiourea	374

TABLE 1-continued

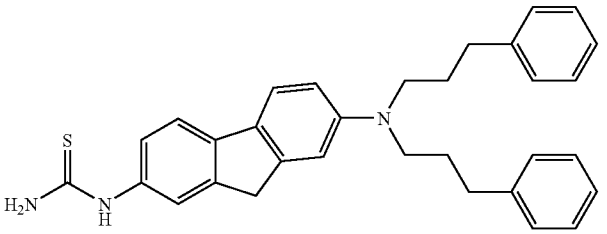
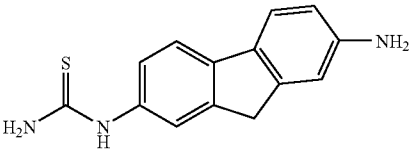
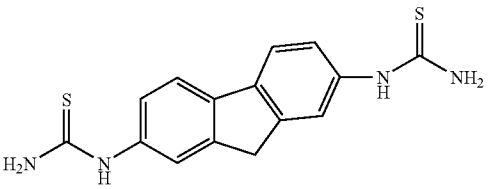
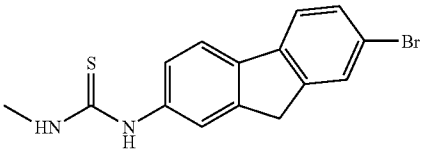
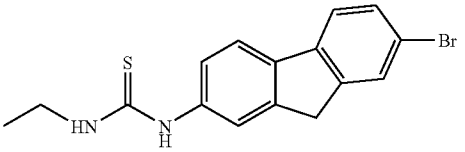
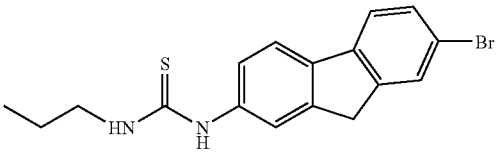
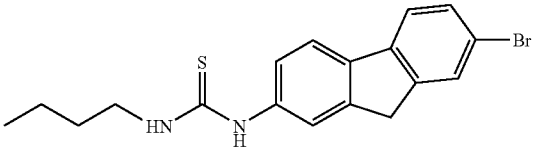
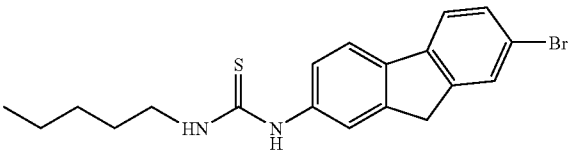
Compound No.	Structure	Name	Molecular Weight (M + 1)
48		{7-[Bis-(3-phenyl-propyl)-amino]-9H-fluoren-2-yl}-thiourea	492
49		(7-Amino-9H-fluoren-2-yl)-thiourea	256
50		(7-Thioureido-9H-fluoren-2-yl)-thiourea	315
51		1-(7-Bromo-9H-fluoren-2-yl)-3-methyl-thiourea	333 335
52		1-(7-Bromo-9H-fluoren-2-yl)-3-ethyl-thiourea	347 349
53		1-(7-Bromo-9H-fluoren-2-yl)-3-propyl-thiourea	361 363
54		1-(7-Bromo-9H-fluoren-2-yl)-3-butyl-thiourea	375 377
55		1-(7-Bromo-9H-fluoren-2-yl)-3-pentyl-thiourea	389 391

TABLE 1-continued

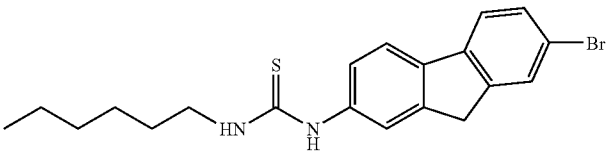
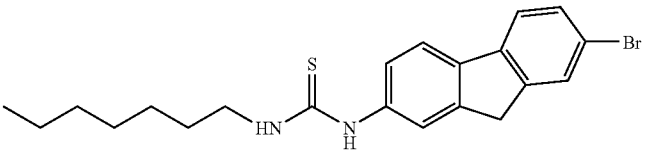
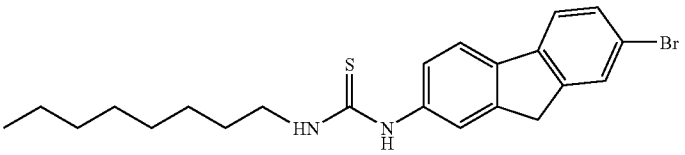
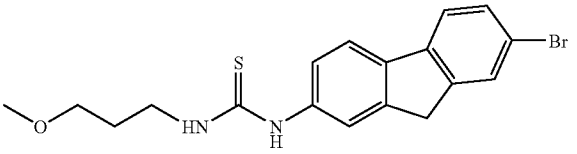
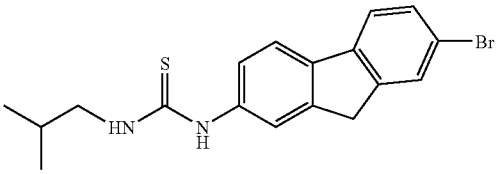
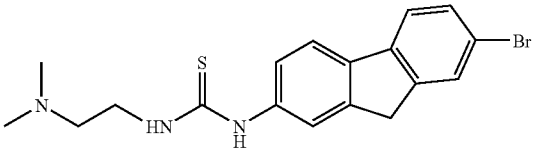
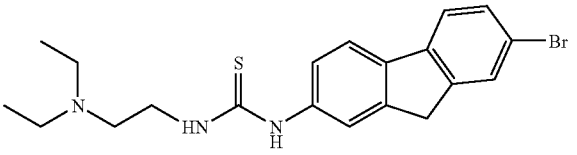
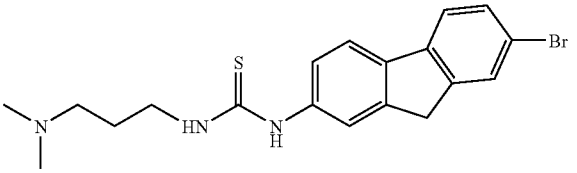
Compound No.	Structure	Name	Molecular Weight (M + 1)
56		1-(7-Bromo-9H-fluoren-2-yl)-3-hexyl-thiourea	403 405
57		1-(7-Bromo-9H-fluoren-2-yl)-3-heptyl-thiourea	417 419
58		1-(7-Bromo-9H-fluoren-2-yl)-3-octyl-thiourea	431 433
59		1-(7-Bromo-9H-fluoren-2-yl)-3-(3-methoxy-propyl)-thiourea	391 393
60		1-(7-Bromo-9H-fluoren-2-yl)-3-isobutyl-thiourea	375 377
61		1-(7-Bromo-9H-fluoren-2-yl)-3-(2-dimethylamino-ethyl)-thiourea	390 392
62		1-(7-Bromo-9H-fluoren-2-yl)-3-(2-diethylamino-ethyl)-thiourea	418 420
63		1-(7-Bromo-9H-fluoren-2-yl)-3-(3-dimethylamino-propyl)-thiourea	404 406

TABLE 1-continued

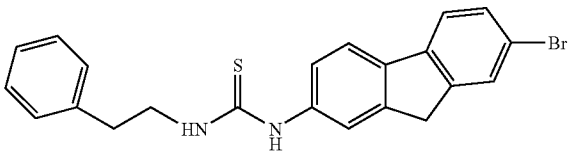
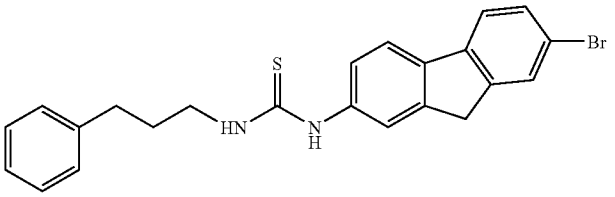
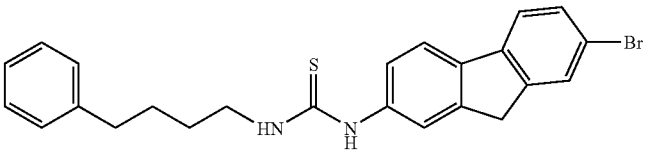
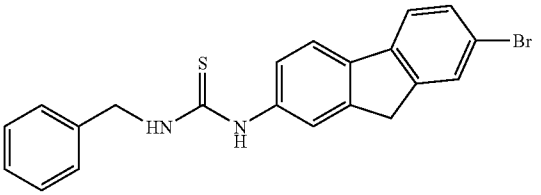
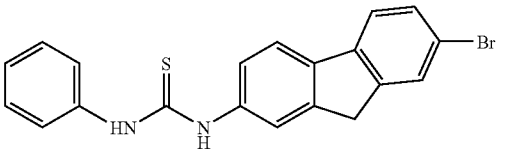
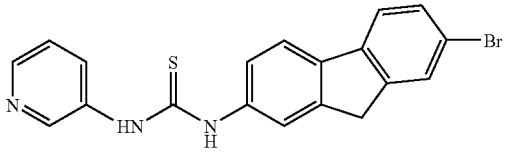
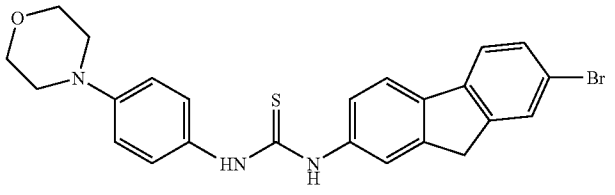
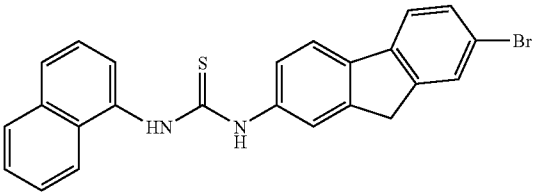
Compound No.	Structure	Name	Molecular Weight (M + 1)
64		1-(7-Bromo-9H-fluoren-2-yl)-3-phenethyl-thiourea	423 425
65		1-(7-Bromo-9H-fluoren-2-yl)-3-(3-phenyl-propyl)-thiourea	437 439
66		1-(7-Bromo-9H-fluoren-2-yl)-3-(4-phenyl-butyl)-thiourea	451 453
67		1-Benzyl-3-(7-bromo-9H-fluoren-2-yl)-thiourea	430 432
68		1-(7-Bromo-9H-fluoren-2-yl)-3-phenyl-thiourea	394 396
69		1-(7-Bromo-9H-fluoren-2-yl)-3-pyridin-3-yl-thiourea	395 397
70		1-(7-Bromo-9H-fluoren-2-yl)-3-(4-morpholin-4-yl-phenyl)-thiourea	480 482
71		1-(7-Bromo-9H-fluoren-2-yl)-3-naphthalen-1-yl-thiourea	445 447

TABLE 1-continued

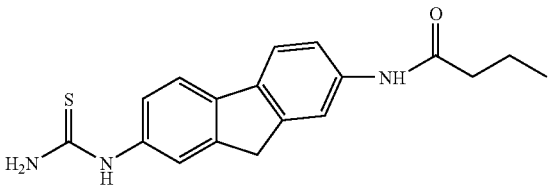
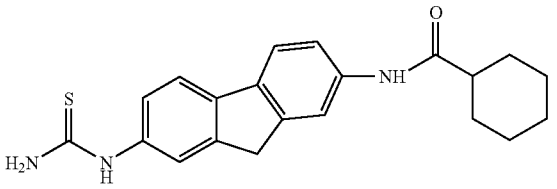
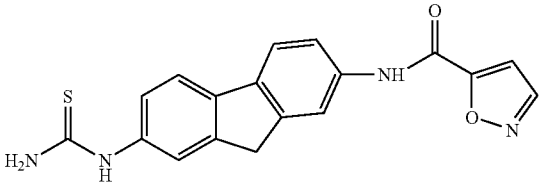
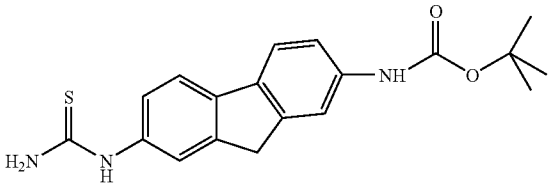
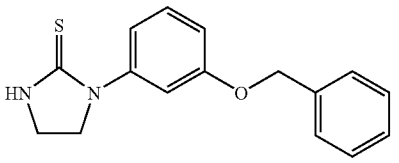
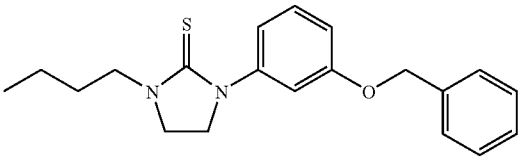
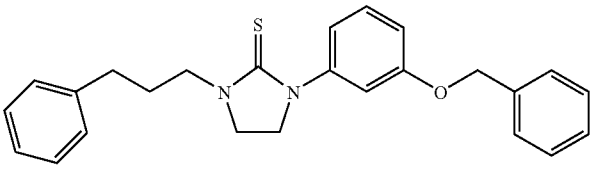
Compound No.	Structure	Name	Molecular Weight (M + 1)
72		N-(7-Thioureido-9H-fluoren-2-yl)-butyramide	326
73		Cyclohexanecarboxylic acid (7-thioureido-9H-fluoren-2-yl)-amide	366
74		Isoxazole-5-carboxylic acid (7-thioureido-9H-fluoren-2-yl)-amide	351
75		(7-Thioureido-9H-fluoren-2-yl)-carbamic acid tert-butyl ester	356
76		1-(3-Benzyloxy-phenyl)-imidazolidine-2-thione	285
77		1-(3-Benzyloxy-phenyl)-3-butyl-imidazolidine-2-thione	341
78		1-(3-Benzyloxy-phenyl)-3-(3-phenyl-propyl)-imidazolidine-2-thione	403

TABLE 1-continued

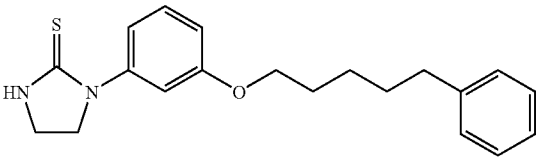
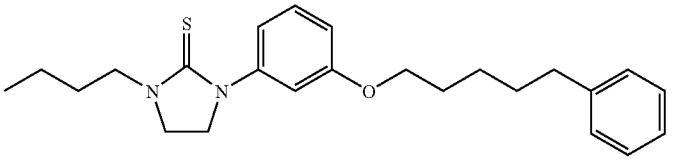
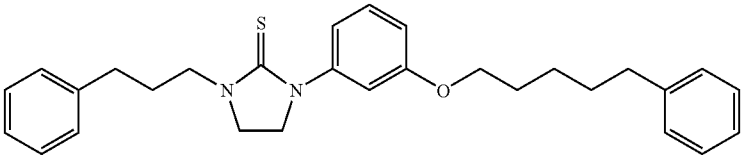
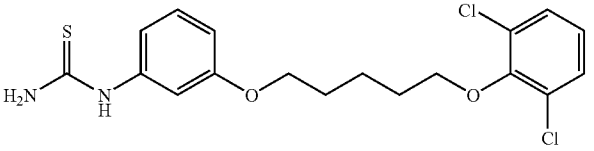
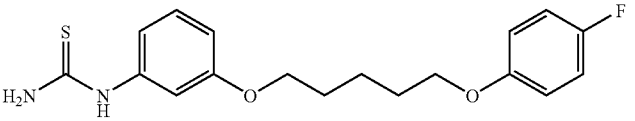
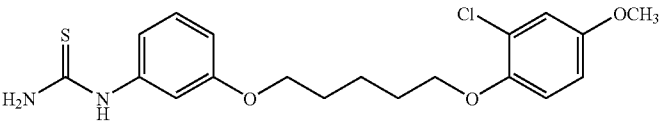
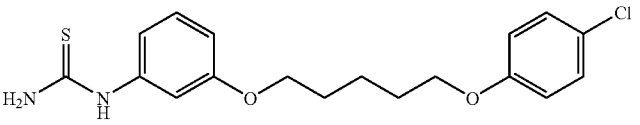
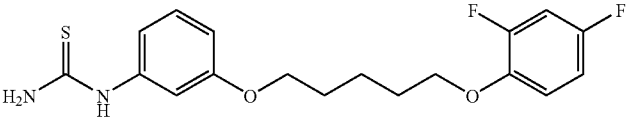
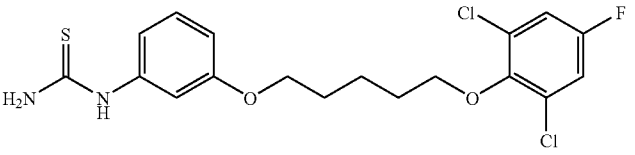
Compound No.	Structure	Name	Molecular Weight (M + 1)
79		1-[3-(5-Phenyl-pentyloxy)-phenyl]-imidazolidine-2-thione	341
80		1-Butyl-3-[3-(5-phenyl-pentyloxy)-phenyl]-imidazolidine-2-thione	397
81		1-[3-(5-Phenyl-pentyloxy)-phenyl]-3-(3-phenyl-propyl)-imidazolidine-2-thione	459
82		{3-[5-(2,6-Dichloro-phenoxy)-pentyloxy]-phenyl}-thiourea	400
83		{3-[5-(4-Fluoro-phenoxy)-pentyloxy]-phenyl}-thiourea	349
84		{3-[5-(2-Chloro-4-methoxy-phenoxy)-pentyloxy]-phenyl}-thiourea	395
85		{3-[5-(4-Chloro-phenoxy)-pentyloxy]-phenyl}-thiourea	365
86		{3-[5-(2,4-Difluoro-phenoxy)-pentyloxy]-phenyl}-thiourea	367
87		{3-[5-(2,6-Dichloro-4-fluoro-phenoxy)-pentyloxy]-phenyl}-thiourea	418

TABLE 1-continued

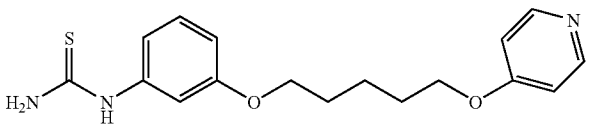
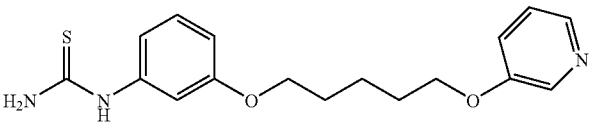
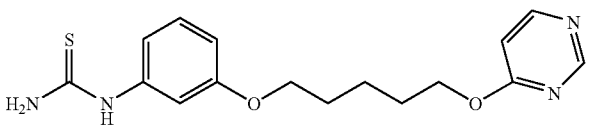
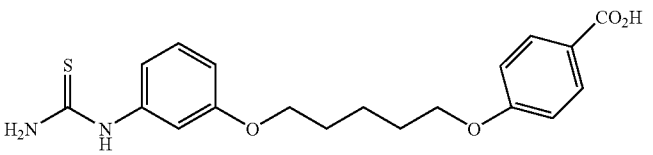
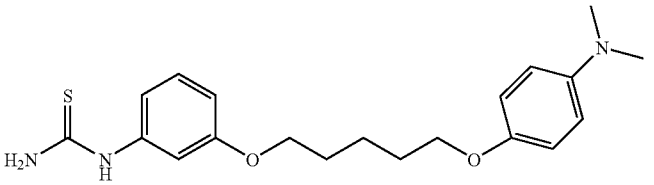
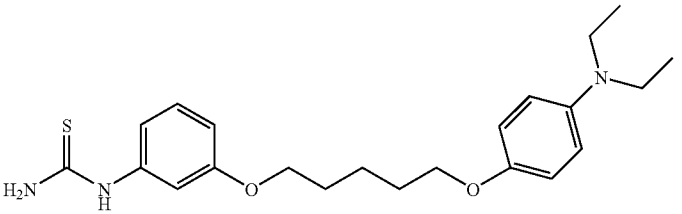
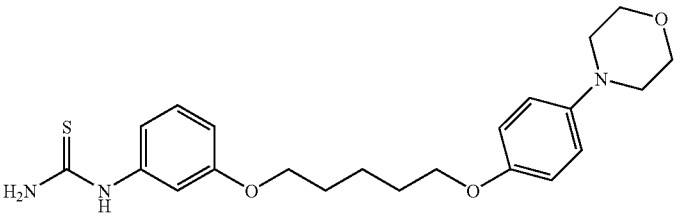
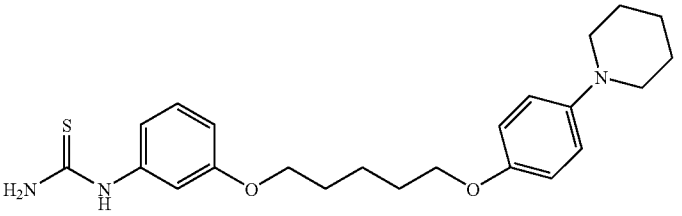
Compound No.	Structure	Name	Molecular Weight (M + 1)
88		{3-[5-(Pyridin-4-yloxy)-pentyloxy]-phenyl}-thiourea	332
89		{3-[5-(Pyridin-3-yloxy)-pentyloxy]-phenyl}-thiourea	332
90		{3-[5-(Pyrimidin-4-yloxy)-pentyloxy]-phenyl}-thiourea	333
91		4-[5-(3-Thioureido-phenoxy)-pentyloxy]-benzoic acid	375
92		{3-[5-(4-Dimethylamino-phenoxy)-pentyloxy]-phenyl}-thiourea	374
93		{3-[5-(4-Diethylamino-phenoxy)-pentyloxy]-phenyl}-thiourea	402
94		{3-[5-(4-Morpholin-4-yl-phenoxy)-pentyloxy]-phenyl}-thiourea	416
95		{3-[5-(4-Piperidin-1-yl-phenoxy)-pentyloxy]-phenyl}-thiourea	414

TABLE 1-continued

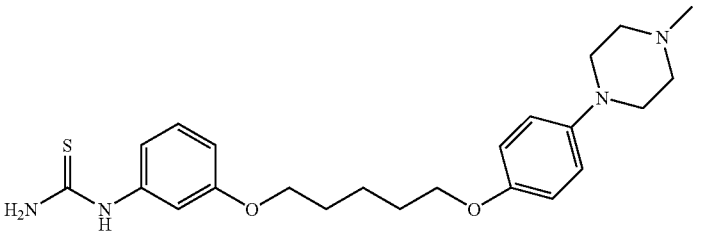
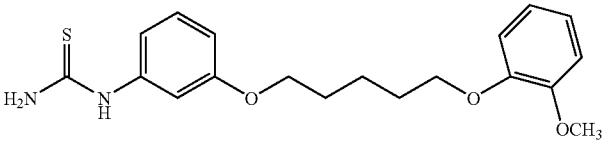
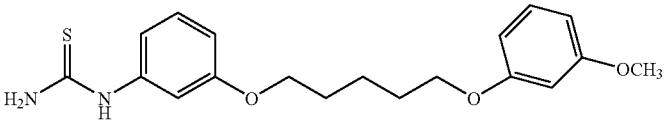
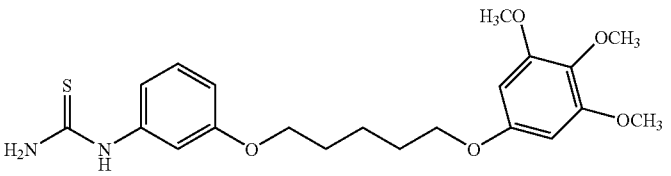
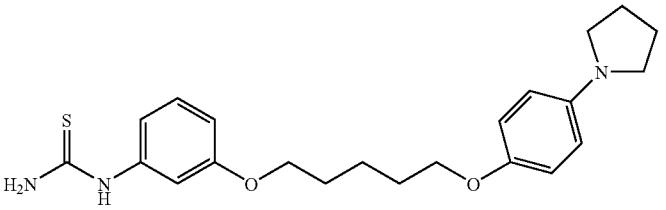
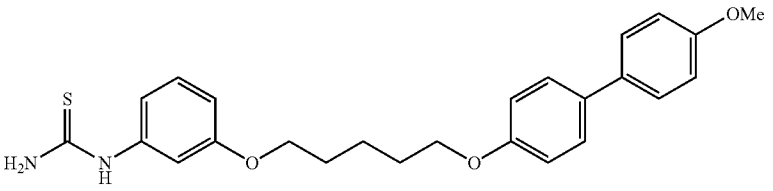
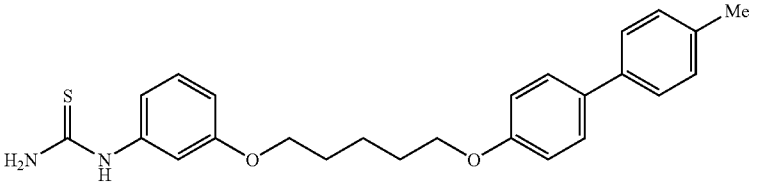
Compound No.	Structure	Name	Molecular Weight (M + 1)
96		(3-{5-[4-(4-Methyl-piperazin-1-yl)-phenoxy]-pentyloxy}-phenyl)-thiourea	429
97		{3-[5-(2-Methoxy-phenoxy)-pentyloxy]-phenyl}-thiourea	361
98		{3-[5-(3-Methoxy-phenoxy)-pentyloxy]-phenyl}-thiourea	361
99		{3-[5-(3,4,5-Trimethoxy-phenoxy)-pentyloxy]-phenyl}-thiourea	421
100		{3-[5-(4-Pyrrolidin-1-yl-phenoxy)-pentyloxy]-phenyl}-thiourea	400
101		{3-[5-(4'-Methoxy-biphenyl-4-yloxy)-pentyloxy]-phenyl}-thiourea	437
102		{3-[5-(4'-Methyl-biphenyl-4-yloxy)-pentyloxy]-phenyl}-thiourea	421

TABLE 1-continued

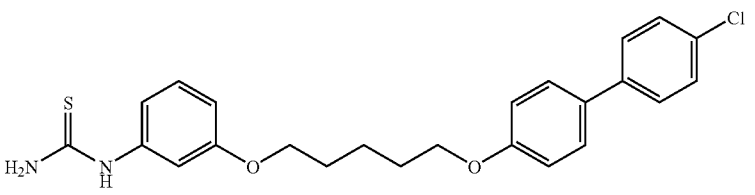
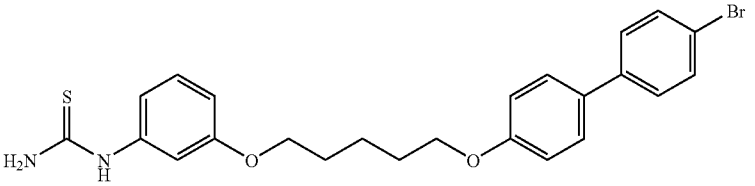
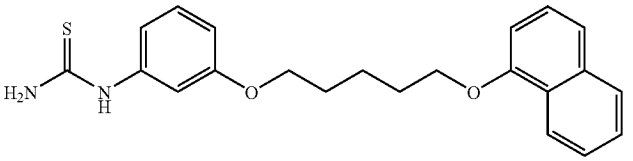
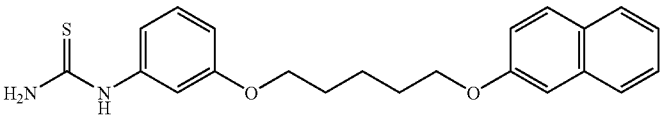
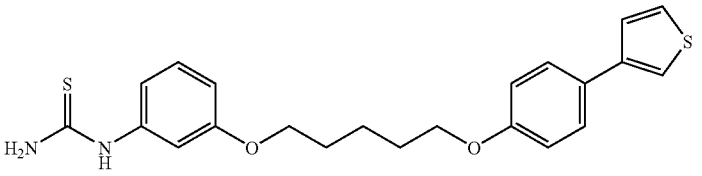
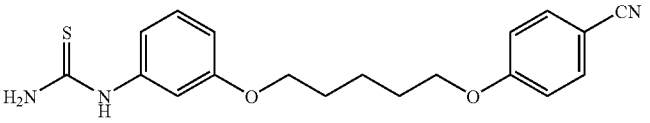
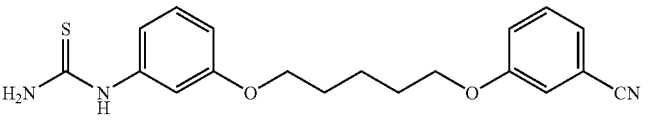
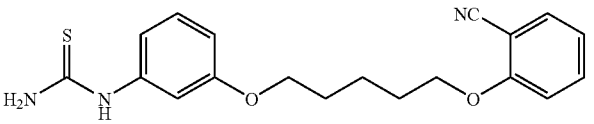
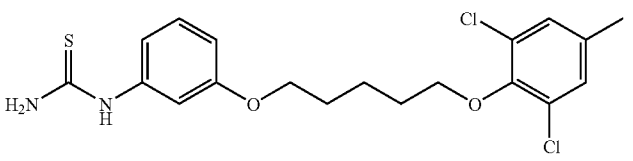
Compound No.	Structure	Name	Molecular Weight (M + 1)
103		{3-[5-(4'-Chloro-biphenyl-4-yloxy)-pentyloxy]-phenyl}-thiourea	441
104		{3-[5-(4'-Bromo-biphenyl-4-yloxy)-pentyloxy]-phenyl}-thiourea	485 487
105		{3-[5-(Naphthalen-1-yloxy)-pentyloxy]-phenyl}-thiourea	381
106		{3-[5-(Naphthalen-2-yloxy)-pentyloxy]-phenyl}-thiourea	381
107		{3-[5-(4-Thiophen-3-yl-phenoxy)-pentyloxy]-phenyl}-thiourea	413
108		{3-[5-(4-Cyano-phenoxy)-pentyloxy]-phenyl}-thiourea	356
109		{3-[5-(3-Cyano-phenoxy)-pentyloxy]-phenyl}-thiourea	356
110		{3-[5-(2-Cyano-phenoxy)-pentyloxy]-phenyl}-thiourea	356
111		{3-[5-(2,6-Dichloro-4-methyl-phenoxy)-pentyloxy-phenyl}-thiourea	414

TABLE 1-continued

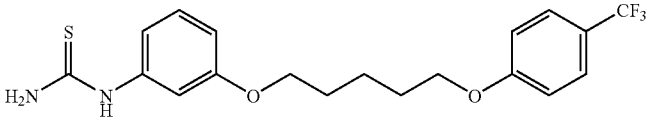
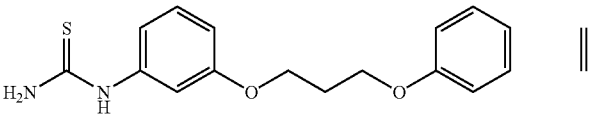
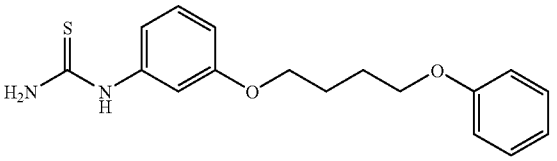
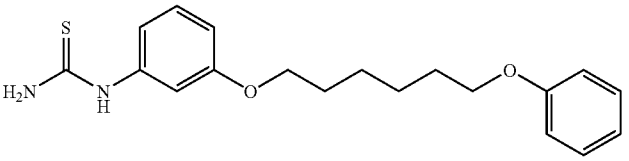
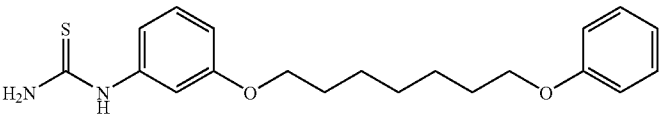
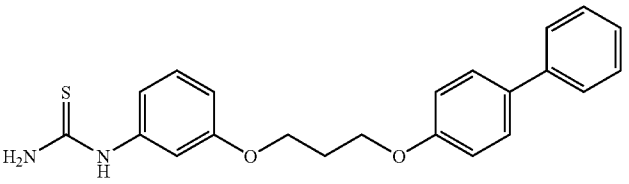
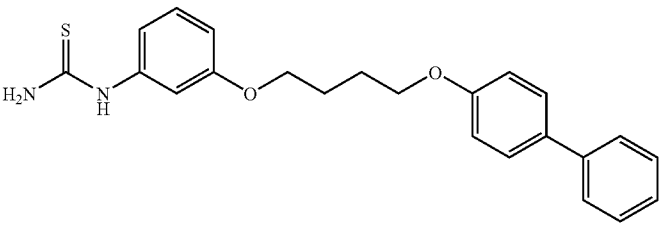
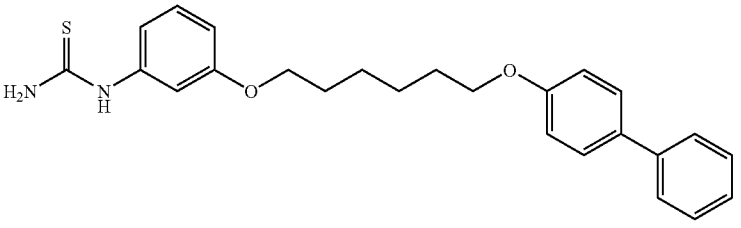
Compound No.	Structure	Name	Molecular Weight (M + 1)
112		{3-[5-(4-Trifluoromethyl-phenoxy)-pentyloxy]-phenyl}-thiourea	399
113		[3-(3-Phenoxy-propoxy)-phenyl]-thiourea	303
114		[3-(4-Phenoxy-butoxy)-phenyl]-thiourea	317
115		[3-(6-Phenoxy-hexyloxy)-phenyl]-thiourea	345
116		[3-(7-Phenoxy-heptyloxy)-phenyl]-thiourea	359
117		{3-[3-(Biphenyl-4-yloxy)-propoxy]-phenyl}-thiourea	379
118		{3-[4-(Biphenyl-4-yloxy)-butoxy]-phenyl}-thiourea	393
119		{3-[6-(Biphenyl-4-yloxy)-hexyloxy]-phenyl}-thiourea	421

TABLE 1-continued

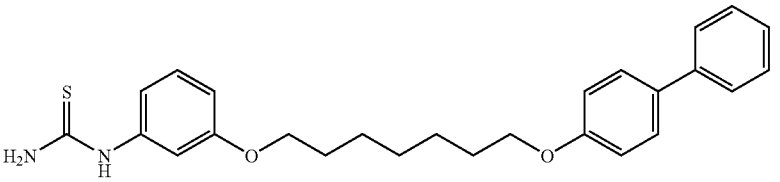
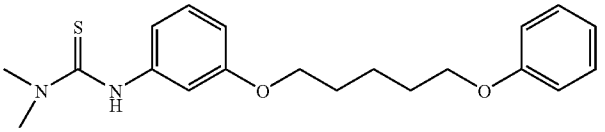
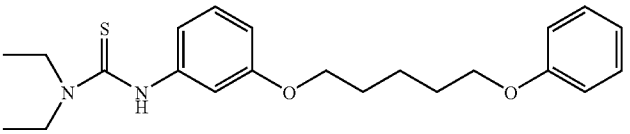
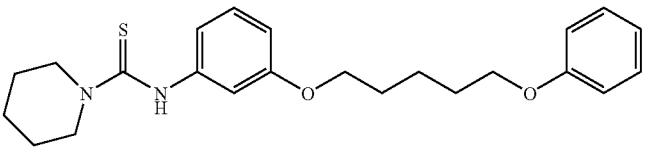
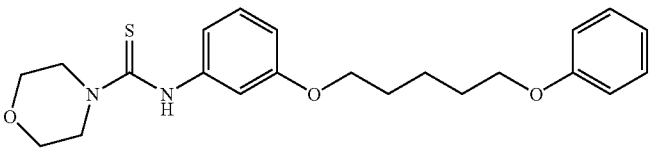
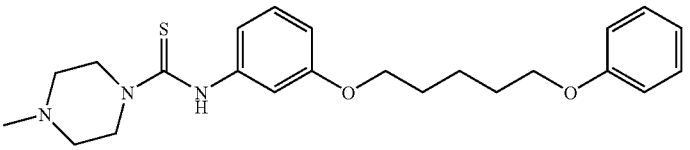
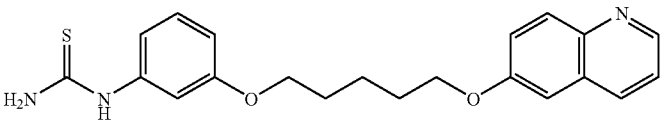
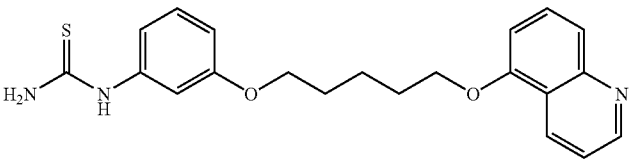
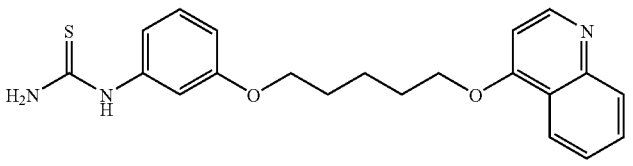
Compound No.	Structure	Name	Molecular Weight (M + 1)
120		{3-[7-(Biphenyl-4-yloxy)-heptyloxy]-phenyl}-thiourea	435
121		1,1-Dimethyl-3-[3-(5-phenoxy-pentyloxy)-phenyl]-thiourea	359
122		1,1-Diethyl-3-[3-(5-phenoxy-pentyloxy)-phenyl]-thiourea	387
123		Piperidine-1-carbothioic acid [3-(5-phenoxy-pentyloxy)-phenyl]-amide	399
124		Morpholine-4-carbothioic acid [3-(5-phenoxy-pentyloxy)-phenyl]-amide	401
125		4-Methyl-piperazine-1-carbothioic acid [3-(5-phenoxy-pentyloxy)-phenyl]-amide	414
126		{3-[5-(Quinolin-6-yloxy)-pentyloxy]-phenyl}-thiourea	382
127		{3-[5-(Quinolin-5-yloxy)-pentyloxy]-phenyl}-thiourea	382
128		{3-[5-(Quinolin-4-yloxy)-pentyloxy]-phenyl}-thiourea	382

TABLE 1-continued

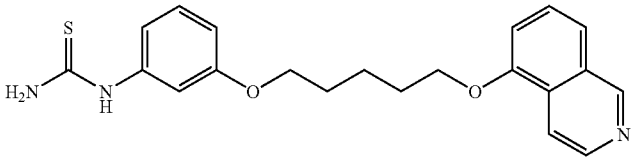
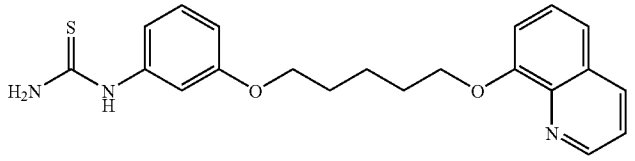
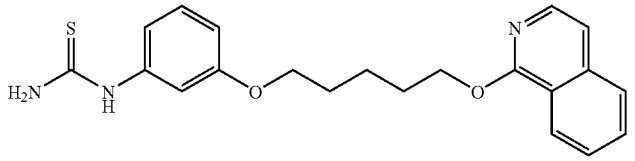
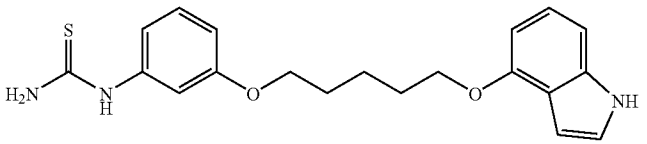
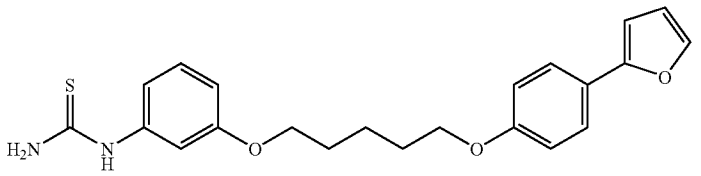
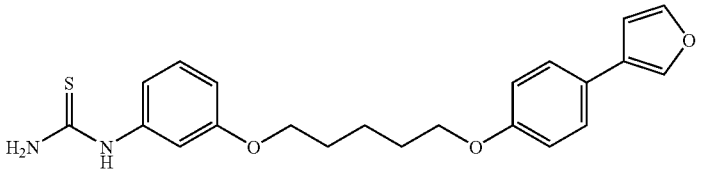
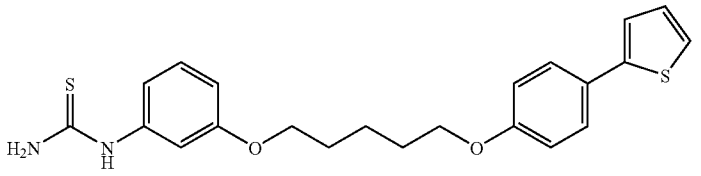
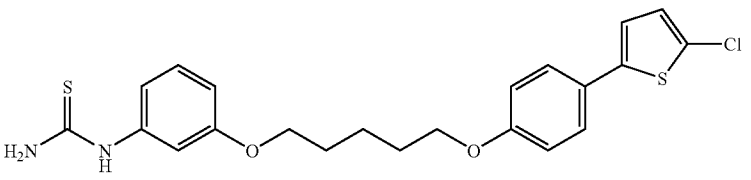
Compound No.	Structure	Name	Molecular Weight (M + 1)
129		{3-[5-(Isoquinolin-5-yloxy)-pentyloxy]-phenyl}-thiourea	382
130		{3-[5-(Quinolin-8-yloxy)-pentyloxy]-phenyl}-thiourea	382
131		{3-[5-(Isoquinolin-1-yloxy)-pentyloxy]-phenyl}-thiourea	382
132		{3-[5-(1H-Indol-4-yloxy)-pentyloxy]-phenyl}-thiourea	370
133		{3-[5-(4-Furan-2-yl-phenoxy)-pentyloxy]-phenyl}-thiourea	397
134		{3-[5-(4-Furan-3-yl-phenoxy)-pentyloxy]-phenyl}-thiourea	397
135		{3-[5-(4-Thiophen-2-yl-phenoxy)-pentyloxy]-phenyl}-thiourea	413
136		(3-{5-[4-(5-Chloro-thiophen-2-yl)-phenoxy]-pentyloxy}-phenyl)-thiourea	447

TABLE 1-continued

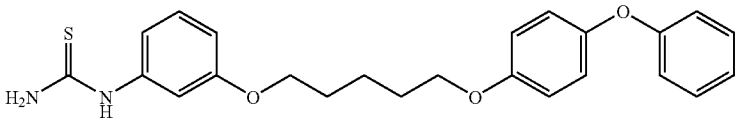
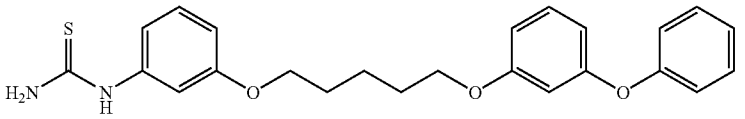
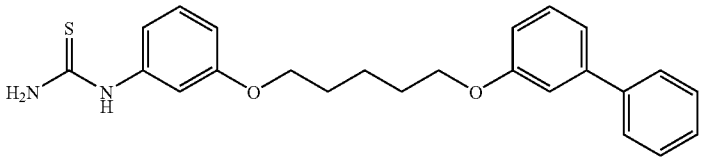
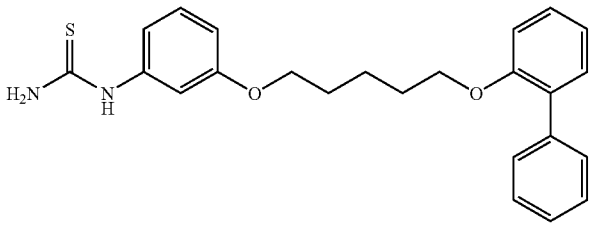
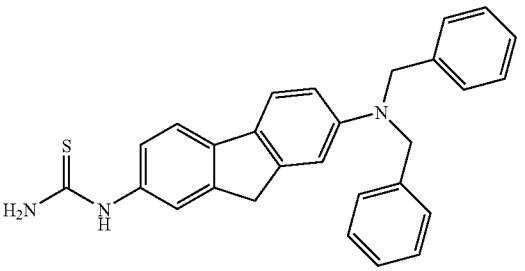
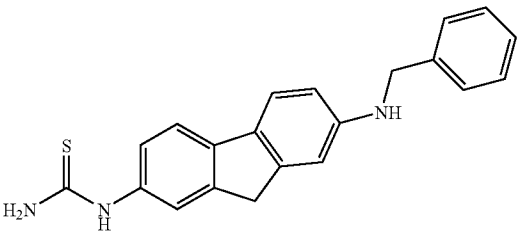
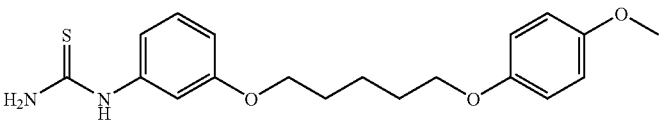
Compound No.	Structure	Name	Molecular Weight (M + 1)
137		{3-[5-(4-Phenoxy-phenoxy)-pentyloxy]-phenyl}-thiourea	423
138		{3-[5-(3-Phenoxy-phenoxy)-pentyloxy]-phenyl}-thiourea	423
139		{3-[5-(Biphenyl-3-yloxy)-pentyloxy]-phenyl}-thiourea	407
140		{3-[5-(Biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea	407
141		(7-Dibenzylamino-9H-fluoren-2-yl)-thiourea	436
142		(7-Benzylamino-9H-fluoren-2-yl)-thiourea	346
143		{3-[5-(4-Methoxy-phenoxy)-pentyloxy]-phenyl}-thiourea	361

TABLE 1-continued

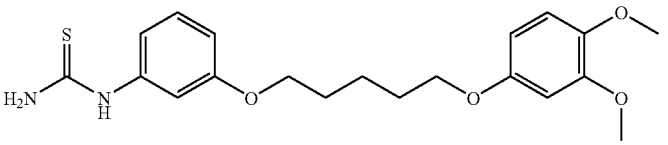
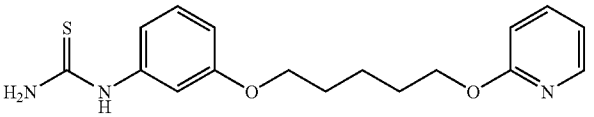
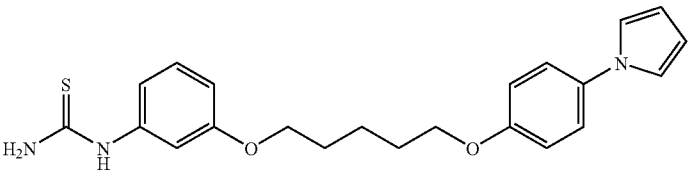
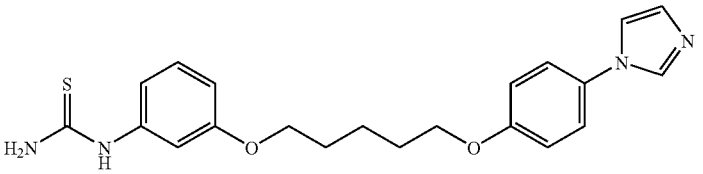
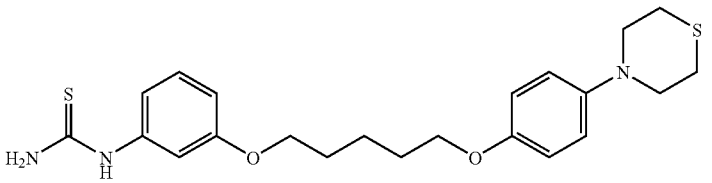
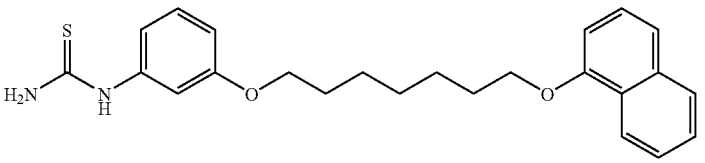
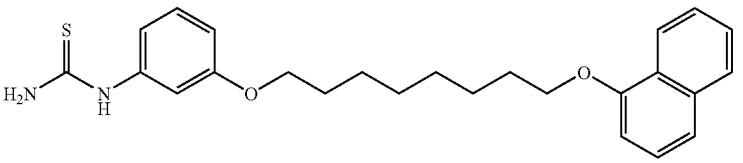
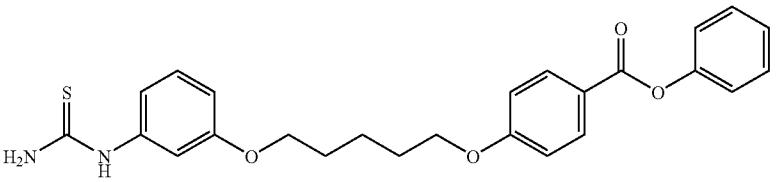
Compound No.	Structure	Name	Molecular Weight (M + 1)
144		{3-[5-(3,4-Dimethoxy-phenoxy)-pentyloxy]-phenyl}-thiourea	391
145		{3-[5-(Pyridin-2-yloxy)-pentyloxy]-phenyl}-thiourea	332
146		{3-[5-(4-Pyrrol-1-yl-phenoxy)-pentyloxy]-phenyl}-thiourea	396
147		{3-[5-(4-Imidazol-1-yl-phenoxy)-pentyloxy]-phenyl}-thiourea	397
148		{3-[5-(4-Thiomorpholin-4-yl-phenoxy)-pentyloxy]-phenyl}-thiourea	432
149		{3-[7-(Naphthalen-1-yloxy)-heptyloxy]-phenyl}-thiourea	409
150		{3-[8-(Naphthalen-1-yloxy)-octyloxy]-phenyl}-thiourea	423
151		4-[5-(3-Thioureido-phenoxy)-pentyloxy]-benzoic acid phenyl ester	451

TABLE 1-continued

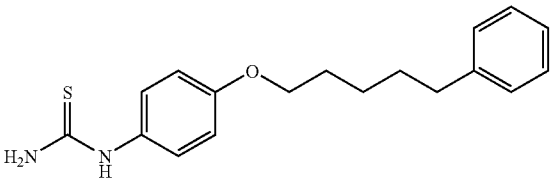
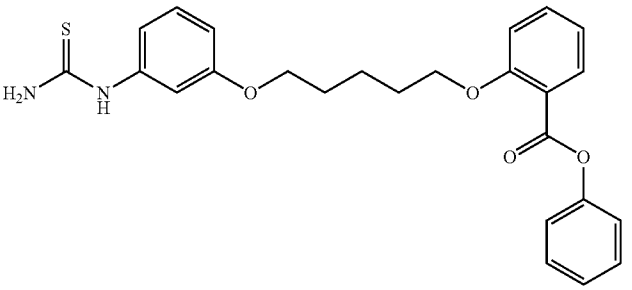
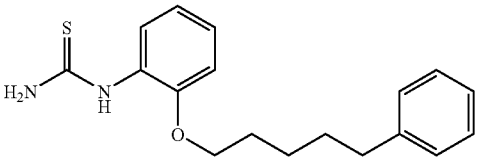
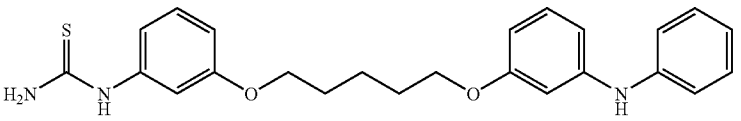
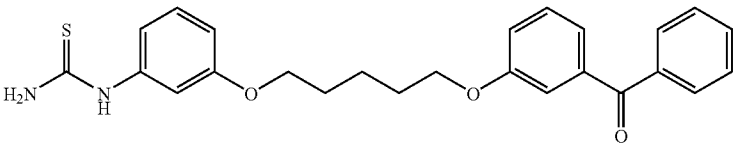
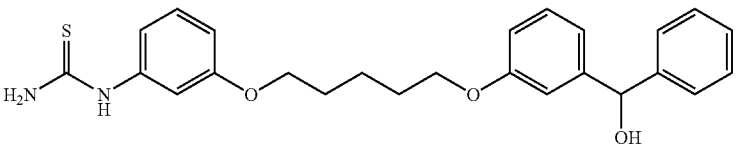
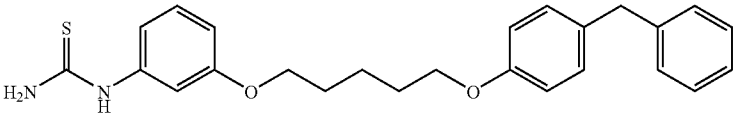
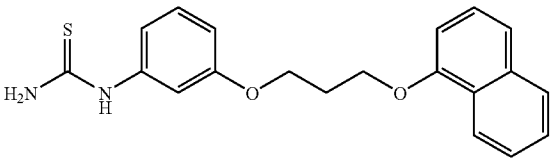
Compound No.	Structure	Name	Molecular Weight (M + 1)
152		[4-(5-Phenyl-pentyloxy)-phenyl]-thiourea	315
153		2-[5-(3-Thioureido-phenoxy)-pentyloxy]-benzoic acid phenyl ester	451
154		[2-(5-Phenyl-pentyloxy)-phenyl]-thiourea	315
155		{3-[5-(3-Phenylamino-phenoxy)-pentyloxy]-phenyl}-thiourea	422
156		{3-[5-(3-Benzoyl-phenoxy)-pentyloxy]-phenyl}-thiourea	435
157		(3-{5-[3-(Hydroxy-phenyl-methyl)-phenoxy]-pentyloxy}-phenyl)-thiourea	437
158		{3-[5-(4-Benzyl-phenoxy)-pentyloxy]-phenyl}-thiourea	421
159		{3-[3-(Naphthalen-1-yloxy)-propoxy]-phenyl}-thiourea	353

TABLE 1-continued

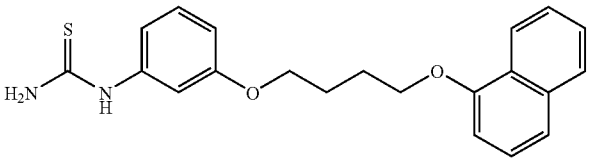
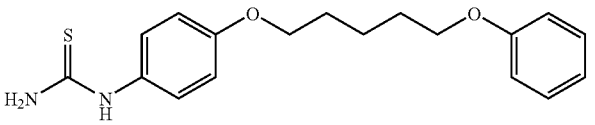
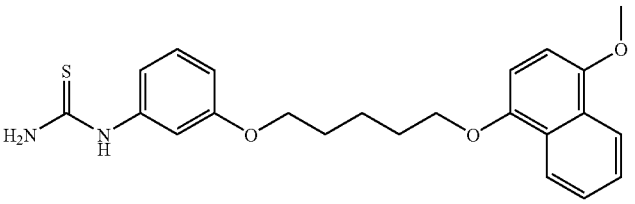
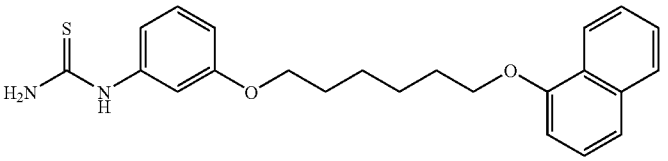
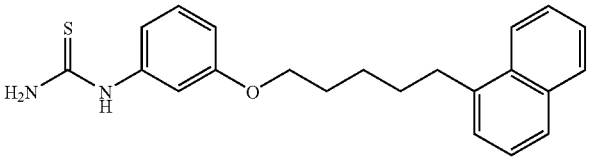
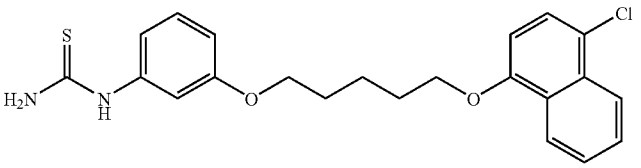
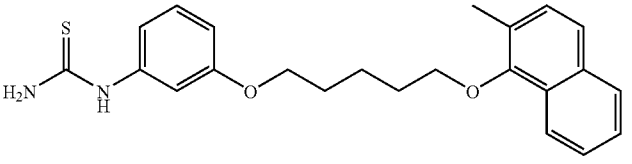
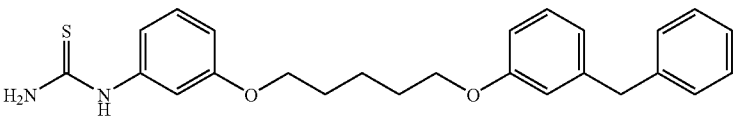
Compound No.	Structure	Name	Molecular Weight (M + 1)
160		{3-[4-(Naphthalen-1-yloxy)-butoxy]-phenyl}-thiourea	367
161		[4-(5-Phenoxy-pentyloxy)-phenyl]-thiourea	331
162		{3-[5-(4-Methoxy-naphthalen-1-yloxy)-pentyloxy]-phenyl}-thiourea	411
163		{3-[6-(Naphthalen-1-yloxy)-hexyloxy]-phenyl}-thiourea	395
164		[3-(5-Naphthalen-1-yl-pentyloxy)-phenyl]-thiourea	365
165		{3-[5-(4-Chloro-naphthalen-1-yloxy)-pentyloxy]-phenyl}-thiourea	415
166		{3-[5-(2-Methyl-naphthalen-1-yloxy)-pentyloxy]-phenyl}-thiourea	395
167		{3-[5-(3-Benzyl-phenoxy)-pentyloxy]-phenyl}-thiourea	421

TABLE 1-continued

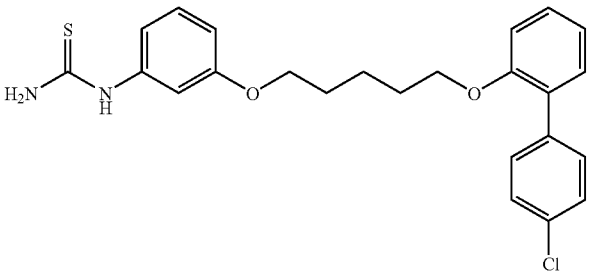
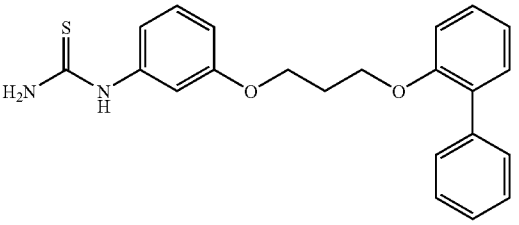
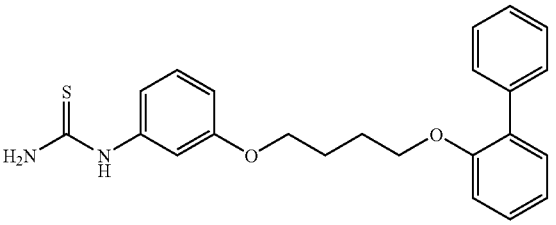
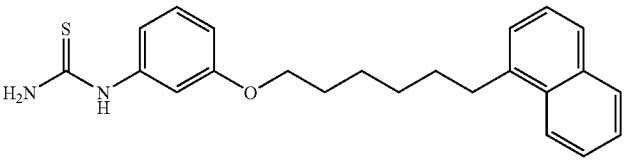
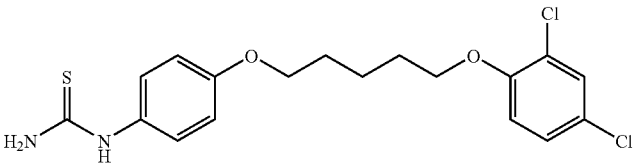
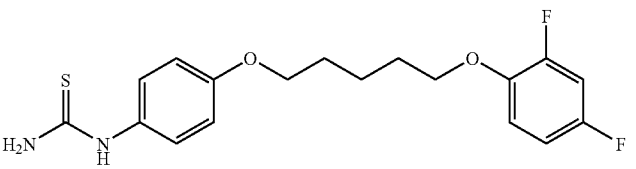
Compound No.	Structure	Name	Molecular Weight (M + 1)
168		{3-[5-(4'-Chloro-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea	441
169		{3-[3-(Biphenyl-2-yloxy)-propoxy]-phenyl}-thiourea	379
170		{3-[4-(Biphenyl-2-yloxy)-butoxy]-phenyl}-thiourea	393
171		[3-(6-Naphthalen-1-yl-hexyloxy)-phenyl]-thiourea	379
172		{4-[5-(2,4-Dichloro-phenoxy)-pentyloxy]-phenyl}-thiourea	340
173		{4-[5-(2,4-Difluoro-phenoxy)-pentyloxy]-phenyl}-thiourea	367

TABLE 1-continued

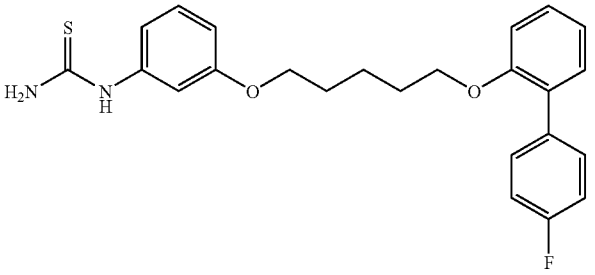
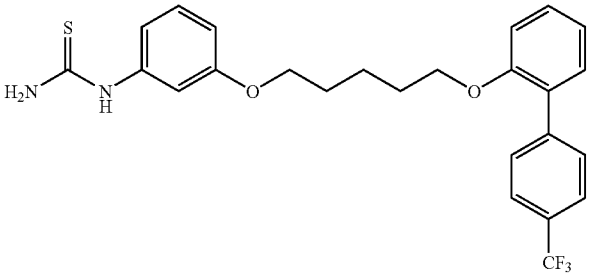
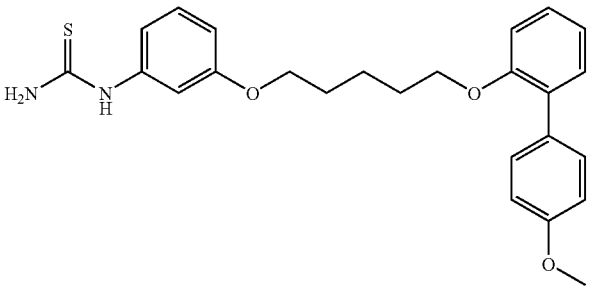
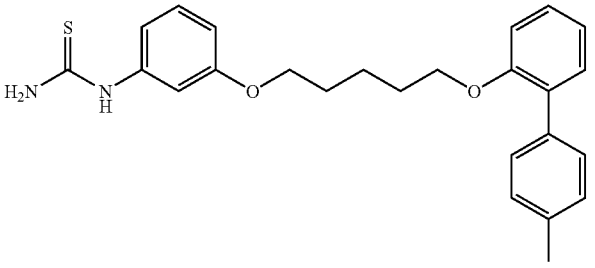
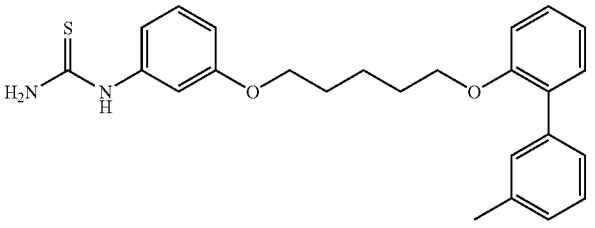
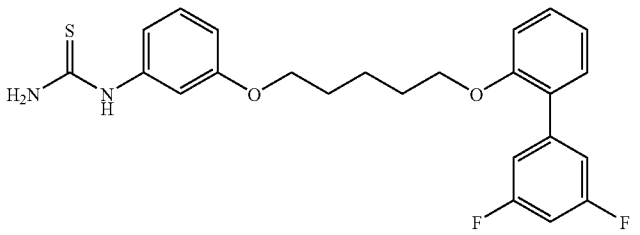
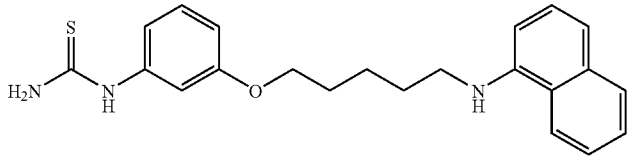
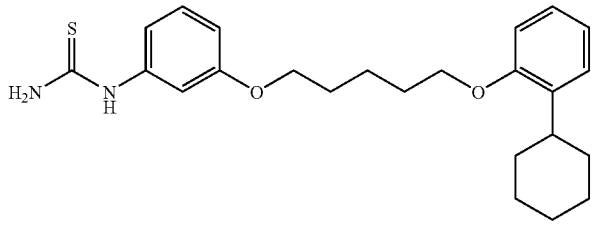
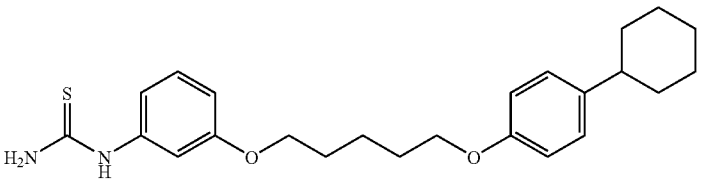
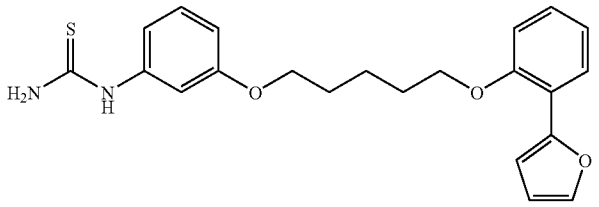
Compound No.	Structure	Name	Molecular Weight (M + 1)
174		{3-[5-(4'-Fluoro-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea	425
175		{3-[5-(4'-Trifluoromethyl-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea	475
176		{3-[5-(4'-Methoxy-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea	437
177		{3-[5-(4'-Methyl-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea	421
178		{3-[5-(3'-Methyl-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea	421

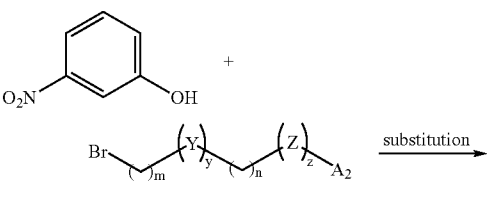
TABLE 1-continued

Compound No.	Structure	Name	Molecular Weight (M + 1)
179		{3-[5-(3',5'-Difluoro-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea	443
180		{3-[5-(Naphthalen-1-ylamino)-pentyloxy]-phenyl}-thiourea	380
181		{3-[5-(2-Cyclohexyl-phenoxy)-pentyloxy]-phenyl}-thiourea	413
182		{3-[5-(4-Cyclohexyl-phenoxy)-pentyloxy]-phenyl}-thiourea	413
183		{3-[5-(2-Furan-2-yl-phenoxy)-pentyloxy]-phenyl}-thiourea	397

[0022] The thiourea compounds described above can be prepared by methods well known in the art. Examples 1-183 below provide detailed descriptions of the preparation of compounds 1-183.

[0023] Scheme I shown below depicts a typical route for synthesizing certain compounds of the invention. Specifically, 3-nitrophenol can first react with a brominated aromatic compound via a substitution reaction to form an alkoxy-containing compound. The alkoxy-containing compound can then be reduced (e.g., by hydrogen or tin chloride) to convert the nitro group to an amino group. The compound thus formed can then be treated with thiocarbonyl diimidazole (TCDI) and a base (e.g., ammonia) to form a compound of the invention (e.g., compounds 1-14, 21-31, 82-140, and 143-183).

Scheme I



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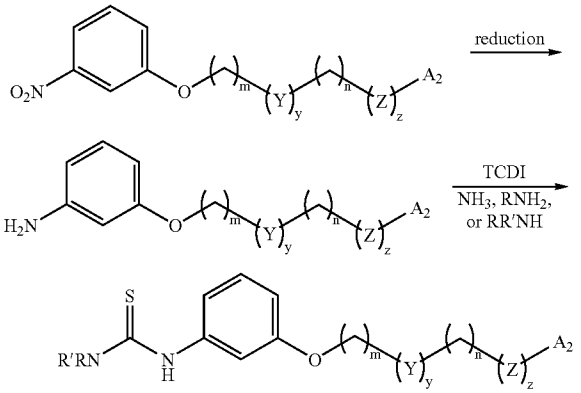
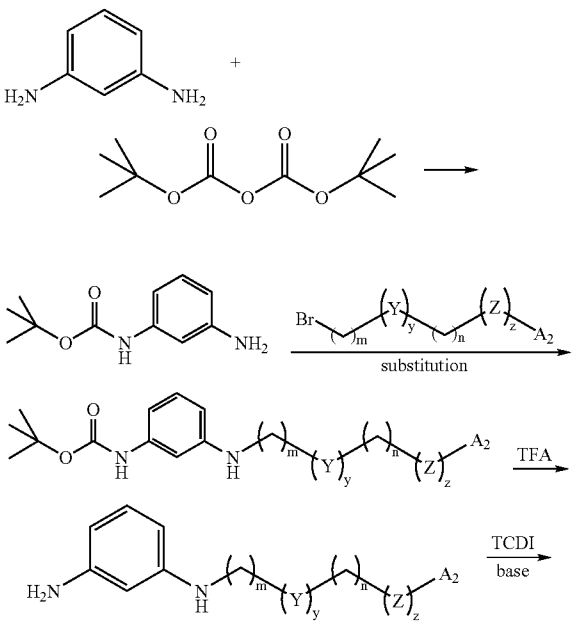


Compounds 1-14, 21-31, and 82-140:
m = 1-4, n = 1-4, y = 0 or 1, z = 0 or 1,
Y = $CH(CH_3)$ or $C(CH_3)_2$, Z = O,
R = H or alkyl, R′ = H or alkyl, or
R, R′, and N = heterocycloalkyl, and
A_2 = aryl or heteroaryl.

[0024] Certain other compounds of the invention can be prepared from benzene-1,3-diamine. For example, as shown in Scheme II below, one of the amino groups on benzene-1,3-diamine can be first protected with a tert-butyloxycarbonyl (BOC) protecting group. The other amino group on benzene-1,3-diamine can then react with a brominated aromatic compound. The compound thus formed can subsequently be deprotected and then treated with thiocarbonyl diimidazole and a base to form compounds of the invention such as compounds 15-20.

Scheme II



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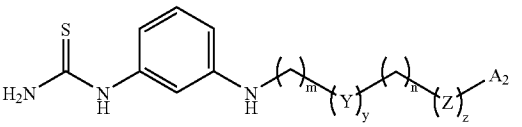
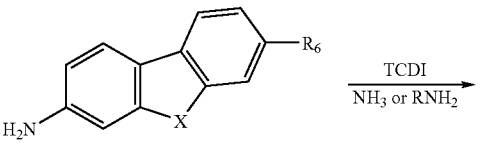
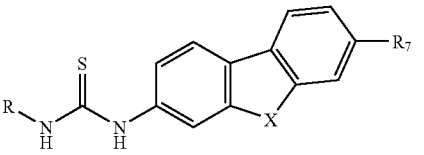


Compounds 15-20:
m = 1-4, n = 1-4, y = 0, z = 0,
and A_2 = aryl.

[0025] Certain other compounds of the invention can be prepared from a monoamino aromatic compound. For example, as shown in Scheme III below, a monoamino aromatic compound can react with thiocarbonyl diimidazole, followed by ammonia or a primary amine, to form a compound of the invention (e.g., compounds 32-38 and 50-71).

Scheme III

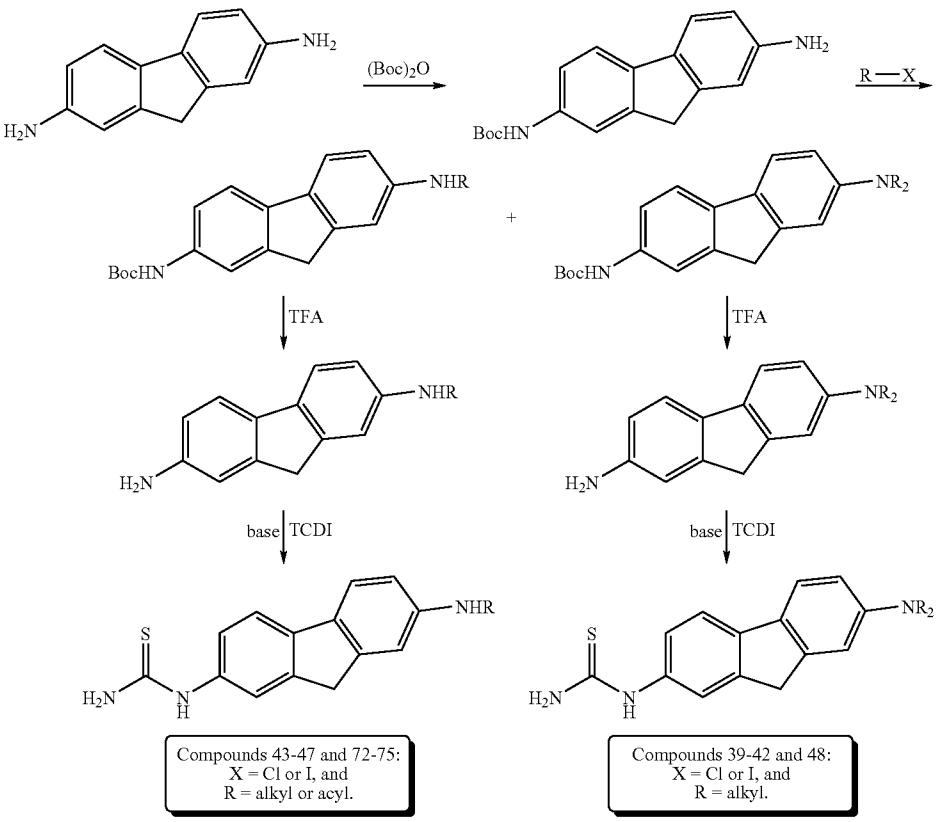




Compounds 32-38 and 50-71:
X = O, CH_2, C(O), N(Et), R_6 = H,
Br, or NH_2,
R_7 = H, Br, or $NHC(S)NH_2$, and
R = H, alkyl, aryl, or heteroaryl.

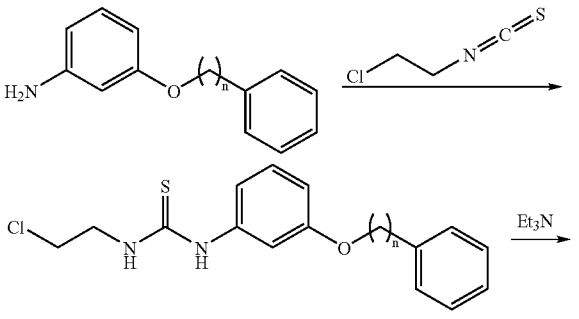
[0026] Certain other compounds of the invention can be prepared from a diamino aromatic compound. For example, as shown in Scheme IV below, one amino group on 9H-fluorene-2,7-diamine can first be protected with a BOC protecting group. The other amino group 9H-fluorene-2,7-diamine can then react with a halo-containing compound to form either a compound containing a secondary amino group or a compound containing a tertiary amino group. The compound thus formed can be deprotected (e.g., by reacting with trifluoroacetic acid) and then treated with thiocarbonyl diimidazole and a base to form a compound of the invention (e.g., compounds 39-48, 72-75, 141, and 142).

Scheme IV



[0027] Certain other compounds of the invention containing an imidazolidinyl ring can be prepared by the method shown in Scheme V. Specifically, an amino-containing compound can first react with 1-chloro-2-isothiocyanatoethane to form a chlorine-containing thiourea compound. The thiourea compound can then react with a base (e.g., triethylamine) to form a compound of the invention containing an imidazolidinyl ring (e.g., compounds 76 and 79). The compound thus formed can optionally react with a halo-containing compound to form another compound of the invention (e.g., compounds 77, 78, 80, and 81).

Scheme V



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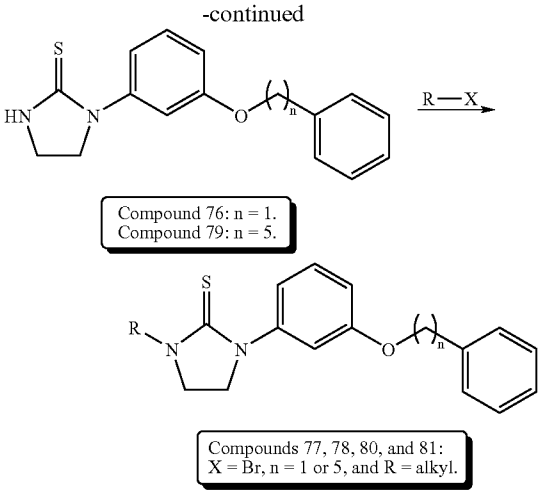


[0028] A thiourea compound synthesized above can be purified by a suitable method such as column chromatography, high-pressure liquid chromatography, or recrystallization.

[0029] Other thiourea compounds can be prepared using other suitable starting materials through the above synthetic routes and others known in the art. The methods described above may also additionally include steps, either before or

after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the thiourea compounds. In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing applicable thiourea compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and I., Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

[0030] The thiourea compounds mentioned herein may contain a non-aromatic double bond and one or more asymmetric centers. Thus, they can occur as racemates and racemic mixtures, single enantiomers, individual diastereomers, diastereomeric mixtures, and cis- or trans-isomeric forms. All such isomeric forms are contemplated.

[0031] Also within the scope of this invention is a pharmaceutical composition containing an effective amount of at least one thiourea compound described above and a pharmaceutical acceptable carrier. Further, this invention covers a method of administering an effective amount of one or more of the thiourea compounds to a patient having hepatitis C virus infection. "An effective amount" refers to the amount of an active thiourea compound that is required to confer a therapeutic effect on the treated subject. Effective closes will vary, as recognized by those skilled in the art, depending on the types of diseases treated, route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatment.

[0032] To practice the method of the present invention, a composition having one or more thiourea compounds can be administered parenterally, orally, nasally, rectally, topically, or buccally. The term "parenteral" as used herein refers to subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, or intracranial injection, as well as any suitable infusion technique.

[0033] A sterile injectable composition can be a solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water. Ringer's solution, and isotonic sodium chloride solution. In addition, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or diglycerides). Fatty acid, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long chain alcohol diluent or dispersant, carboxymethyl cellulose, or similar dispersing agents. Other commonly used surfactants such as Tweens or Spans or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purpose of formulation.

[0034] A composition for oral administration can be any orally acceptable dosage form including capsules, tablets, emulsions and aqueous suspensions, dispersions, and solutions. In the ease of tablets, commonly used carriers include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added.

[0035] A nasal aerosol or inhalation composition can be prepared according to techniques well known in the art of pharmaceutical, formulation, for example, such a composition can be prepared as a solution in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

[0036] A composition having one or more active thiourea compounds can also be administered in the form of suppositories for rectal administration.

[0037] The carrier in the pharmaceutical composition must be "acceptable" in the sense that it is compatible with the active ingredient of the composition (and preferably, capable of stabilizing the active ingredient) and not deleterious to the subject to be treated. One or more solubilizing agents can be utilized as pharmaceutical excipients for delivery of an active thiourea compound. Examples of other carriers include colloidal silicon oxide, magnesium stearate, cellulose, sodium lauryl sulfate, and D&C Yellow #10.

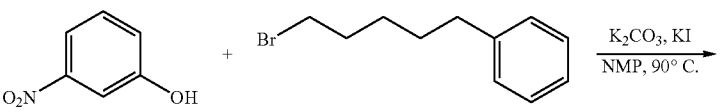
[0038] The thiourea compounds described above can be preliminarily screened for their efficacy in treating hepatitis C virus infection by an in vitro assay (See Examples 141 and 142 below) and then confirmed by animal experiments and clinic trials. Other methods will also be apparent to those of ordinary skill in the art.

[0039] The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety.

Example 1

Preparation, of Compound 1:
1-(3-(5-phenylpentyloxy)phenyl)thiourea

[0040]



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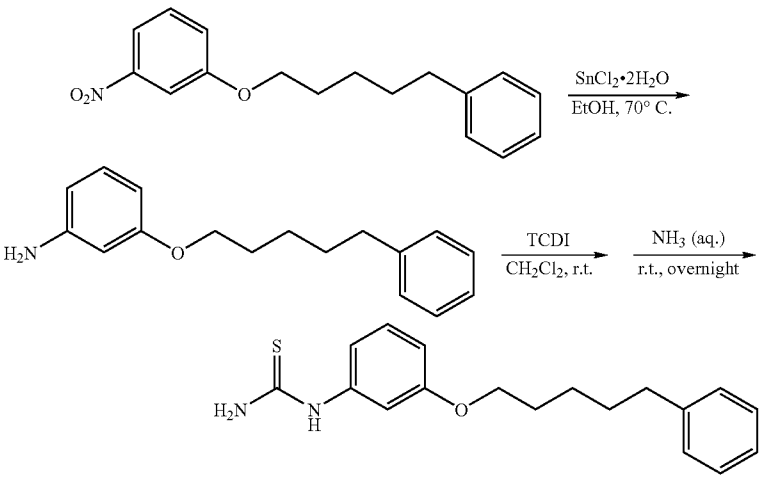


Compound 1

[0041] Potassium carbonate (1.2 g, 8.7 mmol) was added to a stirred suspension of 3-nitrophenol (0.8 g, 5.8 mmol), (5-bromo-pentyl)-benzene (1.32 g, 5.8 mmol), and potassium iodide (0.96 g, 5.8 mmol) in N-methylpyrolidinone (15 mL). The mixture was stirred at 90° C. for 4 hours. After the reaction mixture was cooled to the room temperature, it was quenched with water (30 mL) followed, by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give 1-nitro-3-(5-phenylpentoxy)benzene (1.4 g, 4.93 mmol, yield: 85%) as colorless oil.

[0042] Tin (II) chloride (5.57 g, 24.7 mmol) was added to a solution of 1-nitro-3-(5-phenylpentoxy)benzene (1.4 g, 4.93 mmol) in 35 mL ethanol. The reaction mixture was stirred at 70° C. for 2 hours. After the reaction mixture was cooled to room temperature, a saturated, sodium bicarbonate aqueous solution (50 mL) was added. The resultant, mixture was extracted with ethyl acetate (2×50 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give a crude product as a white solid. The crude product was purified by silica gel column chromatography eluting with ethyl acetate-n-hexane to give 3-(5-phenyl-pentyloxy)phenylamine (1.03 g, 4.04 mmol, yield: 82%) as a white solid.

[0043] A solution of 3-(5-phenyl-pentyloxy)-phenylamine (200 mg, 1.02 mmol) and thiocarbonyl diimidazole (TCDI, 1.90 mg, 1.06 mmol) in dichloromethane (10 mL) was stirred at room temperature for 2 hours. After a 25% aqueous ammonia solution (2.0 mL, excess) was added, the reaction mixture was stirred at room temperature overnight. The solvent was removed and then the residue thus obtained was purified by silica gel column chromatography eluting with methanol-dichloromethane to give [3-(5-phenyl-pentyloxy)phenyl]-thiourea (compound 1) (273 mg, 0.87 mmol, yield: 85%) as a white solid.

[0044] EI-MS (M+1): 315.

Example 2

Preparation of Compound 2:
1-(3-(4-phenylbutoxy)phenyl)thiourea

[0045] Compound 2 was prepared in a manner similar to that described in Example 1.

[0046] EI-MS (M+1): 301.

Example 3

Preparation of Compound 3:
1-(3-(3-phenylpropoxy)phenyl)thiourea

[0047] Compound 3 was prepared in a manner similar to that described in Example 1.

[0048] EI-MS (M+1): 287.

Example 4

Preparation of Compound 4:
1-(3-(6-phenylhexyloxy)phenyl)thiourea

[0049] Compound 4 was prepared in a manner similar to that described in Example 1.

[0050] EI-MS (M+1): 329.

Example 5

Preparation of Compound 5:
1-(3-(7-phenylheptyloxy)phenyl)thiourea

[0051] Compound 5 was prepared in a manner similar to that described in Example 1.

[0052] EI-MS (M+1): 343.

Example 6

Preparation of Compound 6:
1-(3-(8-phenyloctyloxy)phenyl)thiourea

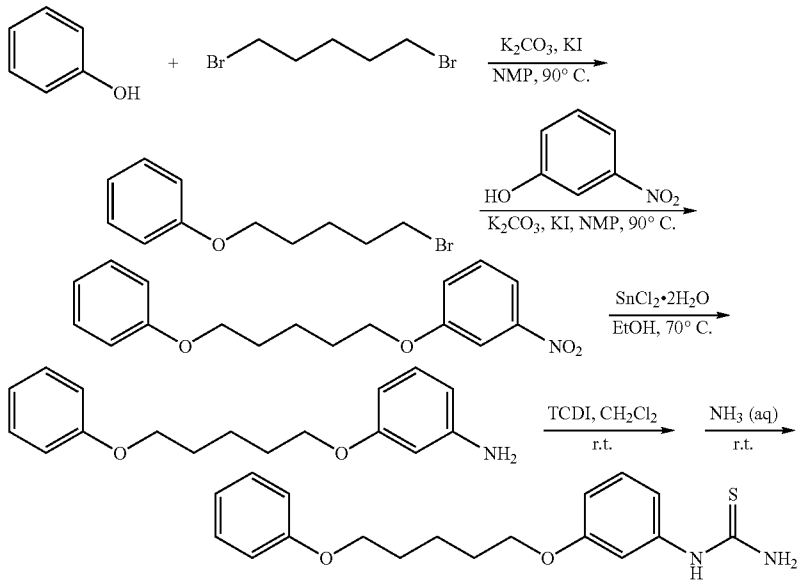
[0053] Compound 6 was prepared in a manner similar to that described in Example 1.

[0054] EI-MS (M+1): 357.

Example 7

Preparation, of Compound 7: 1-(3-(5-phenoxypentyloxy)phenyl)thiourea

[0055]



Compound 7

[0056] Potassium carbonate (10.35 g, 75.0 mmol) was added to a stirred suspension of phenol (4.7 g, 50.0 mmol), 1,5-dibromopentane (12.65 g, 55.0 mmol), and potassium iodide (0.83 g, 5.0 mmol) in N-methylpyrolidinone (100 mL). The reaction mixture was stirred at 90° C. for 4 hours. It was then quenched with water (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give (5-bromopentyloxy-)benzene (12.0 g, 49.38 mmol, yield: 98%) as yellow oil.

[0057] Potassium carbonate (10.35 g, 75.0 mmol) was added to a stirred suspension of (5-bromopentyloxy)benzene (12.0 g, 49.38 mmol), 3-nitrophenol (6.95 g, 50.0 mmol), and potassium iodide (0.83 g, 5.0 mmol) in N-methylpyrolidinone (100 mL). The reaction mixture was stirred at 90° C. for 4 hours. It was then quenched with water (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give 1-nitro-3-(5-phenoxypentoxy) benzene (11.89 g, 39.5 mmol, yield: 80%) as colorless oil.

[0058] Tin (II) chloride (19.78 g, 87.89 mmol) was added to a solution of 1-nitro-3-(5-phenoxypentoxy) benzene (5.29 g, 17.58 mmol) in 100 mL ethanol. The reaction mixture was stirred at 70° C. for 2 hours. After the reaction mixture was cooled to room temperature, a saturated sodium bicarbonate aqueous solution (50 mL) was added. The solution was extracted with ethyl acetate (3×50 mL), and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give a crude product as a white solid. The crude product was purified by silica gel column chromatography eluting with ethyl acetate-n-hexane to give 3-(5-phenoxy-pentyloxy)phenylamine (4.67 g, 17.22 mmol, yield: 98%) as a light yellow solid.

[0059] A solution of 3-(5-phenoxy-pentyloxy)phenylamine (200 mg, 0.74 mmol) and thiocarbonyl diimidazole (TCDI, 158 mg, 0.89 mmol) in dichloromethane (3 mL) was stirred at room temperature for 2 hours. After a 25% ammonia aqueous solution (2 mL, excess) was added, the reaction mixture was stirred at room temperature overnight. The solvent was then removed and the residue thus obtained was purified by silica gel column chromatography eluting with methanol-dichloromethane to give [3-(5-phenoxy-pentyloxy)-phenyl]-thiourea (compound 7) (126 mg, 0.38 mmol yield: 52%) as a white solid.

[0060] EI-MS (M+1): 331.

Example 8

Preparation of Compound 8: ethyl 4-(5-(3-thioureidophenoxy)pentyloxy)benzoate

[0061] Compound 8 was prepared in a manner similar to that described in Example 7,

[0062] EI-MS (M+1): 403.

Example 9

Preparation of Compound 9: 1-(3-(5-(4-bromophenoxy)pentyloxy)phenyl)thiourea

[0063] Compound 9 was prepared in a manner similar to that described in Example 7.

[0064] EI-MS (M+1): 409, 411.

Example 10

Preparation of Compound 10: 1-(3-(3-methyl-5-phenoxypentyloxy)phenyl)thiourea

[0065] Compound 10 was prepared in a manner similar to that, described in Example 7.

[0066] EI-MS (M+1): 345.

Example 11

Preparation of Compound 11: 1-(3-(3,3-dimethyl-5-phenoxypentyloxy)phenyl)thiourea

[0067] Compound 11 was prepared in a manner similar to that described in Example 7.

[0068] EI-MS (M+1): 359.

Example 12

Preparation of Compound 12: 1-(3-(5-(biphenyl-4-yloxy)pentyloxy)phenyl)-thiourea

[0069] Compound 12 was prepared in a manner similar to that described in Example 7.

[0070] EI-MS (M+1): 407.

Example 13

Preparation of Compound 13: 1-(3-(5-(biphenyl-4-yloxy)-3-methylpentyloxy)phenyl)thiourea

[0071] Compound 13 was prepared in a manner similar to that described in Example 7.

[0072] EI-MS (M+1): 421.

Example 14

Preparation of Compound 14: 1-(3-(5-(biphenyl-4-yloxy)-3,3-dimethylpentyloxy)phenyl)thiourea

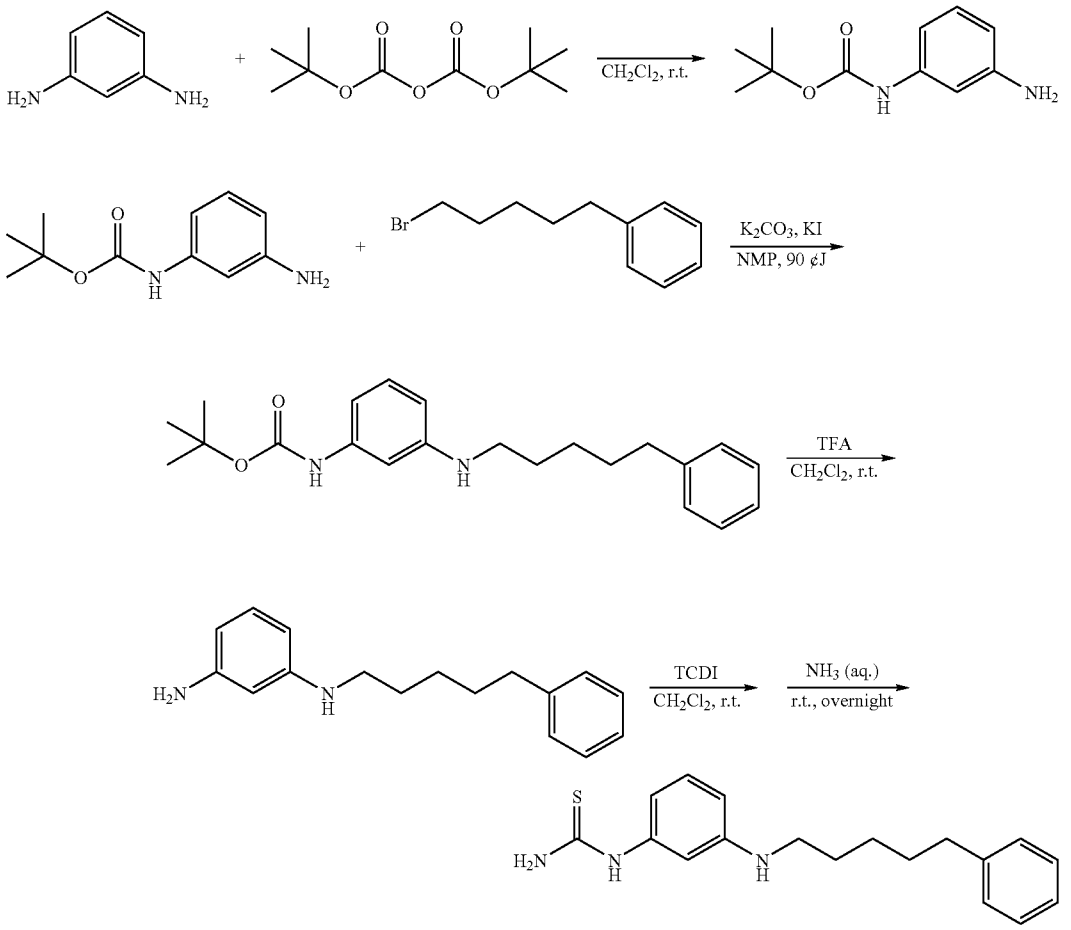
[0073] Compound 14 was prepared in a manner similar to that described in Example 7.

[0074] EI-MS (M+1): 435.

Example 15

Preparation of Compound 15: 1-(3-(5-phenylpentylamino)phenyl)thiourea

[0075]



Compound 15

[0076] $(BOC)_2O$ (10.1 g, 46.3 mmol) was added to a solution of benzene-1,3-diamine (5.0 g, 46.3 mmol) in dichloromethane (80 mL). The reaction mixture was stirred at room temperature for 60 hours. The reaction mixture was quenched with, water (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give (3-aminophenyl)-carbamic acid tert-butyl ester (4.34 g, 20.8 mmol, yield: 45%) as a white solid.

[0077] Potassium carbonate (0.6 g, 4.35 mmol) was added to a stirred suspension of (3-amino-phenyl)-carbamic acid tert-butyl ester (0.6 g, 2.9 mmol), (5-bromo-pentyl)benzene (0.66 g, 2.9 mmol), and potassium iodide (0.48 g, 2.9 mmol) in N-methylpyrolidinone (14 mL). The reaction mixture was stirred at 90° C. for 4 hours. It was quenched with water (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give [3-(5-phenyl-pentylamino)-phenyl]-carbamic acid tert-butyl ester (802 mg, 2.26 mmol, yield: 78%) as yellow oil.

[0078] Trifluoroacetic acid (TFA, 2.0 mL, 26.3 mmol) was added to a solution of [3-(5-phenyl-pentylamino)-phenyl]-carbamic acid tert-butyl ester (802 mg, 2.26 mmol) in 10 mL dichloromethane. The reaction mixture was stirred at room temperature for 1 hour. It was then quenched with water (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give N-(5-phenyl-pentyl)-benzene-1,3-diamine (529 mg, 2.08 mmol, yield: 92%) as light yellow solid.

[0079] A solution of N-(5-phenyl-pentyl)-benzene-1,3-diamine (89 mg, 0.4 mmol) and thiocarbonyl diimidazole (TCDI, 74 mg, 0.42 mmol) in dichloromethane (4 mL) was stirred at room temperature for 2 hours. After a 25% aqueous ammonia solution (2.0 mL, excess) was added, the reaction mixture was stirred at room temperature overnight. The solvent was then removed and the residue thus obtained was purified by silica gel column chromatography eluting with methanol-dichloromethane to give [3-(5-phenyl-pentylamino)-phenyl]-thiourea (compound 17) (113 mg, 0.36 mmol, yield: 90%) as a white solid.

[0080] EI-MS (M+1): 314.

Example 16

Preparation of Compound 16:
1-(3-(4-phenylbutylamino)phenyl)thiourea

[0081] Compound 16 was prepared in a manner similar to that described in Example 15.

[0082] EI-MS (M+1): 300.

Example 17

Preparation of Compound 17:
1-(3-(3-phenylpropylamino)phenyl)thiourea

[0083] Compound 17 was prepared in a manner similar to that described in Example 15.

[0084] EI-MS (M+1): 286.

Example 18

Preparation of Compound 18:
1-(3-(6-phenylhexylamino)phenyl)thiourea

[0085] Compound 18 was prepared in a manner similar to that described in Example 15.

[0086] EI-MS (M+1): 328.

Example 19

Preparation of Compound 19:
1-(3-(7-phenylheptylamino)phenyl)thiourea

[0087] Compound 19 was prepared in a manner similar to that described in Example 15.

[0088] EI-MS (M+1): 342.

Example 20

Preparation of Compound 20:
1-(3-(8-phenyloctylamino)phenyl)thiourea

[0089] Compound 20 was prepared in a manner similar to that described in Example 15.

[0090] EI-MS (M+1): 356.

Example 21

Preparation of Compound 21:
1-methyl-3-(3-(5-phenylpentyloxy)phenyl)thiourea

[0091] Compound 21 was prepared in a manner similar to that described in Example 1.

[0092] EI-MS (M+1): 329.

Example 22

Preparation of Compound 22:
1-ethyl-3-(3-(5-phenylpentyloxy)phenyl)thiourea

[0093] Compound 22 was prepared in a manner similar to that described in Example 1.

[0094] EI-MS (M+1): 343.

Example 23

Preparation of Compound 23:
1-(3-(5-phenylpentyloxy)phenyl)-3-propylthiourea

[0095] Compound 23 was prepared in a manner similar to that described in Example 1.

[0096] EI-MS (M+1): 357.

Example 24

Preparation of Compound 24:
1-butyl-3-(3-(5-phenylpentyloxy)phenyl)thiourea

[0097] Compound 24 was prepared in a manner similar to that described in Example 1.

[0098] EI-MS (M+1): 371.

Example 25

Preparation of Compound 25:
1-pentyl-3-(3-(5-phenylpentyloxy)phenyl)thiourea

[0099] Compound 25 was prepared in a manner similar to that described in Example 1.

[0100] EI-MS (M+1): 385.

Example 26

Preparation of Compound 26:
1-hexyl-3-(3-(5-phenylpentyloxy)phenyl)thiourea

[0101] Compound 26 was prepared in a manner similar to that described in Example 1.

[0102] EI-MS (M+1): 399.

Example 27

Preparation of Compound 27:
1-heptyl-3-(3-(5-phenylpentyloxy)phenyl)thiourea

[0103] Compound 27 was prepared in a manner similar to that described in Example 1.

[0104] EI-MS (M+1): 413.

Example 28

Preparation of Compound 28:
1-octyl-3-(3-(5-phenylpentyloxy)phenyl)thiourea

[0105] Compound 28 was prepared in a manner similar to that described in Example 1.

[0106] EI-MS (M+1): 427.

Example 29

Preparation of Compound 29:
1-phenethyl-3-(3-(5-phenylpentyloxy)phenyl)thiourea

[0107] Compound 29 was prepared in a manner similar to that described in Example 1,

[0108] EI-MS (M+1): 419.

Example 30

Preparation of Compound 30: 1-(3-(5-phenylpentyloxy)phenyl)-3-(3-phenylpropyl)thiourea

[0109] Compound 30 was prepared in a manner similar to that described in Example 1.

[0110] EI-MS (M+1): 433.

Example 31

Preparation of Compound 31: 1-(4-phenylbutyl)-3-(3-(5-phenylpentyloxy)phenyl)thiourea

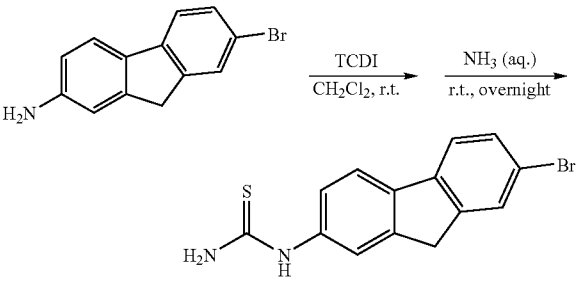
[0111] Compound 31 was prepared in a manner similar to that described in Example 1.

[0112] EI-MS (M+1): 447.

Example 32

Preparation of Compound 32:
1-(7-bromo-9H-fluoren-2-yl)thiourea

[0113]



Compound 32

[0114] A solution of 7-bromo-9H-fluoren-2-ylamine (0.3 g, 1.0 mmol) and thiocarbonyl diimidazole (TCDI, 0.2 g, 1.2 mmol) in dichloromethane (10 mL) was stirred at room temperature for 2 hours. After a 25% aqueous ammonia solution (2.0 mL, excess) was added, the reaction mixture was stirred at room temperature overnight. The solvent was then removed and the residue thus obtained was purified by silica gel column chromatography dining with methanol-dichloromethane to give (7-bromo-9H-fluoren-2-yl)-thiourea (compound 32) (297 rag, 0.93 mmol, yield 93%) as a white solid.

[0115] EI-MS (M+1): 320.

Example 33

Preparation of Compound 33:
1-(9-ethyl-9H-carbazol-3-yl)thiourea

[0116] Compound 33 was prepared in a manner similar to that described in Example 32.

[0117] EI-MS (M+1): 270.

Example 34

Preparation of Compound 34:
1-(9-oxo-9H-fluoren-2-yl)thiourea

[0118] Compound 34 was prepared in a manner similar to that described in Example 32.

[0119] EI-MS (M+1): 255.

Example 35

Preparation of Compound 35:
1-(7-bromo-9-oxo-9H-fluoren-2-yl)thiourea

[0120] Compound 35 was prepared in a manner similar to that described in Example 32.

[0121] EI-MS (M+1): 332, 334.

Example 36

Preparation of Compound 36:
1-(9-oxo-9H-fluoren-3-yl)thiourea

[0122] Compound 36 was prepared in a manner similar to that described in Example 32.

[0123] EI-MS (M+1): 255.

Example 37

Preparation of Compound 37:
1-(9H-fluoren-2-yl)thiourea

[0124] Compound 37 was prepared in a manner similar to that described in Example 32.

[0125] EI-MS (M+1): 241.

Example 38

Preparation of Compound 38:
1-(2-methoxydibenzo[b,d]furan-3-yl)thiourea

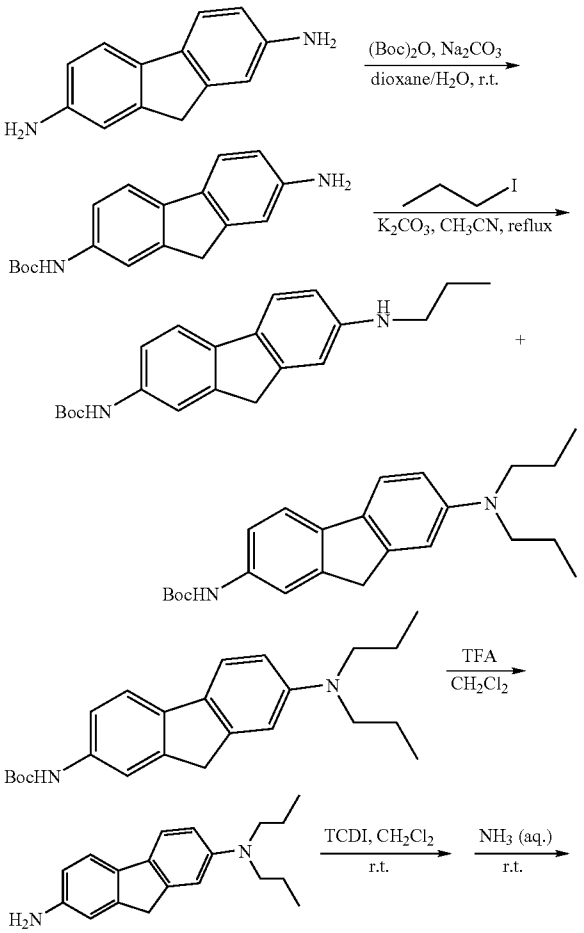
[0126] Compound 38 was prepared in a manner similar to that described in Example 32.

[0127] EI-MS (M+1): 273.

Example 39

Preparation of Compound 39:
1-(7-(dipropylamino)-9H-fluoren-2-yl)thiourea

[0128]



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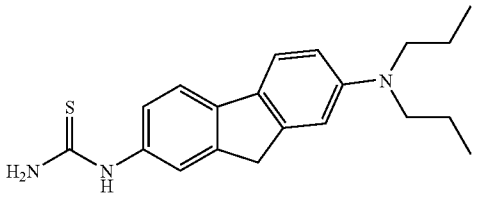


Compound 39

[0129] Sodium carbonate (1.06 g, 10.0 mmol) was added to a solution of 9H-fluorene-2,7-diamine (1.0 g, 5.0 mmol) and $(BOC)_2O$ (1.4 mL, 7.5 mmol) in 1,4-dioxane (20 mL) and H_2O (10 mL). The reaction mixture was stirred at room temperature overnight. It was then quenched with saturated ammonium chloride aqueous solution (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give (7-amino-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (640 mg, 2.16 mmol, yield: 43%) as a yellow solid.

[0130] Potassium carbonate (120 mg, 0.87 mmol) was added to a stirred suspension of (7-amino-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (200 mg, 0.67 mmol), n-propyl iodide (114 mg, 0.67 mmol) in acetonitrile (20 mL). The reaction mixture was stirred at refluxing temperature for 4 hours. It was then quenched with a saturated ammonium chloride aqueous solution (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give ((7-propylamino-9H-fluoren-2-yl)-carbamic acid, tert-butyl ester (91 mg, 0.27 mmol, yield: 40%) as a light brown solid and (7-dipropylamino-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (114 mg, 0.30 mmol, yield: 45%) as a light brown solid.

[0131] Trifluoroacetic acid (TFA, 2.0 mL, 26.3 mmol) was added to a solution of (7-dipropylamino-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (270 mg, 0.71 mmol) in 20 mL dichloromethane. The reaction mixture was stirred at room temperature for 1 hour. It was then quenched with water (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give N,N-dipropyl-9H-fluorene-2,7-diamine (220 mg, 0.78 mmol, yield: 91%) as a light brown solid.

[0132] A solution of N,N-dipropyl-9H-fluorene-2,7-diamine (220 mg, 0.78 mmol) and thiocarbonyl diimidazole (TCDI, 163 mg, 0.92 mmol) in dichloromethane (5 mL) was stirred at room temperature for 2 hours. After a 25% ammonia aqueous solution (2.0 mL, excess) was added, the reaction mixture was stirred at room temperature overnight. The solvent was then removed and the residue thus obtained was purified by silica gel column chromatography eluting with methanol-dichloromethane to give (7-dipropylamino-9H-fluoren-2-yl)-thiourea (compound 39) (231 mg, 0.69 mmol, yield: 88%) as a white solid.

[0133] EI-MS (M+1): 340.

Example 40

Preparation of Compound 40:
1-(7-(diethylamino)-9H-fluoren-2-yl)thiourea

[0134] Compound 40 was prepared in a manner similar to that described in Example 39.

[0135] EI-MS (M+1): 312.

Example 41

Preparation of Compound 41:
1-(7-(dimethylamino)-9H-fluoren-2-yl)thiourea

[0136] Compound 41 was prepared in a manner similar to that described in Example 39.

[0137] EI-MS (M+1): 284.

Example 42

Preparation of Compound 42:
1-(7-(dibutylamino)-9H-fluoren-2-yl)thiourea

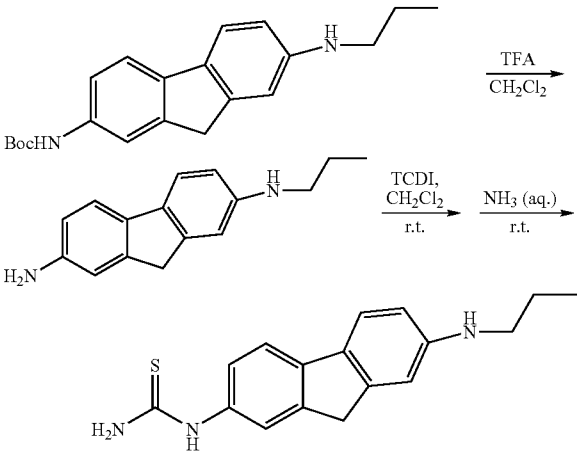
[0138] Compound 42 was prepared in a manner similar to that described in Example 39.

[0139] EI-MS (M+1): 368.

Example 43

Preparation, of Compound 43:
1-(7-(propylamino)-9H-fluoren-2-yl)thiourea

[0140]



Compound 43

[0141] Trifluoroacetic acid (TFA, 2.0 mL, 26.3 mmol) was added, to a solution of (7-propylamine-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (91 mg, 0.27 mmol) prepared in Example 39 in 10 mL dichloromethane. The reaction mixture was stirred at room temperature for 1 hour. It was then quenched with water (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give N^2-propyl-9H-fluorene-2,7-diamine (60 mg, 0.25 mmol, yield: 92%) as a light brown solid.

[0142] A solution of N^2-propyl-9H-fluorene-2,7-diamine (60 mg, 0.25 mmol) and thiocarbonyl diimidazole (53 mg, 0.30 mmol) in dichloromethane (5 mL) was stirred at room temperature for 2 hours. After a 25% ammonia aqueous solution (2.0 mL, excess) was added, the reaction mixture was stirred at room temperature overnight. The solvent was then removed and the residue was purified by silica gel column chromatography eluting with methanol-dichloromethane to give (7-propylamino-9H-fluoren-2-yl)thiourea (compound 43) (68 mg, 0.23 mmol, yield: 90%) as a white solid.

[0143] EI-MS (M+1): 298.

Example 44

Preparation of Compound 44:
1-(7-(ethylamino)-9H-fluoren-2-yl)thiourea

[0144] Compound 44 was prepared in a manner similar to that described in Example 43.

[0145] EI-MS (M+1): 284.

Example 43

Preparation of Compound 45:
1-(7-(methylamino)-9H-fluoren-2-yl)thiourea

[0146] Compound 45 was prepared in a manner similar to that, described in Example 43,

[0147] EI-MS (M+1): 270.

Example 46

Preparation of Compound 46:
1-(7-(butylamino)-9H-fluoren-2-yl)thiourea

[0148] Compound 46 was prepared in a manner similar to that described in Example 43.

[0149] EI-MS (M+1): 312.

Example 47

Preparation of Compound 47: 1-(7-(3-phenylpropylamino)-9H-fluoren-2-yl)thiourea

[0150] Compound 47 was prepared in a manner similar to that described in Example 43.

[0151] EI-MS (M+1): 374.

Example 48

Preparation of Compound 48: 1-(7-(bis(3-phenylpropyl)amino)-9H-fluoren-2-yl)thiourea

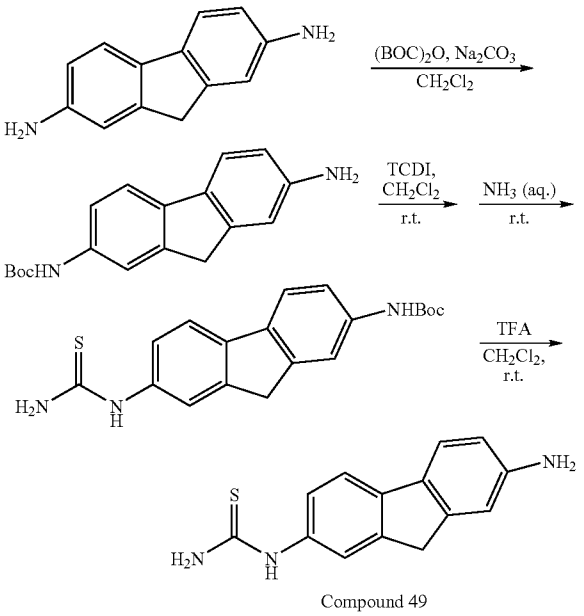
[0152] Compound 48 was prepared in a manner similar to that described in Example 43.

[0153] EI-MS (M+1): 492.

Example 49

Preparation of Compound 49:
1-(7-amino-9H-fluoren-2-yl)thiourea

[0154]



Compound 49

[0155] Sodium carbonate (1.06 g, 10.0 mmol) was added to a solution of 9H-fluorene-2,7-diamine (1.0 g, 5.0 mmol) and $(BOC)_2O$ (1.4 mL, 7.5 mmol) in dioxane (20 mL) and H_2O (10 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. It was then quenched with water (30 mL) followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give (7-amino-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (640 mg, 2.16 mmol, yield: 43%) as a yellow solid.

[0156] A solution of (7-amino-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (1.16 mg, 0.39 mmol) and thiocarbonyl diimidazole (81 mg, 0.45 mmol) in dichloromethane (5 mL) was stirred at room temperature for 2 hours. Alter a 25% ammonia aqueous solution (2.0 mL, excess) was added, the reaction mixture was stirred at room temperature overnight. The solvent was then removed and the residue thus obtained was purified by silica gel column chromatography eluting with methanol-dichloromethane to give (7-thioureido-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (118 mg, 0.33 mmol, yield: 85%) as a white solid.

[0157] Trifluoroacetic acid (TFA, 2.0 mL, 26.3 mmol) was added to a solution of (7-thioureido-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (75 mg, 0.21 mmol) in 2 ml, dichloromethane. The reaction mixture was stirred at room temperature for 1 hour. It was then quenched with water (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give (7-amino-9H-fluoren-2-yl)-thiourea (compound 49) (51 mg, 0.20 mmol, yield: 95%) as a white solid.

[0158] EI-MS (M+1): 256.

Example 50

Preparation of Compound 50:
1,1'-(9H-fluorene-2,7-diyl)dithiourea

[0159] Compound 50 was prepared in a manner similar to that described in Example 32.

[0160] EI-MS (M+1): 315.

Example 51

Preparation of Compound 51:
1-(7-bromo-9H-fluoren-2-yl)-3-methylthiourea

[0161] Compound 51 was prepared in a manner similar to that described in Example 32.

[0162] EI-MS (M+1): 333, 335.

Example 52

Preparation of Compound 52:
1-(7-bromo-9H-fluoren-2-yl)-3-ethylthiourea

[0163] Compound 52 was prepared in a manner similar to that described in Example 32.

[0164] EI-MS (M+1): 347, 349.

Example 53

Preparation of Compound 53:
1-(7-bromo-9H-fluoren-2-yl)-3-propylthiourea

[0165] Compound 53 was prepared in a manner similar to that described in Example 32.

[0166] EI-MS (M+1): 361, 363.

Example 54

Preparation of Compound 54:
1-(7-bromo-9H-fluoren-2-yl)-3-butylthiourea

[0167] Compound 54 was prepared in a manner similar to that described in Example 32.

[0168] EI-MS (M+1): 375, 377.

Example 55

Preparation of Compound 55:
1-(7-bromo-9H-fluoren-2-yl)-3-pentylthiourea

[0169] Compound 55 was prepared in a manner similar to that described in Example 32.

[0170] EI-MS (M+1): 389, 391.

Example 56

Preparation of Compound 56:
1-(7-bromo-9H-fluoren-2-yl)-3-hexylthiourea

[0171] Compound 56 was prepared in a manner similar to that described in Example 32.

[0172] EI-MS (M+1): 403, 405.

Example 57

Preparation of Compound 57: 1-(7-bromo-9H-fluoren-2-yl)-3-heptylthiourea

[0173] Compound 57 was prepared in a manner similar to that described in Example 32,

[0174] EI-MS (M+1): 417, 419.

Example 58

Preparation of Compound 58: 1-(7-bromo-9H-fluoren-2-yl)-3-octylthiourea

[0175] Compound 58 was prepared in a manner similar to that described in Example 32.

[0176] EI-MS (M+1): 431, 433.

Example 59

Preparation of Compound 59: 1-(7-bromo-9H-fluoren-2-yl)-3-(3-methoxypropyl)thiourea

[0177] Compound 59 was prepared in a manner similar to that described in Example 32.

[0178] EI-MS (M+1): 391, 393.

Example 60

Preparation of Compound 60: 1-(7-bromo-9H-fluoren-2-yl)-3-isobutylthiourea

[0179] Compound 60 was prepared in a manner similar to that described in Example 32.

[0180] EI-MS (M+1): 375, 377.

Example 61

Preparation of Compound 61: 1-(7-bromo-9H-fluoren-2-yl)-3-(2-(dimethylamino)ethyl)thiourea

[0181] Compound 61 was prepared in a manner similar to that described in Example 32.

[0182] EI-MS (M+1): 390, 392.

Example 62

Preparation of Compound 62: 1-(7-bromo-9H-fluoren-2-yl)-3-(2-(diethylamino)ethyl)thiourea

[0183] Compound 62 was prepared in a manner similar to that described in Example 32.

[0184] EI-MS (M+1): 418, 420.

Example 63

Preparation of Compound 63: 1-(7-bromo-9H-fluoren-2-yl)-3-(3-(dimethylamino)propyl)thiourea

[0185] Compound 63 was prepared in a manner similar to that described in Example 32.

[0186] EI-MS (M+1): 404, 406.

Example 64

Preparation of Compound 64: 1-(7-bromo-9H-fluoren-2-yl)-3-phenethylthiourea

[0187] Compound 64 was prepared in a manner similar to that described in Example 32.

[0188] EI-MS (M+1): 423, 425.

Example 65

Preparation of Compound 65: 1-(7-bromo-9H-fluoren-2-yl)-3-(3-phenylpropyl)thiourea

[0189] Compound 65 was prepared in a manner similar to that described in Example 32.

[0190] EI-MS (M+1): 437, 439.

Example 66

Preparation of Compound 66: 1-(7-bromo-9H-fluoren-2-yl)-3-(4-phenylbutyl)thiourea

[0191] Compound 66 was prepared in a manner similar to that described in Example 32,

[0192] EI-MS (M+1): 451, 453.

Example 67

Preparation of Compound 67: 1-benzyl-3-(7-bromo-9H-fluoren-2-yl)thiourea

[0193] Compound 67 was prepared in a manner similar to that described in Example 32.

[0194] EI-MS (M+1): 430, 432.

Example 68

Preparation of Compound 68: 1-(7-bromo-9H-fluoren-2-yl)-3-phenylthiourea

[0195] Compound 68 was prepared in a manner similar to that described in Example 32.

[0196] EI-MS (M+1): 394, 396.

Example 69

Preparation of Compound 69: 1-(7-bromo-9H-fluoren-2-yl)-3-(pyridin-3-yl)thiourea

[0197] Compound 69 was prepared in a manner similar to that described in Example 32.

[0198] EI-MS (M+1): 395, 397.

Example 70

Preparation of Compound 70: 1-(7-bromo-9H-fluoren-2-yl)-3-(4-morpholinophenyl)thiourea

[0199] Compound 70 was prepared in a manner similar to that described in Example 32.

[0200] EI-MS (M+1): 480, 482.

Example 71

Preparation of Compound 71: 1-(7-bromo-9H-fluoren-2-yl)-3-(naphthalen-1-yl)thiourea

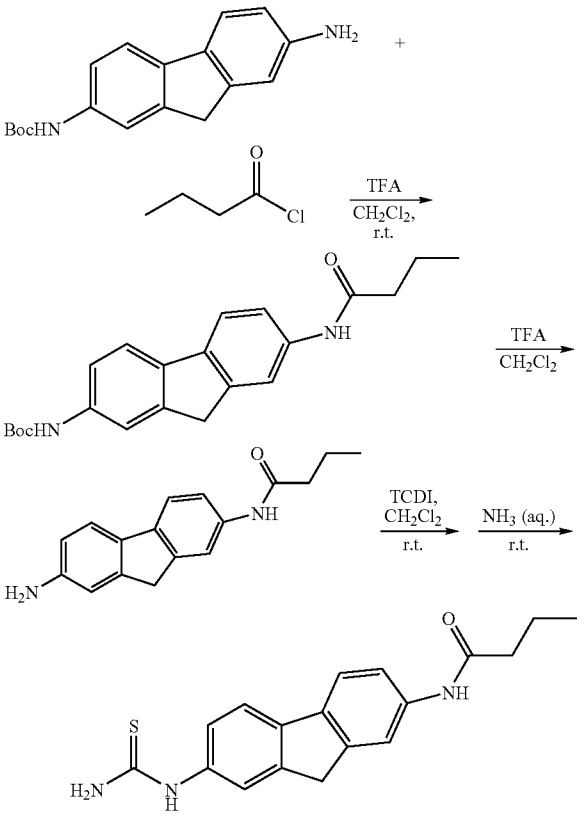
[0201] Compound 71 was prepared in a manner similar to that described in Example 32.

[0202] EI-MS (M+1): 445, 447.

Example 72

Preparation of Compound 72: N-(7-thioureido-9H-fluoren-2-yl)butyramide

[0203]



Compound 72

[0204] Triethylamine (37 mg, 0.37 mmol) was added to a solution of (7-amino-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (100 mg, 0.34 mmol) and n-butyryl chloride (36 mg, 0.34 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 4 hours. It was then quenched with excess saturated ammonium chloride aqueous solution (30 mL), followed by extraction with dichloromethane (30 mL×3). The organic layers were combined, washed, with brine, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel to give (7-butylamino-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (99 mg, 0.27 mmol, yield: 80%) as a white solid.

[0205] Trifluoroacetic acid (TFA, 2.0 mL, 26.3 mmol) was added to a solution of (7-butyrylamino-9H-fluoren-2-yl)-carbamic acid tert-butyl ester (99 mg, 0.27 mmol) in 2 mL dichloromethane. The reaction mixture was stirred at room temperature for 1 hour. It was then quenched with water (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give N-(7-amino-9H-fluoren-2-yl)-butyramide (69 mg, 0.26 mmol, yield: 95%) as a yellow solid.

[0206] A solution of N-(7-amino-9H-fluoren-2-yl)-butyramide (69 mg, 0.26 mmol) and thiocarbonyl diimidazole (55 mg, 0.30 mmol) in dichloromethane (2 mL) was stirred at room temperature for 2 hours. After a 25% ammonia aqueous solution (2.0 mL, excess) was added, the reaction mixture was stirred at room temperature overnight. The solvent was removed and then the residue thus obtained was purified by silica gel column chromatography eluting with methanol-dichloromethane to give N-(7-thioureido-9H-fluoren-2-yl)-butyramide (compound 72) (75 mg, 0.23 mmol, yield: 90%) as a white solid.

[0207] EI-MS (M+1): 326.

Example 73

Preparation of Compound 73: N-(7-thioureido-9H-fluoren-2-yl)cyclohexanecarboxamide

[0208] Compound 73 was prepared in a manner similar to that described in Example 72.

[0209] EI-MS (M+1): 366.

Example 74

Preparation of Compound 74: N-(7-thioureido-9H-fluoren-2-yl)isoxazole-5-carboxamide

[0210] Compound 74 was prepared in a manner similar to that described in Example 72.

[0211] EI-MS (M+1): 351.

Example 75

Preparation of Compound 75: tert-butyl 7-thioureido-9H-fluoren-2-ylcarbamate

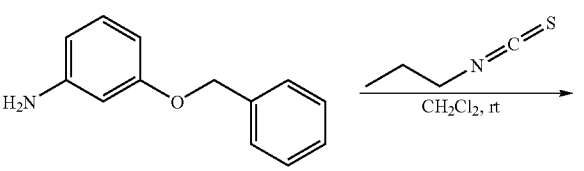
[0212] Compound 75 was prepared in a manner similar to that described in Example 72.

[0213] EI-MS (M+1): 356.

Example 76

Preparation of Compound 76: 1-(3-(benzyloxy)phenyl)imidazolidine-2-thione

[0214]



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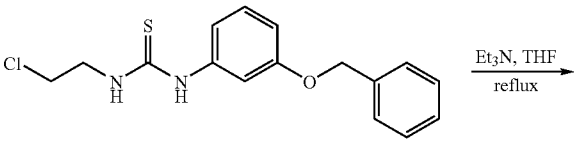
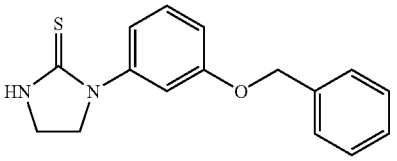




Compound 76

[0215] 2-Chloroethyl isothiocyanate (293 mg, 2.4 mmol) was added to a solution of 3-benzyloxy-phenylamine (398 mg, 2.0 mmol) in dichloromethane (4 mL). The reaction mixture was stirred at room temperature overnight, it was quenched with water (30 mL), followed by extraction with dichloromethane (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give 1-(3-benzyloxyphenyl)-3-(2-chloro-ethyl)-thiourea (627 mg, 1.96 mmol, yield: 98%) as colorless oil.

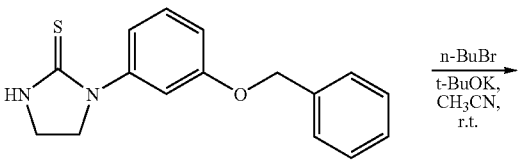
[0216] Triethylamine (2.0 mL, excess) was added to a solution of 1-(3-benzyloxyphenyl)-3-(2-chloro-ethyl)-thiourea (187 mg, 0.58 mmol) in dry THF (3 mL). The reaction mixture was stirred at refluxing temperature for 6 hours, it was then, quenched with a saturated ammonium chloride aqueous solution (30 mL), followed by extraction with ethyl acetate (30 mL×3). The organic layers were combined, washed with brine, and concentrated under vacuum. The residue thus obtained was subjected to column chromatography on silica gel to give 1-(3-benzyloxy-phenyl)-imidazolidine-2-thione (compound 76) as a white solid (150 mg, 0.52 mmol, yield: 90%).

[0217] EI-MS (M+1): 285.

Example 77

Preparation of Compound 77: 1-(3-(benzyloxy)phenyl)-3-butyl-imidazolidine-2-thione

[0218]



Compound 76

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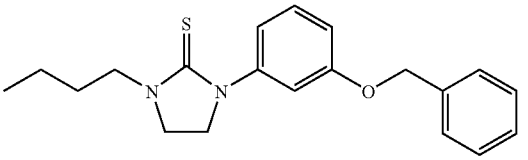


Compound 77

[0219] A suspension of Compound 76, i.e., 1-(3-benzyloxy-phenyl)-imidazolidine-2-thione (71 mg, 0.25 mmol) and potassium tert-butoxide (56 mg, 0.50 mmol) in acetonitrile (1 mL) was cooled in an ice bath and stirred at 0° C. for 30 minutes, followed by addition of a solution of n-butyl bromide (41 mg, 0.30 mmol) in acetonitrile (1 mL). After 5 minutes, the ice bath was removed and the reaction mixture was stirred at room temperature for 3 hours. The reaction was then quenched with water, followed by extraction with ethyl acetate (20 mL×3). The organic layers were combined and washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude mixture thus obtained was purified with silica gel column chromatography to yield 1-(3-benzyloxy-phenyl)-3-butyl-imidazolidine-2-thione (compound 77) as yellow oil (59 mg, 0.18 mmol, yield: 72%).

[0220] EI-MS (M+1): 341.

Example 78

Preparation of Compound 78: 1-(3-benzyloxy-phenyl)-3-(3-phenyl-propyl)imidazolidine-2-thione

[0221] Compound 78 was prepared in a manner similar to that described in Example 77.

[0222] EI-MS (M+1): 403.

Example 79

Preparation of Compound 79: 1-[3-(5-phenyl-pentyloxy)-phenyl]-imidazolidine-2-thione

[0223] Compound 79 was prepared in a manner similar to that, described in Example 76.

[0224] EI-MS (M+1): 341.

Example 80

Preparation of Compound 80: 1-butyl-3-[3-(5-phenyl-pentyloxy)-phenyl]-imidazolidine-2-thione

[0225] Compound 80 was prepared in a manner similar to that described in Example 77.

[0226] EI-MS (M+1): 397.

Example 81

Preparation of Compound 81: 1-[3-(5-phenyl-pentyloxy)-phenyl]-3-(3-phenyl-propyl)-imidazolidine-2-thione

[0227] Compound 81 was prepared in a manner similar to that, described in Example 77.

[0228] EI-MS (M+1): 459.

Example 82

Preparation of Compound 82: {3-[5-(2,6-dichloro-phenoxy)-pentyloxy]-phenyl}-thiourea

[0229] Compound 82 was prepared in a manner similar to that described in Example 7.

[0230] EI-MS (M+1): 400.

Example 83

Preparation of Compound 83: {3-[5-(4-fluoro-phenoxy)-pentyloxy]-phenyl}-thiourea

[0231] Compound 83 was prepared in a manner similar to that described in Example 7,

[0232] EI-MS (M+1): 349.

Example 84

Preparation of Compound 84: {3-[5-(2-chloro-4-methoxy-phenoxy)pentyloxy]-phenyl}-thiourea

[0233] Compound 84 was prepared in a manner similar to that described in Example 7,

[0234] EI-MS (M+1): 395.

Example 85

Preparation of Compound 85: {3-[5-(4-chloro-phenoxy)-pentyloxy]-phenyl}-thiourea

[0235] Compound 85 was prepared in a manner similar to that described in Example 7.

[0236] EI-MS (M+1): 365.

Example 86

Preparation of Compound 86: {3-[5-(2,4-difluoro-phenoxy)-pentyloxy]-phenyl}-thiourea

[0237] Compound 86 was prepared in a manner similar to that described in Example 7.

[0238] EI-MS (M+1): 367.

Example 87

Preparation of Compound 87: {3-[5-(2,6-dichloro-4-fluoro-phenoxy)pentyloxy]-phenyl}-thiourea

[0239] Compound 87 was prepared in a manner similar to that described in Example 7.

[0240] EI-MS (M+1): 418.

Example 88

Preparation of Compound 88: {3-[5-(pyridin-4-yloxy)-pentyloxy]-phenyl}-thiourea

[0241] Compound 88 was prepared in a manner similar to that described in Example 7.

[0242] EI-MS (M+1): 332.

Example 89

Preparation of Compound 89: {3-[5-(pyridin-3-yloxy)-pentyloxy]-phenyl}-thiourea

[0243] Compound 89 was prepared in a manner similar to that described in Example 7,

[0244] EI-MS (M+1): 332.

Example 90

Preparation of Compound 90: {3-[5-(pyrimidin-4-yloxy)-pentyloxy]-phenyl}-thiourea

[0245] Compound 90 was prepared in a manner similar to that described in Example 7,

[0246] EI-MS (M+1): 333.

Example 91

Preparation of Compound 91: 4-[5-(3-thioureido-phenoxy)-pentyloxy]-benzoic acid

[0247] Compound 91 was prepared in a manner similar to that described in Example 7.

[0248] EI-MS (M+1): 375.

Example 92

Preparation of Compound 92: {3-[5-(4-dimethylamino-phenoxy)-pentyloxy]-phenyl}-thiourea

[0249] Compound 92 was prepared in a manner similar to that described in Example 7.

[0250] EI-MS (M+1): 374.

Example 93

Preparation of Compound 93: {3-[5-(4-diethylamino-phenoxy)-pentyloxy]-phenyl}-thiourea

[0251] Compound 93 was prepared in a manner similar to that described in Example 7.

[0252] EI-MS (M+1): 402.

Example 94

Preparation of Compound 94: {3-[5-(4-morpholin-4-yl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0253] Compound 94 was prepared in a manner similar to that described in Example 7.

[0254] EI-MS (M+1): 416.

Example 95

Preparation of Compound 95: {3-[5-(4-piperidin-1-yl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0255] Compound 95 was prepared in a manner similar to that described in Example 7,

[0256] EI-MS (M+1): 414.

Example 96

Preparation of Compound 96: {3-[5-(4-methyl-piperazin-1-yl)-phenoxy]-pentyloxy}-phenyl)-thiourea

[0257] Compound 96 was prepared in a manner similar to that described in Example 7.

[0258] EI-MS (M+1): 429.

Example 97

Preparation of Compound 97: {3-[5-(2-methoxy-phenoxy)-pentyloxy]-phenyl}-thiourea

[0259] Compound 97 was prepared in a manner similar to that described in Example 7.

[0260] EI-MS (M+1): 361.

Example 98

Preparation of Compound 98: {3-[5-(3-methoxy-phenoxy)-pentyloxy]-phenyl}-thiourea

[0261] Compound 98 was prepared in a manner similar to that described in Example 7.

[0262] EI-MS (M+1): 361.

Example 99

Preparation of Compound 99: {3-[5-(3,4,5-trimethoxy-phenoxy)-pentyloxy]-phenyl}-thiourea

[0263] Compound 99 was prepared in a manner similar to that described in Example 7.

[0264] EI-MS (M+1): 421.

Example 100

Preparation of Compound 100: {3-[5-(4-pyrrolidin-1-yl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0265] Compound 100 was prepared in a manner similar to that described in Example 7.

[0266] EI-MS (M+1): 400.

Example 101

Preparation of Compound 101: {3-[5-(4-methoxy-biphenyl-4-yloxy)-pentyloxy]-phenyl}-thiourea

[0267] Compound 101 was prepared in a manner similar to that described in Example 7.

[0268] EI-MS (M+1): 437.

Example 102

Preparation of Compound 102: {3-[5-(4'-methyl-biphenyl-4-yloxy)-pentyloxy]-phenyl}-thiourea

[0269] Compound 102 was prepared in a manner similar to that described in Example 7.

[0270] EI-MS (M+1): 421.

Example 103

Preparation of Compound 103: {3-[5-(4'-chloro-biphenyl-4-yloxy)-pentyloxy]-phenyl}-thiourea

[0271] Compound 103 was prepared in a manner similar to that described in Example 7.

[0272] EI-MS (M+1): 441.

Example 104

Preparation of Compound 104: {3-[5-(4'-bromo-biphenyl-4-yloxy)-pentyloxy]-phenyl}-thiourea

[0273] Compound 104 was prepared in a manner similar to that described in Example 7.

[0274] EI-MS (M+1): 485, 487.

Example 105

Preparation of Compound 105: {3-[5-(naphthalen-1-yloxy)-pentyloxy]-phenyl}-thiourea

[0275] Compound 105 was prepared in a manner similar to that described in Example 7.

[0276] EI-MS (M+1): 381.

Example 106

Preparation of Compound 106: {3-[5-(naphthalen-2-yloxy)-pentyloxy]-phenyl}-thiourea

[0277] Compound 106 was prepared in a manner similar to that described in Example 7.

[0278] EI-MS (M+1): 381.

Example 107

Preparation of Compound 107: {3-[5-(4-thiophen-3-yl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0279] Compound 107 was prepared in a manner similar to that described in Example 7.

[0280] EI-MS (M+1): 413.

Example 108

Preparation of Compound 108: {3-[5-(4-cyano-phenoxy)-pentyloxy]-phenyl}-thiourea

[0281] Compound 108 was prepared in a manner similar to that described in Example 7.

[0282] EI-MS (M+1): 356.

Example 109

Preparation of Compound 109: {3-[5-(3-cyano-phenoxy)-pentyloxy]-phenyl}-thiourea

[0283] Compound 109 was prepared in a manner similar to that described in Example 7.

[0284] EI-MS (M+1): 356.

Example 110

Preparation of Compound 110: {3-[5-(2-cyano-phenoxy)-pentyloxy]-phenyl}-thiourea

[0285] Compound 110 was prepared in a manner similar to that described in Example 7.

[0286] EI-MS (M+1): 356.

Example 111

Preparation of Compound 111: {3-[5-(2,6-dichloro-4-methyl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0287] Compound 111 was prepared in a manner similar to that described in Example 7.

[0288] EI-MS (M+1): 414.

Example 112

Preparation of Compound 112: {3-[5-(4-trifluoromethyl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0289] Compound 112 was prepared in a manner similar to that described in Example 7.

[0290] EI-MS (M+1): 399.

Example 113

Preparation of Compound 113: [3-(3-phenoxy-propoxy)-phenyl]-thiourea

[0291] Compound 113 was prepared in a manner similar to that described in Example 7.

[0292] EI-MS (M+1): 303.

Example 114

Preparation of Compound 114: [3-(4-phenoxy-butoxy)-phenyl]-thiourea

[0293] Compound 114 was prepared in a manner similar to that described in Example 7.

[0294] EI-MS (M+1): 317.

Example 115

Preparation of Compound 115: [3-(6-phenoxy-hexyloxy)-phenyl]-thiourea

[0295] Compound 115 was prepared in a manner similar to that described in Example 7.

[0296] EI-MS (M+1): 345.

Example 116

Preparation of Compound 116: [3-(7-phenoxy-heptyloxy)-phenyl]-thiourea

[0297] Compound 116 was prepared in a manner similar to that described in Example 7.

[0298] EI-MS (M+1): 359.

Example 117

Preparation of Compound 117: {3-[3-(biphenyl-4-yloxy)-propoxy]-phenyl}-thiourea

[0299] Compound 117 was prepared in a manner similar to that described in Example 7.

[0300] EI-MS (M+1): 379.

Example 118

Preparation of Compound 118: {3-[4-(biphenyl-4-yloxy)-butoxy]-phenyl}-thiourea

[0301] Compound 118 was prepared in a manner similar to that described in Example 7.

[0302] EI-MS (M+1): 393.

Example 119

Preparation of Compound 119: {3-[6-(biphenyl-4-yloxy)-hexyloxy]-phenyl}-thiourea

[0303] Compound 119 was prepared in a manner similar to that described in Example 7.

[0304] EI-MS (M+1): 421.

Example 120

Preparation of Compound 120: {3-[7-(biphenyl-4-yloxy)-heptyloxy]-phenyl}-thiourea

[0305] Compound 120 was prepared in a manner similar to that described in Example 7.

[0306] EI-MS (M+1): 435.

Example 121

Preparation of Compound 121: 1,1-dimethyl-3-[3-(5-phenoxy-pentyloxy)-phenyl]-thiourea

[0307] Compound 121 was prepared in a manner similar to that described in Example 1.

[0308] EI-MS (M+1): 359.

Example 122

Preparation of Compound 122: 1,1-Diethyl-3-[3-(5-phenoxy-pentyloxy)-phenyl]-thiourea

[0309] Compound 122 was prepared in a manner similar to that described in Example 1.

[0310] EI-MS (M+1): 387.

Example 123

Preparation of Compound 123: piperidine-1-carbothioic acid [3-(5-phenoxy-pentyloxy)-phenyl]-amide

[0311] Compound 123 was prepared in a manner similar to that described in Example 1.

[0312] EI-MS (M+1): 399.

Example 124

Preparation of Compound 124: morpholine-4-carbothioic acid [3-(5-phenoxy-pentyloxy)-phenyl]-amide

[0313] Compound 124 was prepared in a manner similar to that described in Example 1.

[0314] EI-MS (M+1): 401.

Example 125

Preparation of Compound 125: 4-methyl-piperazine-1-carbothioic acid [3-(5-phenoxy-pentyloxy)-phenyl]-amide

[0315] Compound 125 was prepared in a manner similar to that described in Example 1.

[0316] EI-MS (M+1): 414.

Example 126

Preparation of Compound 126: {3-[5-(quinolin-6-yloxy)-pentyloxy]-phenyl}-thiourea

[0317] Compound 126 was prepared in a manner similar to that described in Example 1.

[0318] EI-MS (M+1): 382.

Example 127

Preparation of Compound 127: {3-[5-(quinolin-5-yloxy)-pentyloxy]-phenyl}-thiourea

[0319] Compound 127 was prepared in a manner similar to that described in Example 1.

[0320] EI-MS (M+1): 382.

Example 128

Preparation of Compound 128: {3-[5-(quinolin-4-yloxy)-pentyloxy]-phenyl}-thiourea

[0321] Compound 128 was prepared in a manner similar to that described in Example 1.

[0322] EI-MS (M+1): 382.

Example 129

Preparation of Compound 129: {3-[5-(isoquinolin-5-yloxy)-pentyloxy]-phenyl}-thiourea

[0323] Compound 129 was prepared in a manner similar to that described in Example 1.

[0324] EI-MS (M+1): 382.

Example 130

Preparation of Compound 130: {3-[5-(quinolin-8-yloxy)-pentyloxy]-phenyl}-thiourea

[0325] Compound 130 was prepared in a manner similar to that described in Example 1.

[0326] EI-MS (M+1): 382.

Example 131

Preparation of Compound 131: {3-[5-(isoquinolin-1-yloxy)-pentyloxy]-phenyl}-thiourea

[0327] Compound 131 was prepared in a manner similar to that described in Example 1.

[0328] EI-MS (M+1): 382.

Example 132

Preparation of Compound 132: {3-[5-(1H-indol-4-yloxy)-pentyloxy]-phenyl}-thiourea

[0329] Compound 132 was prepared in a manner similar to that described in Example 1.

[0330] EI-MS (M+1): 370.

Example 133

Preparation of Compound 133: {3-[5-(4-furan-2-yl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0331] Compound 133 was prepared in a manner similar to that described in Example 1.

[0332] EI-MS (M+1): 397.

Example 134

Preparation of Compound 134: {3-[5-(4-furan-3-yl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0333] Compound 134 was prepared in a manner similar to that described in Example 1.

[0334] EI-MS (M+1): 397.

Example 135

Preparation of Compound 135: {3-[5-(4-thiophen-2-yl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0335] Compound 135 was prepared in a manner similar to that described in Example 1.

[0336] EI-MS (M+1): 413.

Example 136

Preparation of Compound 136: (3-{5-[4-(5-chloro-thiophen-2-yl)-phenoxy]-pentyloxy}-phenyl)-thiourea

[0337] Compound 136 was prepared in a manner similar to that described in Example 1.

[0338] EI-MS (M+1): 447.

Example 137

Preparation of Compound 137: {3-[5-(4-phenoxy-phenoxy)-pentyloxy]-phenyl}-thiourea

[0339] Compound 137 was prepared in a manner similar to that described in Example 1.

[0340] EI-MS (M+1): 423.

Example 138

Preparation of Compound 138: {3-[5-(3-phenoxy-phenoxy)-pentyloxy]-phenyl}-thiourea

[0341] Compound 138 was prepared in a manner similar to that described in Example 1.

[0342] EI-MS (M+1): 423.

Example 139

Preparation of Compound 139: {3-[5-(biphenyl-3-yloxy)-phenyloxy]-phenyl}-thiourea

[0343] Compound 139 was prepared in a manner similar to that described in Example 1.

[0344] EI-MS (M+1): 407.

Example 140

Preparation of Compound 140: {3-[5-(biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea

[0345] Compound 140 was prepared in a manner similar to that described in Example 1.

[0346] EI-MS (M+1): 407.

Example 141

Preparation of Compound 141: (7-Dibenzylamino-9H-fluoren-2-yl)-thiourea

[0347] Compound 141 was prepared in a manner similar to that described in Example 39.

[0348] EI-MS (M+1): 436.

Example 142

Preparation of Compound 142: (7-Benzylamino-9H-fluoren-2-yl)-thiourea

[0349] Compound 142 was prepared in a manner similar to that described in Example 39.

[0350] EI-MS (M+1): 346.

Example 143

Preparation of Compound 143: {3-[5-(4-Methoxy-phenoxy)-pentyloxy]-phenyl}-thiourea

[0351] Compound 143 was prepared in a manner similar to that described in Example 7.

[0352] EI-MS (M+1): 361.

Example 144

Preparation of Compound 144: {3-[5-(3,4-Dimethoxy-phenoxy)pentyloxy]-phenyl}-thiourea

[0353] Compound 144 was prepared in a manner similar to that described in Example 7.

[0354] EI-MS (M+1): 391.

Example 145

Preparation of Compound 145: {3-[5-(Pyridin-2-yloxy)-pentyloxy]-phenyl}-thiourea

[0355] Compound 145 was prepared in a manner similar to that described in Example 7.

[0356] EI-MS (M+1): 382.

Example 146

Preparation of Compound 146: {3-[5-(4-Pyrrol-1-yl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0357] Compound 146 was prepared in a manner similar to that described in Example 7.

[0358] EI-MS (M+1): 382.

Example 147

Preparation of Compound 147: {3-[5-(4-Imidazol-1-yl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0359] Compound 147 was prepared in a manner similar to that described in Example 7.

[0360] EI-MS (M+1): 397.

Example 148

Preparation of Compound 148: {3-[5-(4-Thiomorpholin-4-yl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0361] Compound 148 was prepared in a manner similar to that described in Example 7.

[0362] EI-MS (M+1): 432.

Example 149

Preparation of Compound 149: {3-[7-(Naphthalen-1-yloxy)-heptyloxy]-phenyl}-thiourea

[0363] Compound 149 was prepared in a manner similar to that described in Example 7.

[0364] EI-MS (M+1): 409.

Example 150

Preparation of Compound 150: {3-[8-(Naphthalen-1-yloxy)-octyloxy]-phenyl}-thiourea

[0365] Compound 150 was prepared in a manner similar to that described in Example 7,

[0366] EI-MS (M+1): 423.

Example 151

Preparation of Compound 151: 4-[5-(3-Thioureido-phenoxy)-pentyloxy]-benzoic acid phenyl ester

[0367] Compound 151 was prepared in a manner similar to that described in Example 7.

[0368] EI-MS (M+1): 451.

Example 152

Preparation of Compound 152: [4-(5-Phenyl-pentyloxy)-phenyl]-thiourea

[0369] Compound 152 was prepared in a manner similar to that described in Example 7.

[0370] EI-MS (M+1): 315.

Example 153

Preparation of Compound 153: 2-[5-(3-Thioureido-phenoxy)-pentyloxy]-benzoic acid phenyl ester

[0371] Compound 153 was prepared in a manner similar to that described in Example 7.

[0372] EI-MS (M+1): 451.

Example 154

Preparation of Compound 154: [2-(5-Phenyl-pentyloxy)-phenyl]-thiourea

[0373] Compound 154 was prepared in a manner similar to mat described in Example 7.

[0374] EI-MS (M+1): 315.

Example 135

Preparation of Compound 155: {3-[5-(3-Phenylamino-phenoxy)-pentyloxy]-phenyl}-thiourea

[0375] Compound 155 was prepared in a manner similar to that described in Example 7.

[0376] EI-MS (M+1): 422.

Example 156

Preparation of Compound 156: {3-[5-(3-Benzoyl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0377] Compound 156 was prepared in a manner similar to that described in Example 7,

[0378] EI-MS (M+1): 435.

Example 157

Preparation of Compound 157: (3-{5-[3-(Hydroxy-phenyl-methyl)-phenoxy]-pentyloxy}-phenyl)-thiourea

[0379] Compound 157 was prepared in a manner similar to that described in Example 7.

[0380] EI-MS (M+1): 437.

Example 158

Preparation of Compound 158: {3-[5-(4-Benzyl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0381] Compound 158 was prepared in a manner similar to that described in Example 7.

[0382] EI-MS (M+1): 421.

Example 159

Preparation of Compound 159: {3-[3-(Naphthalen-1-yloxy)-propoxy]-phenyl}-thiourea

[0383] Compound 159 was prepared in a manner similar to that described in Example 7.

[0384] EI-MS (M+1): 353.

Example 160

Preparation of Compound 160: {3-[4-(Naphthalen-1-yloxy)-butoxy]-phenyl}-thiourea

[0385] Compound 160 was prepared in a manner similar to that described in Example 7.

[0386] EI-MS (M+1): 367.

Example 161

Preparation of Compound 161: [4-(5-Phenoxy-pentyloxy)-phenyl]-thiourea

[0387] Compound 161 was prepared in a manner similar to that described in Example 7.

[0388] EI-MS (M+1): 381.

Example 162

Preparation of Compound 162: {3-[5-(4-Methoxy-naphthalen-1-yloxy)-pentyloxy]-phenyl}-thiourea

[0389] Compound 162 was prepared in a manner similar to that described in Example 7.

[0390] EI-MS (M+1): 411.

Example 163

Preparation of Compound 163: {3-[6-(Naphthalen-1-yloxy)-hexyloxy]-phenyl}-thiourea

[0391] Compound 163 was prepared in a manner similar to that described in Example 7.

[0392] EI-MS (M+1): 395.

Example 164

Preparation of Compound 164: [3-(5-Naphthalen-1-yl-pentyloxy)-phenyl]-thiourea

[0393] Compound 164 was prepared in a manner similar to that described in Example 7.

[0394] EI-MS (M+1): 365.

Example 165

Preparation of Compound 165: {3-[5-(4-Chloro-naphthalen-1-yloxy)-pentyloxy]-phenyl}-thiourea

[0395] Compound 165 was prepared in a manner similar to that described in Example 7.

[0396] EI-MS (M+1): 415.

Example 166

Preparation of Compound 166: {3-[5-(2-Methyl-naphthalen-1-yloxy)-pentyloxy]-phenyl}-thiourea

[0397] Compound 166 was prepared in a manner similar to that described in Example 7.

[0398] EI-MS (M+1): 395.

Example 167

Preparation of Compound 167: {3-[5-(3-Benzyl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0399] Compound 167 was prepared in a manner similar to that described in Example 7.

[0400] EI-MS (M+1): 421.

Example 168

Preparation of Compound 168: {3-[5-(4'-Chloro-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea

[0401] Compound 168 was prepared in a manner similar to that described in Example 7.

[0402] EI-MS (M+1): 441.

Example 169

Preparation of Compound 169: {3-[3-(Biphenyl-2-yloxy)-propoxy]-phenyl}-thiourea

[0403] Compound 169 was prepared in a manner similar to that described in Example 7.

[0404] EI-MS (M+1): 379.

Example 170

Preparation of Compound 170: {3-[4-(Biphenyl-2-yloxy)-butoxy]-phenyl}-thiourea

[0405] Compound 170 was prepared in a manner similar to that described in Example 7.

[0406] EI-MS (M+1): 393.

Example 171

Preparation of Compound 171: [3-(6-Naphthalen-1-yl-hexyloxy)-phenyl]-thiourea

[0407] Compound 171 was prepared in a manner similar to that described in Example 7.

[0408] EI-MS (M+1): 379.

Example 172

Preparation of Compound 172: {4-[5-(2,4-Dichloro-phenoxy)-pentyloxy]-phenyl}-thiourea

[0409] Compound 172 was prepared in a manner similar to that described in Example 7.

[0410] EI-MS (M+1): 340.

Example 173

Preparation of Compound 173: {4-[5-(2,4-Difluoro-phenoxy)-pentyloxy]-phenyl}-thiourea

[0411] Compound 173 was prepared in a manner similar to that described in Example 7.

[0412] EI-MS (M+1): 367.

Example 174

Preparation of Compound 174: {3-[5-(4'-Fluoro-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea

[0413] Compound 174 was prepared in a manner similar to that described in Example 7.

[0414] EI-MS (M+1): 425.

Example 175

Preparation of Compound 175: {3-[5-(4'-Trifluoromethyl-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea

[0415] Compound 175 was prepared in a manner similar to that described in Example 7.

[0416] EI-MS (M+1): 475.

Example 176

Preparation of Compound 176: {3-[5-(4'-Methoxy-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea

[0417] Compound 176 was prepared in a manner similar to that described in Example 7.

[0418] EI-MS (M+1): 437.

Example 177

Preparation of Compound 177: {3-[5-(4'-Methyl-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea

[0419] Compound 177 was prepared in a manner similar to that described in Example 7.

[0420] EI-MS (M+1): 421.

Example 178

Preparation of Compound 178: {3-[5-(3'-Methyl-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea

[0421] Compound 178 was prepared in a manner similar to that described in Example 7.

[0422] EI-MS (M+1): 421.

Example 179

Preparation of Compound 179: {3-[5-(3',5'-Difluoro-biphenyl-2-yloxy)-pentyloxy]-phenyl}-thiourea

[0423] Compound 179 was prepared in a manner similar to that described in Example 7,

[0424] EI-MS (M+1): 443.

Example 180

Preparation of Compound 180: {3-[5-(Naphthalen-1-ylamino)-pentyloxy]-phenyl}-thiourea

[0425] Compound 180 was prepared in a manner similar to that described in Example 7,

[0426] EI-MS (M+1): 380.

Example 181

Preparation of Compound 181: {3-[5-(2-Cyclohexyl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0427] Compound 181 was prepared in a manner similar to that described in Example 7.

[0428] EI-MS (M+1): 413.

Example 182

Preparation of Compound 182: {3-[5-(4-Cyclohexyl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0429] Compound 182 was prepared in a manner similar to that described in Example 7.

[0430] EI-MS (M+1): 413.

Example 183

Preparation of Compound 183: {3-[5-(2-Furan-2-yl-phenoxy)-pentyloxy]-phenyl}-thiourea

[0431] Compound 183 was prepared in a manner similar to that described in Example 7.

[0432] EI-MS (M+1): 397.

Example 184

Assay for Inhibition of HCV Replication

[0433] Dulbecco's modified Eagle's medium (DMEM) high glucose, fetal bovine serum (FBS), G4.18 (geneticin), and blasticidin were purchased from Invitrogen (Carlsbad, Calif.). A reporter cell line, Ava5-EG(Δ4AB)SEAP, for HCV drug screening was derived from HCV replicon cells (Ava5). See, e.g., Lee et al., *Anal. Biochem.* 316:162-70 and Lee et at, *J. Virol. Methods* 116:27-33. EG(Δ4AB)SEAP is a reporter gene consisting of enhanced green fluorescent protein (EG), an NS3-NS4A protease decapeptide recognition sequence (Δ4AB), and secreted alkaline phosphatase (SEAP). See, e.g., Lee et al., *Anal. Biochem.* 316: 162-70. A reporter gene, EG(Δ4AB)SEAP, was stably integrated in the Ava5 cells to generate Ava5-EG(Δ4AB)SEAP cells. The cells were cultured in a medium containing 500 μg/ml G418 (geneticin) and 10 μg/ml blasticidin in a 5% CO_2 incubator.

[0434] Ava5-EG(Δ4AB)SEAP cells were seeded in 96-well plates (5×10^3 cells/100 μl/well). After incubation for 1 day, the cells were treated with various concentrations of a test compound for 48 hours. Each culture medium was replenished with a fresh medium containing the test compound at the same concentration to remove the accumulated SEAP. The cells were then incubated for another 24 hours. The culture medium was collected and subjected to SEAP activity assays. The SEAP activities were measured using the Phospha-Light assay kit (Tropix, Foster, Calif., USA) according to manufacturer's instructions. Of note, SEAP activity in the culture medium, can be used to reflect anti-HCV activity. See, e.g., Lee et al., *J. Virol. Methods* 116:27-33.

[0435] Compounds 1-42, 45-62, 64-91, 93-135, and 137-183 were tested for their efficacy in inhibiting HCV replication. Unexpectedly, 119 test compounds showed low EC_{50} values (i.e., the concentration of a test compound at which 50% HCV replication is inhibited) between 0.001 μM and 1 μM. Among them, 63 test compounds showed EC_{50} values as low as between 0.001 μM and 0.1 μM.

Example 185

Cytotoxicity Assay

[0436] Cell viability was determined by the MTS assay similar to that described in Cory et al., *Cancer Commun.* 3:207-12. In short, Ava5-EG(Δ4AB)SEAP cells were seeded in 96-well plates (5×10^3 cells/100 μl/well). 100 μL/well solution containing phenol red-free DMEM, MTS (tetrazolium compound [3-(4,5-dimethylthiozol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt]; Promega, Madison, Wis.) and phenazine methosulfate (PMS; Sigma, St. Louis, Mo.) at a ratio of 80:20:1 to each well. The cells were incubated with test compounds for 1-4 hours at 37° C. in a humidified, 5% CO_2 incubator and the absorbance was then measured at 490 nm.

[0437] Compounds 1-42, 45-62, 64-91, 93-135, and 137-183 were tested in the above cytotoxicity assay. Unexpectedly, all test compounds showed CC_{50} values (i.e., the concentration of a test compound at which 50% of the cells are killed) above 1 μM. Specifically, 67 of the tested compounds showed CC_{50} values above 50 μM, 88 of the tested compounds showed CC_{50} values between 10 μM and 50 μM, and 23 of the test compounds showed CC_{50} values between 1 μM and 10 μM. Most of the effective compounds exerted little cytotoxicity.

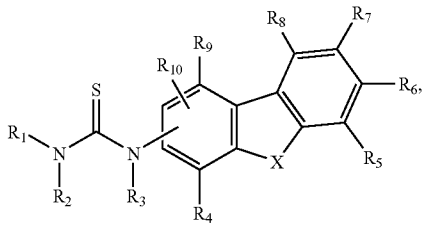
OTHER EMBODIMENTS

[0438] All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

[0439] From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the scope of the following claims.

What is claimed is:

1. A compound of formula (II):



(II)

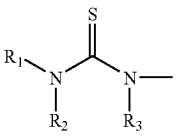
wherein

X is O, $N(R_a)$, $C(R_aR_b)$, or C(O);

each of R_1, R_2, and R_3, independently, is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, aryl, or heteroaryl; or R_2 and R_3, together with the two nitrogen atoms to which they are bonded and the carbon atom bonded to both of the two nitrogen atoms, are C_3-C_{20} heterocycloalkyl; and

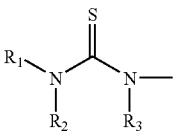
each of R_4, R_5, R_6, R_7, R_8, R_9 and R_{10}, independently, is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, aryl, heteroaryl, halo, $N(R_cR_d)$, $N(R_c)$—C(S)—$N(R_dR_e)$; $N(R_c)$—$C(O)R_d$, or $N(R_c)$—C(O)O—R_d; in which each of R_a, R_b, R_c, R_d, and R_e, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl;

provided that if R_{10} is at the 3-position, then



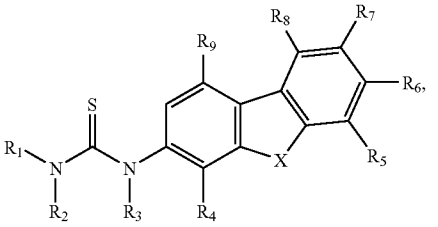
is at the 4-position;

and if R_{10} is at the 4-position, then



is at the 3-position.

2. The compound of claim 1, wherein the compound has the following formula;



wherein X, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are as defined in claim 1.

3. The compound of claim 2, wherein each of R_1, R_2, and R_3, independently, is H, aryl optionally substituted with C_1-C_{20} heterocycloalkyl, heteroaryl, or C_1-C_{10} alkyl optionally substituted with C_1-C_{10} alkoxy, aryl, N(RR'), in which each of R and R', independently, is H or C_1-C_{10} alkyl.

4. The compound of claim 3, wherein each of R_4, R_5, R_6, R_7, R_8, and R_9, independently, is H, halo, $N(R_cR_d)$, $N(R_c)$—C(S)—$N(R_dR_e)$; $N(R_c)$—$C(O)R_d$, or $N(R_c)$—C(O)O—R_d.

5. The compound of claim 4, wherein each of R_4, R_5, R_6, R_7, R_8, and R_9 is H and R_6 is H, halo, $N(R_cR_d)$, $N(R_c)$—C(S)—$N(R_dR_e)$; $N(R_c)$—$C(O)R_d$, or $N(R_c)$—C(O)O—R_d.

6. The compound of claim 2, wherein each of R_1, R_2, and R_3 is H.

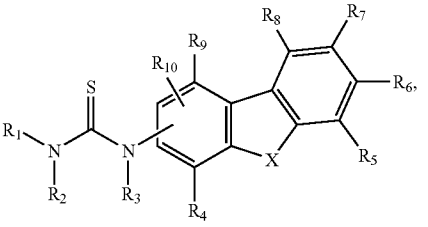
7. The compound of claim 6, wherein each of R_4, R_5, R_7, R_8, and R_9 is H and R_6 is H, halo, $N(R_cR_d)$, $N(R_c)$—C(S)—$N(R_dR_e)$, $N(R_c)$—C(O)—R_d, or $N(R_c)$—C(O)O—R_d.

8. The compound of claim 1, wherein each of R_1, R_2, and R_3 is H.

9. The compound of claim 1, wherein R_1 is $(CH_2)_nCH_3$, in which n is 1, 2, 3, 4, 5, or 6; and each of R_2 and R_3 is H

10. The compound of claim 1, wherein the compound is one of compounds of compounds 38, 40, 42, and 45-48.

11. A method for treating hepatitis C virus infection, comprising administering to a subject in need thereof an effective amount of a compound of formula (II):



(II)

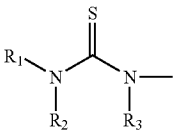
wherein

X is O, $N(R_a)$, $C(R_aR_b)$, or C(O);

each of R_1, R_2, and R_3, independently, is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, aryl, or heteroaryl; or R_2 and R_3, together with the two nitrogen atoms to which they are bonded and the carbon atom bonded to both of the two nitrogen atoms, are C_3-C_{20} heterocycloalkyl; and

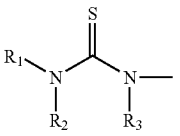
each of R_4, R_5, R_6, R_7, R_8, R_9, and R_{10}, independently, is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, aryl, heteroaryl, halo, $N(R_cR_d)$, $N(R_c)$—C(S)—$N(R_dR_e)$; $N(R_c)$—$C(C)R_d$, or $N(R_c)$—C(O)O—R_d; in which each of R_a, R_b, R_c, R_d, and R_e, independently, is H, C_1-C_{10} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} heterocycloalkyl, aryl, or heteroaryl;

provided that if R_{10} is at the 3-position, then



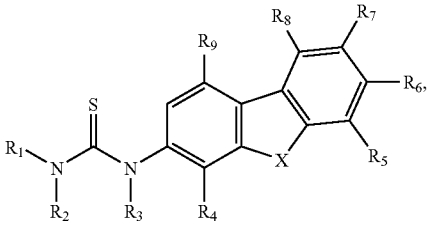
is at the 4-position;

and if R_{10} is at the 4-position, then



is at the 3-position.

12. The method of claim 11, wherein the compound has the following formula;



wherein X, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are as defined in claim 11.

13. The method of claim 12, wherein each of R_1, R_2, and R_3, independently, is H, aryl optionally substituted with C_1-C_{20} heterocycloalkyl, heteroaryl, or C_1-C_{10} alkyl optionally substituted with C_1-C_{10} alkoxy, aryl, N(RR'), in which each of R and R', independently, is H or C_1-C_{10} alkyl.

14. The method of claim 13, wherein each of R_4, R_5, R_6, R_7, R_8, and R_9, independently, is H, halo, $N(R_cR_d)$, $N(R_c)$—C(S)—$N(R_dR_e)$; $N(R_c)$—$C(O)R_d$, or $N(R_c)$—C(O)O—R_d.

15. The method of claim 14, wherein each of R_4, R_5, R_7, R_8, and R_9 is H and R_6 is H, halo, $N(R_cR_d)$, $N(R_c)$—C(S)—$N(R_dR_e)$; $N(R_c)$—$C(O)R_d$, or $N(R_c)$—C(O)O—R_d.

16. The method of claim 12, wherein each of R_1, R_2, and R_3 is H.

17. The method of claim 16, wherein each of R_4, R_5, R_7, R_8, and R_9 is H and R_6 is H, halo, $N(R_cR_d)$, $N(R_c)$—C(S)—$N(R_dR_e)$, $N(R_c)$—$C(O)R_d$, or $N(R_c)$—C(O)O—R_d.

18. The method of claim 11, wherein each of R_1, R_2, and R_3 is H.

19. The method of claim 11, wherein R_1 is $(CH_2)_nCH_3$, in which n is 1, 2, 3, 4, 5, or 6; and each of R_2 and R_3 is H

20. The method of claim 11, wherein the compound is one of compounds of compounds 38, 40, 42, and 45-48.

* * * * *