

THE PATENT ACT 1970

Section 25(1) read with Rule 55

IN THE MATTER OF: Patent Application No. 9668/DELNP/2007

IN The Matter of: Representation by the way opposition filed under section 25(1)

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA- APPLICANT

AND

- 1) Fresenius Kabi Oncology Limited
- 2) BDR Pharmaceutical International Pvt. Ltd.
- 3) Umesh Shah
- 4) Sheela Pawar
- 5) Indian Pharmaceuticals Alliance (IPA)

} OPPONENTS

1) Details and important dates of Application filed by The Regent of the University of California before IPO for grant of the Patent are mentioned herein below

Indian Patent Application No.:	9668/DELNP/2007
Applicant:	The Regent of the University of California
Priority Application Nos.	USA - 60/680,835, USA - 60/750,351, USA - 60/756,552
Priority Date	13/05/2005, 15/12/2005, 06/01/2006
International Application No.:	PCT/US2006/011417
International Filing Date:	29/03/2006
Indian Filing Date:	13/12/2007
Request for Examination:	13/05/2009
First Examination Report:	24/05/2013
Reply to FER:	11/02/2014
Opposition filed by Fresenius Kabi Oncology Limited	05/12/2012
Opposition filed by BDR Pharmaceutical International Pvt. Ltd.	24/07/2013

Opposition filed by Mr Umesh Shah	18/02/2015
Opposition filed by Ms Sheela Pawar	28/07/2015
Opposition filed by Indian Pharmaceutical Alliance	12/01/2016

2) Hearing Held on 02nd and 03rd July 2015

Persons present

- a) Mr Vishal Sudan; on behalf of Fresenius Kabi Oncology Ltd.
- b) Ms Rajeshwari Hariharan; on behalf of BDR pharmaceutical International Pvt. Ltd.
- c) Mr. G. Natraj; on behalf of Mr Umesh Shah
- d) Ms Archana Shankar, Devinder Singh Rawat, Gitika Suri and Lars Genieser; on behalf of Applicant

Hearing Held on 25th July 2016

- a) Ms Kiran Rao Parmar; on behalf of Ms Sheela Pawar
- b) Ms Archana Shankar, Devinder Singh Rawat, Gitika Suri; on behalf of Applicant

3) PRE GRANT OPPOSITIONS AND THEIR GROUNDS OF OPPOSITIONS:

(a) **Grounds of Opposition Filed by FRESENIUS KABI ONCOLOGY LIMITED (Referred as Opponent 1 herein after):-**

(b) The opponent has taken following specific grounds of the present pre-grant opposition against grant of instant application.

- (i) Section 25(1)(e) -Lack of Inventive step
- (ii) Section 25(1)(f) – Not an Invention
- (iii) Section 25(1)(g)-Lack of Clarity and Sufficiency
- (iv) Section 25(1)(h)- Section 8 requirement not complied

(b) Grounds of Opposition Filed by BDR (Referred as Opponent 2 herein after):-

- (i) Section 25(1)(b)- Lack of Novelty
- (ii) Section 25(1)(e)
- (iii) Section 25(1)(f)

(iv) Section 25(1)(h)

(c) Grounds of Opposition Filed by Mr Umesh Shah(Referred as Opponent 3 herein after):-

(i) Section 25(1)(b)

(ii) Section 25(1)(e)

(iii) Section 25(1)(f)

(iv) Section 25(1)(g)

(d) Grounds of Opposition Filed by IPA (Referred as Opponent 4 herein after):-

(i) Section 25(1)(b)

(ii) Section 25(1)(e)

(iii) Section 25(1)(f)

(e) Grounds of Opposition Filed by Ms Sheela Pawar(Referred as Opponent 5 herein after):-

(i) Section 25(1)(i)-Application not filed in prescribed time period

(ii) Section 25(1)(h)

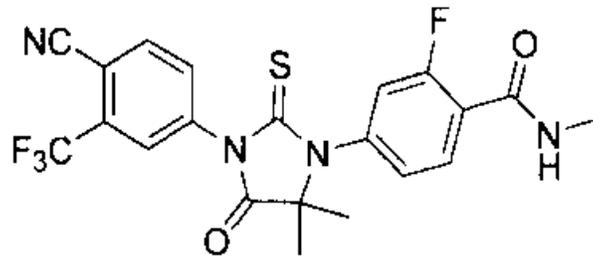
4) List of documents Cited By Opponents

S.No.	Document
1	US5411981
2	US4097578
3	US4636505
4	US6518257
5	US6087509
6	2440/DEL/1996
7	USRE35956
8	US5434176

9	US5589497
10	US5656651/ WO97/00071
11	US5627201
12	J. Med Chem 2004 July 15; 47(15) ,3765-76.
13	US2004/0116417
14	Med Chem, 2002, Singh et al.
15	US5750553
16	US2006/135583
17	US2005/159468
18	j MED Dort et al 2000
19	J med 2005, Soderholm
20	J steroid Biochem Molec 1994 Philibert
21	J steroid Biochem Molec 1994 Berlin
22	Colgate-Palmolive Company (Hendrickson's) Application-[1977] R.P.C. 233 at pg 250
23	Article " Structure –Activity Relationship Thiohydantoin Androgen Receptor Antagonists for Castration Resistant Prostate Cancer (CRPC)" by Jung et al. J. Medicinal Chem. 2010
24	Berner Vs Andrew John Manson [383 US 519]
25	European Board of Appeals decision T-609/02
26	Manickam Vs Chinnasamy, C.R.P.PD. No. 58 of 2010 and M.P. No. 1 of 2010
27	Supreme court Decision; Novartis Vs Union of India and Others
28	Inteleectual Property Appealte Board ; O.A./8/2009/PT/CH

5) Present invention relates to diarylhydantoin compounds including diarylthiohydantoins, and methods for synthesizing them. The compounds of the claim are used for the treatment of hormone refractory prostate cancer. The application was filed as national phase with 46 numbers of claims. Whereas, at the time of reply to FER the number of claims were reduced to 15 in number. At the time filing of application as national phase markush structure compounds in claim 1 were claimed. At the amended stage in claim 1 the claim was restricted to a single compound. The set of claims at the time of amendment is as follows:-

1. A compound having the formula

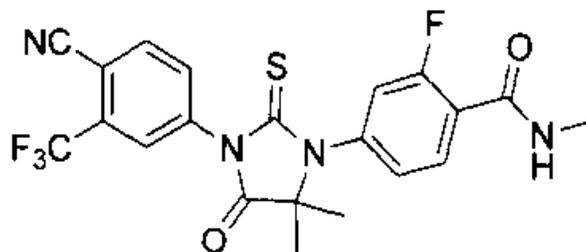


2. A compound as claimed in claim 1, for treatment of a hyperproliferative disorder.
3. A pharmaceutical composition comprising a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.
4. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.001 mg per kg body weight per day to about 100 mg per kg body weight per day for treatment of a hyperproliferative disorder.
5. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.01 mg per kg body weight per day to about 100 mg per kg body weight per day for treatment of a hyperproliferative disorder.
6. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day for treatment of a hyperproliferative disorder.
7. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of about 1 mg per kg body weight per day for treatment of a hyperproliferative disorder.
8. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is prostate cancer.
9. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7 wherein the hyperproliferative disorder is hormone refractory prostate cancer.
10. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7 wherein the hyperproliferative disorder is hormone sensitive prostate cancer.
11. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7 wherein the hyperproliferative disorder is breast cancer.
12. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7 wherein the hyperproliferative disorder is ovarian cancer.

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

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

15. A method of synthesizing the compound comprising:



mixing N-Methyl-2-fluoro-4-(1, 1-dimethyl-cyanomethyl)-aminobenzamide and 4-Isothiocyanto-2

trifluoromethylbenzonitrile in DMF and heating to form a first mixture;

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

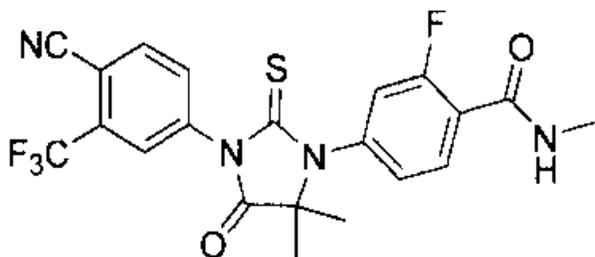
refluxing the second mixture; and

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

isolating the compound from the organic layer.

At the time of hearing the applicant further deleted the claims and retained only three claims which are as given below:-

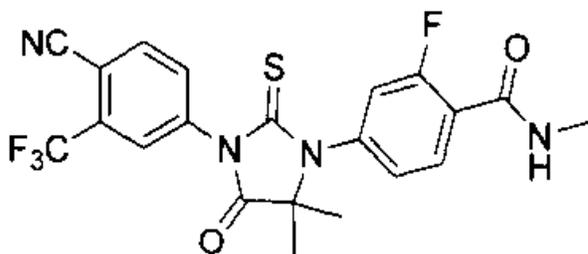
1) A compound having the formula



or a Pharmaceutical acceptable salt thereof

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

3) A method of synthesizing the compound comprising:



mixing N-Methyl-2-fluoro-4-(1, 1-dimethyl-cyanomethyl)-aminobenzamide and 4-Isothiocyanato-2-trifluoromethylbenzonitrile in DMF and heating to form a first mixture;
 adding an alcohol and an acid to the first mixture to form a second mixture;
 refluxing the second mixture; and
 cooling the second mixture, combining the second mixture with water and extracting an organic layer;
 isolating the compound from the organic layer.

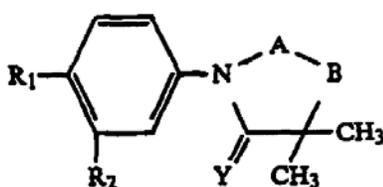
6.) Grounds Of Opposition :- Section 25(1)(b)

6.1) Opponent 1, Opponent 2, Opponent 3 and Opponent 4 relied on US 5441981 (US'981) for the lack of novelty of the impugned invention. The argument given by opponents is as follows:

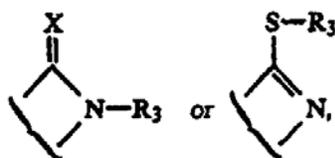
US'981 discloses imidazolidine compounds and compositions thereof having anti-androgenic activity.

US'981 discloses:

"A compound of the formula



wherein R_1 is $-\text{CN}$, $-\text{NO}_2$ or halogen, R_2 is $-\text{CF}_3$ or halogen, $-\text{A-B}-$ is of



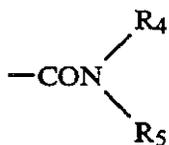
X is $-\text{O}-$ or $-\text{S}-$,

R3 is hydrogen, alkyl, alkenyl or alkynyl of up to 12 carbon atoms, **aryl** and aralkyl of up to 12 carbon atoms, **all optionally substituted** by --OH, **halogen**, --SH, --CN, acyl and acyloxy of up to 7 carbon atoms, --aryl, --O--aryl, --O--aralkyl --S-- aryl of up to 12 carbon atoms

the aryl and aralkyl **being optionally substituted by** halogen, --CF3, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl or alkynyloxy with the sulfur being optionally oxidized to sulfone or sulfoxide, free, esterified, **amidified or salified carboxy**, --NH2, mono and dialkylamino and heterocyclic of 3 to 6 ring members and containing at least one heteroatom selected from the group consisting of oxygen, sulfur and nitrogen, the alkyl, alkenyl and alkynyl being optionally interrupted by at least one oxygen, nitrogen or sulfur optionally oxidized to sulfoxide or sulfone, trialkylsilyl with the alkyl having 1 to 6 carbon atoms and acyl and acyloxy of an organic carboxylic acid of 1 to 7 carbon atoms and

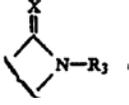
Y is --O--, --S-- or --NH--,".

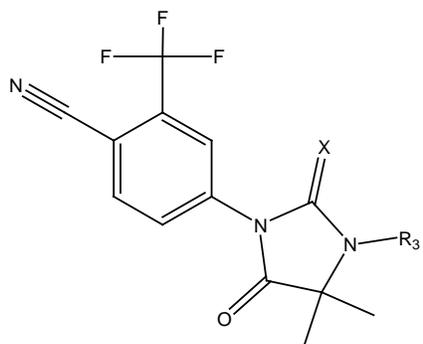
In column 03, lines 05-09, D1 specifically defines that "The amidified or salified carboxy are of the type



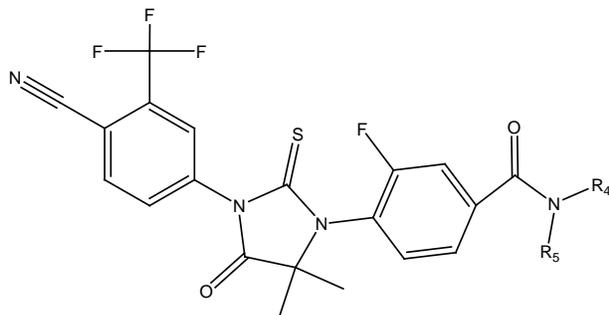
Wherein, **R4** and **R5** are individually selected from the group consisting of hydrogen and alkyl of 1 to 4 carbon atoms such as **methyl**, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl and tert-butyl...."

By substituting the compound of formula (I) with the definitions of the various groupi.e. **R1= -CN**, **R2= -**

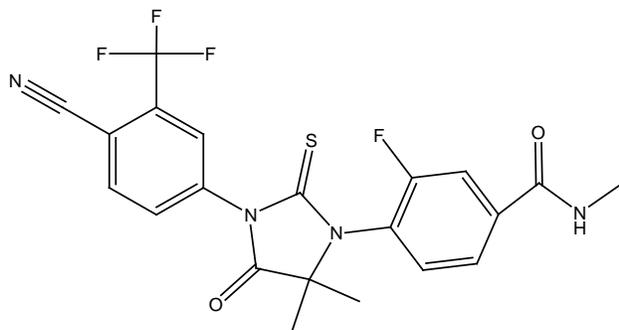
CF3, **Y= -O** and **-A-B=** , the compound of below formula would be formed:



Again, selecting X = -S- and R3= aryl being optionally substituted by **halogen, amidified or salified carboxy** (taking halogen as Fluorine); the compound of below formula would be formed:



Again, R4 and R5 are hydrogen and methyl respectively. Therefore, the compound of below formula would be formed:

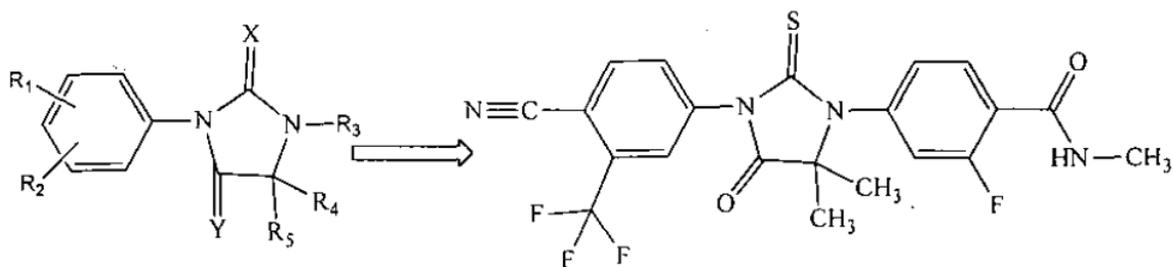


The above represented compound is identical to the compound of claim 1 i.e. Enzalutamide. Therefore, in view of above analysis it is clear that the compound of claim 1 was already disclosed in US'981. Hence, the subject matter of claim 1 lacks novelty over US'981.

6.2) Opponent 2 and Opponent 4 also cited Document US6087509 (US'509)

US'509 is generally drawn to compounds having anti-androgenic activity. US' 509 discloses a family of compounds phenyl, phenylimidazolidines represented by a Markush structure. A Markush family of compounds is represented at column 1, lines 10-45. The compound claimed in the impugned application is embraced by the family of compounds/Markush structure represented at column 1. US'509 also discloses the use of compounds for anti-androgenic activity useful against tumors.

The compound Enzalutamide as claimed in impugned application can be arrived by making relevant substitutions in the Markush structure as shown below:



R1 is -CN (Column-1, Line 23-24)

R2 is -CF3 (Column-1, Line 23-24)

R3 is Aryl substituted with one or more halogen and amidified carboxy (Column-1, Line 26-35)

R4 and R5 is Alkyl containing at most 4 carbon atoms (Column-1, Line 36-38)

X and Y is-S- and -O- (Column-1, Line 44-45)

Opponents argued that US'509 directly discloses amidified diaryl hydantoin compounds. They also argued that substitutions required to be made in the Markush structure of US' 509 are direct, there is no need for any contemplation or selection of several elements and making further sub-substitutions on a previously substituted compound -all the substitutions are direct. Therefore, there is no application of hindsight or any instance of "cherry-picking". Thus, US'509 fully and completely anticipates the compounds as claimed in claim 1.

6.3) The Opponent 3 also cited documents 2440/DEL/1996, US 5434176 (US'176) and US 5750553 (US'553) for the lack of novelty. In the aforementioned documents compounds in markush structure have been claimed. The opponent argued that the impugned invention is disclosed if we make by suitable selection of the substituents disclosed in the cited documents.

6.4) Applicant's Argument

- 1) The applicant argued there is no disclosure, leave apart enabling disclosure, of 'DIARYL COMPOUNDS' in the cited prior art document. The Opponent themselves have admitted to this difference.
- 2) There is no example compound/test compound in prior art documents that is a diaryl compound, or is even close to the structure of Enzalutamide.
- 3) Each element of the impugned claim is not found in any of the prior art.
- 4) Applicant further argued that for a prior art document to be an anticipating document, it must disclose subject matter which, if performed, would necessarily result in an infringement of the patent, and it has to enable a person skilled in the art to be able to perform the invention without exercise of any inventive

ingenuity. The said disclosure has to be an “unambiguous clear and a direct disclosure (enabling disclosure).” Therefore, if the disclosure is not an enabling disclosure the said document cannot be said to anticipate the invention.

7.) Grounds Of Opposition :- Section 25(1)(E)

7.1) Opponent 1 relied on following documents

- 1) US 4511981 (US'981)
- 2) US 6518257 (US'257)
- 3) US4636505 (US'505)
- 4) J Med Chem. 2004 Jul15;47(15), 3765-16; A ligand-based approach to identify quantitative structure-activity relationships for the androgen receptors. (Referred as D1 hereinafter)

The arguments and submissions given by the Opponent 1 are being as given below.

➤ **OBVIOUS SELECTION OF VARIOUS GROUPS DISCLOSED IN US'981 IN VIEW OF D1:**

Claim 1

The opponent argued that subject matter of the opposed application does not involve an inventive step and is obvious over US'981 in view of D1. As discussed under the novelty arguments that all the substitutes were already disclosed in US'981, although generically. The opponent argued that, the applicant has made an obvious selection of various substituents disclosed in US'981 in view of D1, so as to arrive at the compound Enzalutamide covered in claim 1 of the opposed application.

D1 describes a ligand based approach to identify structure activity relationships (SAR) for androgen receptors. As admitted, the applicant was looking for alternate compounds with high binding affinity to the androgen receptors (see background of the opposed application). Therefore, the applicant looking for the development of alternate anti-androgen compounds of high binding affinity would find D1 as a potential prior art.

D1 states that *“The goal of these studies was to identify structural features necessary for high binding affinity and optimization of selective androgen receptor modulators (SARMs).”*

The opponent highlighted that, the applicant has merely selected various groups disclosed in US'981 in view of the teachings of D1. The opponent explained as how the selections of various groups which are disclosed generically are specifically suggested in D1 as shown below for ready reference:

➤ **GROUP R1- OBVIOUS SELECTION OF CYANO GROUP FROM THE GENERIC DISCLOSURE OF US'981:**

As shown above under the discussions of novelty grounds, starting from the formula (I) of US'981, there are three options to select R1 i.e. out of NO₂, Halogen and Cyano group. The opponent argued that, the applicant has made obvious selection of R1 as cyano in view of the teaching of D1.

D1 teaches that H-bond acceptor is favored at this position. Again, D1 specifically suggested that cyano group is favored at this position.

D1 states that, "a red (negative charge) polyhedra near the nitro group of compound S-4 suggests that an H-bond acceptor is favored at the para position of the A-ring. Substitution of the nitro group to cyano group maintains high binding affinity, as would be expected (see D1, page 3773, right side column).

Based on above, it is clear that the applicant has made an obvious selection of R1 as cyano group which indeed is H-bond acceptor. Therefore, R1 = - CN is an obvious selection in view of the teachings of D1.

➤ **GROUP R2: OBVIOUS SELECTION OF CF₃ (TRIFLUOROMETHYL) GROUP FROM THE GENERIC DISCLOSURE OF D1:**

Again, as shown above under the discussions of novelty grounds, starting from the formula (I) of US'981, there are two options to select R2 i.e. out of CF₃ or halogen. The opponent argued that, the applicant has made obvious selection of R2 as CF₃ in view of the teaching of D1.

D1 teaches that a group with hydrophobic characteristics is required at this position. Again, D1 specifically suggested that trifluoromethyl (CF₃) is favored at this position.

D1 states that "A green contour representing favorable hydrophobic interaction is seen at the 3-position of the A-ring. Compound S-4 contains a trifluoromethyl group at this position; however, substitutions to iodine and chlorine maintained high binding affinity (see D1, page 3773).

Based on above, it is clear that the applicant has made an obvious selection of R2 = -CF₃ in view of the teachings of D1.

➤ **GROUP R3: OBVIOUS SELECTION OF FLUORO-N-METHYLBENZAMIDE (OR ARYL SUBSTITUTED WITH FLUORO AND METHYLCARBAMOYL) FROM THE GENERIC DISCLOSURE OF US'981:**

D1 teaches that the compounds having affinity to androgen receptors occupy space in the MET780, CYS784, and MET787 region. D1 teaches that only bicalutamide derivatives occupy space in the MET787 and MET 780 region of the androgen receptors. Here, it should be noted that bicalutamide has second ring (aryl ring) named as B-ring in D1. Therefore, it is clear that, only the compounds containing second ring can occupy space in MET787 and MET780 region. Further, D1 teaches that B-ring substituted with acetamido is favored at this position.

D1 states that, "*The CoMFA model at a 30% contour level overlapped with the homology model aids in identification of amino acids bordering the B-ring (Figure 4b). According to the homology model, the **B-ring lies in a subpocket bordered by MET780, CYS784, and MET787. A predominance of steric hindrance at this position is well supported by MET780 and MET787, which appear to border the acetamido group at the para position of compound S-4.** These methionine residues also portray why moderately sized meta substituents result in poor binding affinity. **Bulky residues at the para position also decrease binding affinity likely because of unfavorable steric interaction with the residues of this subpocket**" (see page 3773, left hand column, first para).*

Therefore, only aryl ring (B-ring) occupies position in the MET780, CYS784 and MET787 region. Again, D1 clarifies that aryl ring can be substituted with moderately sized para substituents.

D1 particularly suggests that "*Functional groups such as the acetamido group can only be accommodated at the para position of the B-ring" (see page 3775, left hand column, last lines of the last para).*

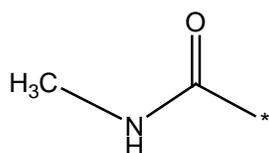
Therefore, D1 teaches that the group R3 is an aryl ring specifically substituted at para-position with moderately sized groups (e.g. acetamido). Therefore, in view of the teachings of D1, the applicant has selected aryl ring which is substituted at para- position with the methylcarbamoyl group.

The applicant argued that D1 does not talk about methylcarbamoyl group. The applicant submitted that D1 suggested acetamido group which is different than the methylcarbamoyl group.

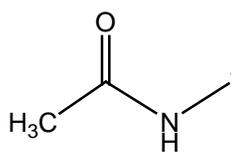
In this regard, the opponent clarified that D1 at first place suggests that, only a moderately sized group can be accommodated specifically at para position. Further, D1 suggests that groups such as acetamido (molecular formula C₂H₄NO) can be favored. Therefore, in view of teachings of D1 the applicant has selected aryl ring substituted with methylcarbamoyl specifically at para-position.

Here, the opponent argued that there is no major difference in the group methylcarbamoyl and the group acetamido. The opponent states that both the groups are moderately sized and therefore can be interchangeably substituted at para-position in view of the teachings of D1. Further, the argued that methylcarbamoyl and acetamido have the same molecular formula C₂H₄NO. Therefore, in view of the teachings of D1 the applicant has selected methylcarbamoyl without ingenuity of thought. Therefore, selection of R3 in view of D1 lacks inventive step, as well.

The opponent hereby represents the pictorial representation of both the groups for the ready reference:



Methylcarbamoyl



Acetamido

Again, the fact that the applicant has selected methylcarbamoyl (which is disclosed in **US'981**) again supports the opponent's argumentation that the opposed application is merely based on the disclosure provided in **US'981**.

Based on above discussion, it is clear that aryl substituted with methylcarbamoyl group or methylbenzamide is an obvious selection in view of D1.

With regard to fluoro substitution at ortho position to the methylcarbamoyl group, the opponent submitted that **US'981** clearly suggests that aryl is further substituted by halogen (see column 03, lines 05-09 of **US'981**).

Also, D1 suggests that "*Bulky para substituents and moderately sized meta and ortho substituents, however, would result in unfavourable steric interaction according to the model*" (see page 3772, right hand column, third par, last four lines).

Therefore, D1 clearly mentions that even moderately sized groups are not favoured at ortho and meta position of the aryl ring. Therefore, the only option is halogens out of the disclosure given in US'981 at this position.

Also, the applicant has not shown substantiated that substitution of fluoro is required for the requisite activity. The opponent argued that TIER 1 COMPOUNDS at page 103 of the opposed application, where the compound RD153 (last compound in the left hand column, page 103) is listed in the TIER 1 COMPOUNDS along with Enzalutamide. RD153 does not have fluoro substitution; therefore, there is no difference in the activity of Enzalutamide and RD153 compound.

Moreover, use of fluoro group at the ortho position relative to the amide group is a well known strategy in the art for suppressing metabolic susceptibility of a compound. Therefore, in view of above discussion it is clear that substitution of fluoro at the ortho position of methylcarbamoyl is an obvious choice for the person skilled in the art, as well.

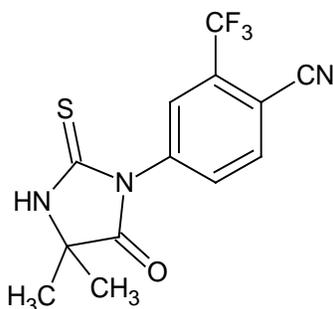
In summary, starting from the formula (I) of US'981 as shown above, the specific choice of R1, R2 and R3 is taught in D1. Therefore, the subject matter of US'981 is obvious to the person skill in view of D1.

Again, US'981 specifies that compounds of US'981 have antiandrogen activities. US'981 specifically discloses the pharmacological data of compounds having R1= -CN and R2= -CF3 (e.g. example 15) specifically. US'981 provides data that compound of example 15 have antiandrogenic activity and concludes that it is devoid of agonist activity.

Column 49, lines 25-67 describes the determination of anti-androgen activity

PRODUCT OF EXAMPLE	ANTAGONISM IN MG/KG	PERCENT
11	3	83
12	0.1	12
	0.3	36
	1	68
	3	94
	10	99
12	(Agonism) 10	0
14	Antagonism 3	87
15	0.3	4
	1	82

The compound of example 15 is represented hereinbelow for the ready reference of the Ld. Controller:



Example 15: 4-(4,4-dimethyl-5-oxo-3-thioxo-1-imidazolidinyl)-1-trifluoromethyl-benzonitrile

Therefore, the difference between the compound of example 15 and compound of the opposed application is FLUORO-N-METHYLBENZAMIDE as shown in below table:

Example 15 of D1	Claim 1 of the opposed application (Enzalutamide)	Differences between the structures

Therefore, the difference between the specific compound of US'981 and Enzalutamide is the moiety "Fluoro-N-Methylbenzamide" as shown in the above table.

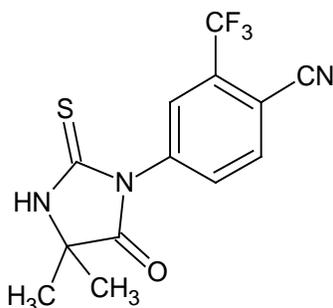
As shown earlier, the moiety is disclosed generically under group R3 of the US'981 (refer to novelty ground). Also, D1 suggests that aryl ring substituted with moderately sized groups such as acetamido is required at this position to improve the binding affinity of the compounds for androgen receptors. Therefore, selection of fluoro-N-methylbenzamide is obvious over US'981 in view of D1.

Therefore, it was submitted that in view of above, a person skilled in the art looking for alternate compounds would find US'981 as highly relevant prior art, which discloses the Enzalutamide, although generically. To this, D1 further removes uncertainty and provides clear directions to select the groups required for the selectivity of a compound for androgen receptors. Thus combining the

teachings of US'981 and D1, a person having ordinary skill in the art would reach the subject matter of the opposed application without ingenuity of thought.

➤ **SELECTION OF A LEAD COMPOUND:**

US'981 discloses potential anti-androgenic compound in Example 15 which is structurally represented below (see column 18, line 19-line 49 of D1):



US'981 provides data that shows that the compound of example 15 have anti-androgenic activity and is devoid of agonist activity (Column 49, lines 25-67).

Therefore, person skill in the art would find compound of example 15 as a lead compound for further development of compounds in the field.

➤ **OBVIOUSNESS / LACK OF INVENTIVE STEP: US'981 IN VIEW OF US'257 IN COMBINATION WITH AND D1**

The opponent submitted that choice of the moiety "FLUORO-N-METHYLBENZAMIDE" is obvious over the teachings of US'981 in view of US'257:

➤ **Teachings of D1:**

D1 provides guidelines to improve the binding affinity of androgen receptors.

As mentioned above (not repeated again for the sake of brevity), D1 teaches that, aryl ring substituted with moderately sized groups such as acetamido is required to improve the binding affinity of the compounds for androgen receptors (see page 3773, left hand column, first para).

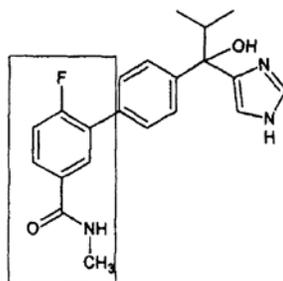
➤ **D1 in view of US'257:**

US'257 specifically provides disclosure of the compounds containing fluoroaryl ring substituted with methylcarbamoyl, as suggested by D1.

US'257 discloses compounds useful for the prophylaxis or treatment of various diseases such as tumor prostatic hypertrophy etc. US257 states that "The compound of the present invention and a salt thereof have a steroid C17,20-lyase inhibitory activity and are useful for the prophylaxis or treatment of various diseases such as primary tumor, its metastasis and recurrence thereof, various symptoms that accompany these cancers, prostatic hypertrophy, virilism, hirsutism, male pattern alopecia, precocious puberty, endometriosis, uterus myoma, mastopathy, polycystic ovary syndrome and the like in mammal, which are affected by sex steroids and metabolites thereof" (See US'257, Column 73, under heading industrial applicability)

Therefore, US'257 has the same technical field as that of the opposed application, and therefore a person looking for alternate compounds in the field would find this document as highly relevant prior art.

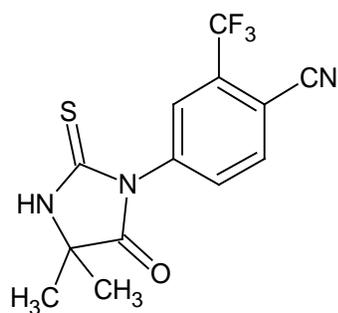
US'257 in Column 49 line 30- line 67 describes example 51 Production of 6-fluoro-4'-[1-hydroxy-1-(1H-imidazol-4-yl)-2-methylpropyl]-N-methyl[1,1'-biphenyl]-3-carboxamide. This can be structurally depicted as shown below:



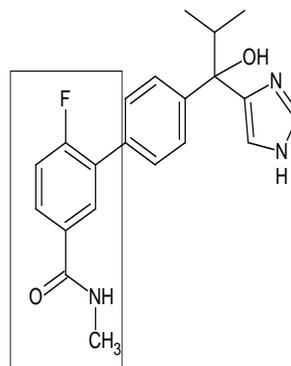
➤ **COMBINING THE TEACHINGS OF US'257 AND D1:**

Therefore as suggested by D1 the moiety "FLUORO-N-METHYLBENZAMIDE" is specifically taught in US'257. Hence, combining the teachings of US'257 and D1, person skill in the art would arrive at the compound Enzalutamide without ingenuity of thought.

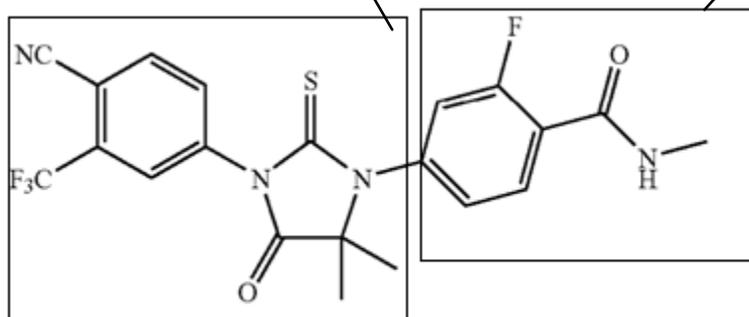
Pictorial representation of the teachings of US'981 and US'257 are shown hereinbelow:



Structure of US'981



Structure of US'257



The applicant argued that in US'257 fluoro is at para-position to the methylcarbamoyl group, while in Enzalutamide it is at ortho-position to that of methylcarbamoyl.

The opponent submitted that the applicant has not substantiated that position of fluoro has any effect on the activity of the compound.

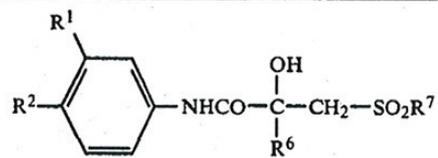
Also, as mentioned earlier, it is well known fact that fluoro group at the ortho position to the amide group suppress the metabolic susceptibility. Therefore, position of fluoro at ortho position to the amide group is common general knowledge and therefore cannot be considered inventive.

Therefore, in view of above it is clear that the subject matter of claim 1 lacks inventive step over US'981 in view of D1 in combination with D257. Hence, ought to be rejected on this ground as well.

➤ **OBVIOUSNESS / LACK OF INVENTIVE STEP: US'981 IN VIEW OF US'505:**

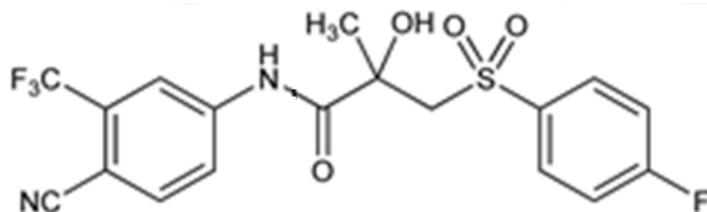
The opponent submitted that the subject matter of claim 1 obvious over US'981 in view of US'505.

US'505 describes the compound as highlighted below (see column 14 of US'505):



R ¹	R ²	R ⁶	R ⁷	m.p. (°C.)
CF ₃	NO ₂	CH ₃	phenyl	149-151
CF ₃	NO ₂	CH ₃	4-fluorophenyl	188-189
CF ₃	NO ₂	CH ₃	pyrid-2-yl	148-150
CF ₃	NO ₂	CH ₃	ethyl	135-136
CF ₃	NO ₂	CH ₃	n-propyl	118-119
CF ₃	NO ₂	CH ₃	n-pentyl	104-105
CF ₃	CN	CH ₃	phenyl	172-173.5
CF ₃	CN	CH ₃	4-fluorophenyl	189-191
CF ₃	CN	CH ₃	ethyl	116-118
CF ₃	CN	CH ₃	n-propyl	117-119
CF ₃	CN	CF ₃	ethyl	164-165
Cl	NO ₂	CH ₃	ethyl	145-146
Cl	NO ₂	CH ₃	n-butyl	116-118
Cl	CN	CH ₃	ethyl	135-136
CH ₃ O	CN	CH ₃	phenyl	172-173

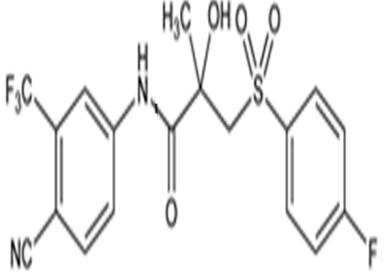
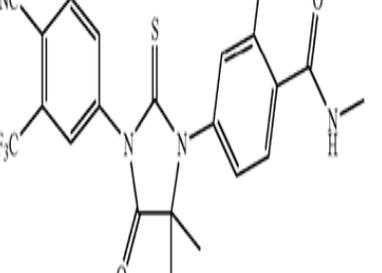
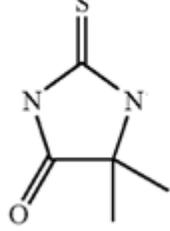
- Therefore, by selecting R¹= CF₃, R²= -CN, R⁶=-CH₃ and R⁷= 4-fluorophenyl the compound of below formula will be formed:



- The compound which is depicted above is generically known as Bicalutamide (admitted prior art in the opposed application) and is an oral non-steroidal anti-androgen and is approved for use in the treatment of prostate cancer. Bicalutamide is marketed with the brand names **Casodex** and **Cosudex** (specifically claimed in US'505).

The opponent hereby represents the difference between the compound Bicalutamide and Enzalutamide in the below table:

Table 2:

Structure of D3	Claim 1 of the opposed application (Enzalutamide)	Differences between the structures
		

➤ **COMBINING THE TEACHINGS OF US'981 AND US'505:**

- US'981 teaches that the lead compound contains a substituted phenyl and imidazole ring with the same substituents as that of the impugned invention. US'505 teaches two terminal substituted phenyl rings. Thus in combination one has the motivation to arrive at the impugned application. Thus a person skilled in the art looking for alternate compounds with high potency to antagonize the androgen activity and which have minimal agonist activity would look into other known antiandrogens as mentioned in US'981 to US'505. Out of the said documents the active of US'505 namely bicalutamide is admittedly known. So the applicant already knew about compound with two phenyl rings at both end and the same being for the same purpose. Hence combining the teachings of US'981 and US'505 one would arrive at the impugned application without ingenuity of thought. It is stated that such structural similarity of the compounds of the prior art provides enough incentive to reach the impugned invention.

- As for the amide substitutions on the phenyl ring, there are many compounds in opposed application which do not have the said substituent and yet are shown to be residing in the TIER 1 Compounds.

So given the teachings of US'981, US'257, US'505 and D1 it was obvious to try with reasonable expectation of success to combine the teachings and arrive at the subject matter of the claim 1.

- It is further stated that the data provided in the specification does not show unexpected properties. It is stated that as mentioned above that in view of the structural similarity with the prior art compounds of US'981 and US'505 or US'981 plus US'257 in view of US'981 it was expected that the compound arrived by such combination would have high potency to antagonize the androgen activity and have minimal

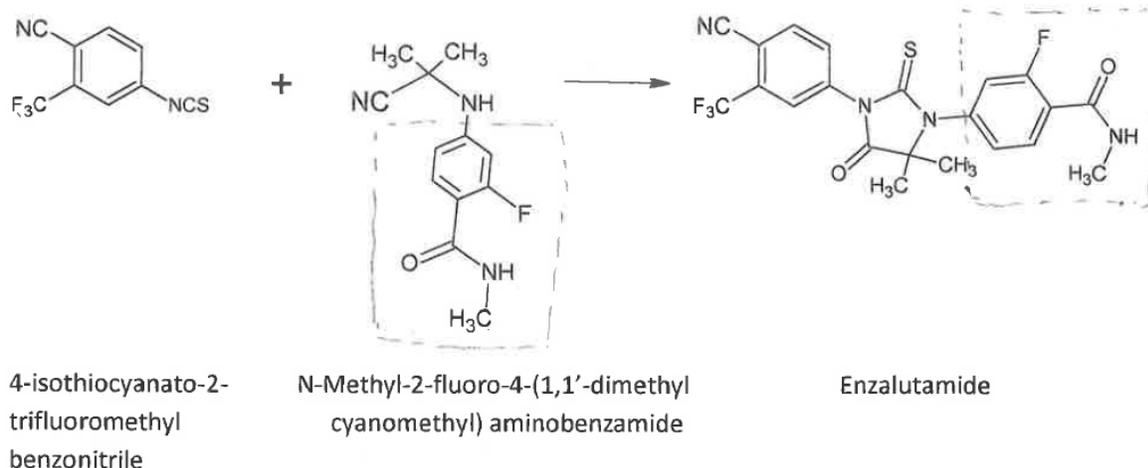
agonist activity. The applicant has at the most verified the result. As mentioned above the applicant was aware of the properties of bicalutamide, the compound of US'505 and tried to find alternate compounds. This is evident as the applicant has mentioned that identification of compound having high potency to antagonize the androgen activity and which have minimal agonist activity was required. So given the teachings of US981 and US'257 as well as US'505 (bicalutamide) in view of D1 it was obvious to try with reasonable expectation of success to combine the teachings and arrive at the compound also having such properties.

The Opponent states that the applicant is merely formulating an alternative compound for the androgen receptor antagonist with no demonstration of enhanced efficacy and therefore is not entitled to a patent and ought to be rejected in toto.

LACK OF INVENTIVE STEP/ Claim 15:

The opponent 1 submitted that the process of claim 15 is obvious to a person skill in the art over US US4097578 (hereinafter referred as US'578).

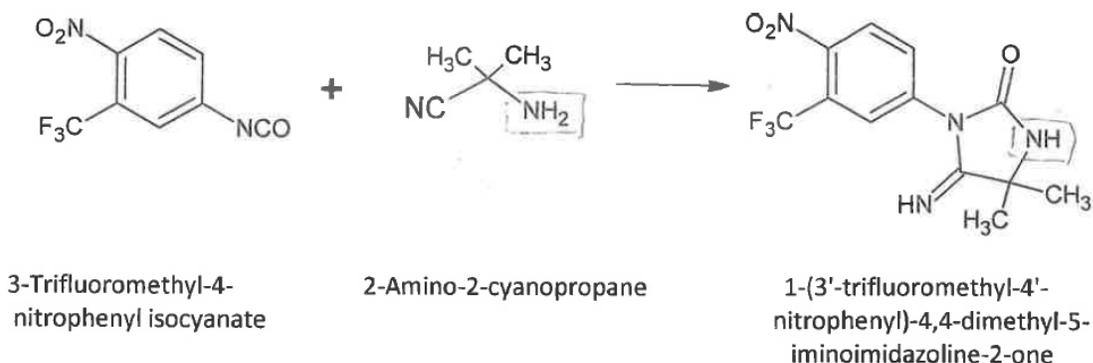
The opponent schematically draws the process of claim 15



As evident from the above scheme that, 2-fluoro-3-aminobenzamide (or FLUORO-N-METHYLBENZAMIDE) moiety does not take part in the reaction and remain intact in the obtained product. Therefore, the alleged claim covers a process to form imidazolidine ring.

The opponent argued that the process of claim 15 is obvious and lacks inventive step in view of D4. D4 discloses, "EXAMPLE 1 1-(3'-trifluoromethyl-4'-nitrophenyl)-4,4-dimethyl-5-iminoimidazoline-2-one

1 ml of triethylamine was added to a mixture of 49.6g of 3-trifluoromethyl-4-nitrophenyl isocyanate in 500 ml of tetrahydrofuran and then 18 g of 2-amino-2-cyanopropane were rapidly added thereto. The mixture was stirred for 72 hours at 20° C and was evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel and was eluted with an 8-2 methylene chloride-acetone mixture to obtain 27 g of 1-(3'-trifluoromethyl-4'-nitrophenyl)-4,4 -dimethyl-5-imino-imidazoline-2-one melting at 168° C." The opponent hereby schematically draws the process of example 1 US'578 as hereinbelow:

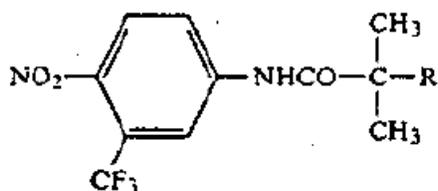


Therefore, it is clear that the formation of imidazolidine ring was already known in the prior art. The applicant has merely replaced the reactants involved in the process. Accordingly, the claimed process of claim 15 is novel but cannot be considered in view of US'578, which explicitly discloses the exact reaction conditions and parameters to form the imidazolidine ring.

7.2) Arguments given by Opponent 2

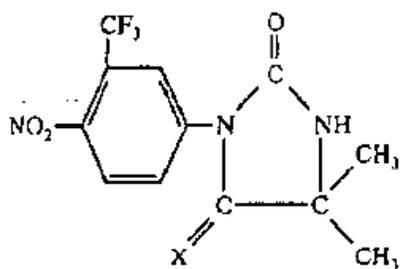
The submission given by opponent 2 is as given below

It is submitted that the claims of the impugned application are obvious in view of what was already known in the art. The Applicant admits in the background of the specification (para 0005) that US 5705654 (hereinafter referred as US'654) discloses diarylhydantoin derivatives with the same basic moiety as the compounds claimed. The use of such compounds in hormone refractory prostate cancer was also known in prior art. For example, US 4636505 (hereinafter referred as US'505), discloses acylanilide derivative having antiandrogenic property. One such compound is disclosed in the background of US'505 which was generically known as Flutamide. The structure of same is represented herein below.



Structure of Flutamide

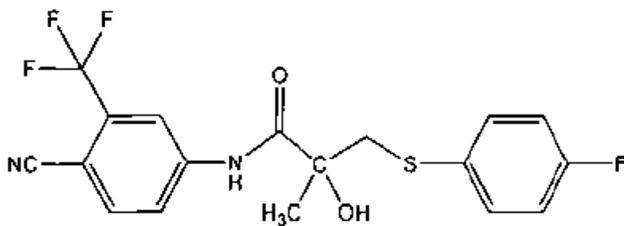
Flutamide has a nitro group substitution at 4-position of phenyl ring. Later, similar compound with hydantoin moiety attached to the phenyl ring was synthesized as disclosed by US4097578 (hereinafter referred as US'578). But such compound resulted in hepatotoxicity. The compound disclosed by US' 578 is represented herein below. This compound is generically known as Nilutamide.



X=Oxygen

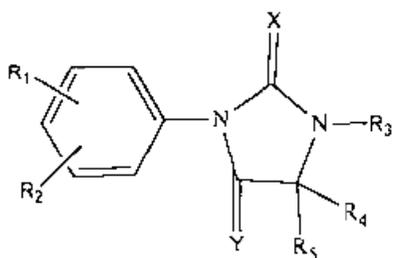
Structure of Nilutamide

In order to solve the problem of hepatotoxicity (as reported in US'505, column 7, line 40-46), the nitro group attached to the 4-position of the phenyl ring was replaced with a cyano group and this led to synthesis of series of compounds known as Bicalutamide derivatives. The same is disclosed in US4636505 (hereinafter referred as US' 505). The compounds disclosed by US'505 are generically represented herein below.



Structure of Bicalutamide derivative

The above compound was also known for antiandrogenic activity. Similarly, US6087509 (hereinafter referred as US'509) published in year 2000 discloses hydroxylated phenylimidazolidines. The structure of such compound is represented herein below.

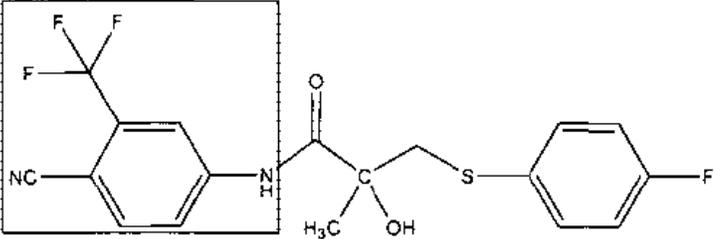
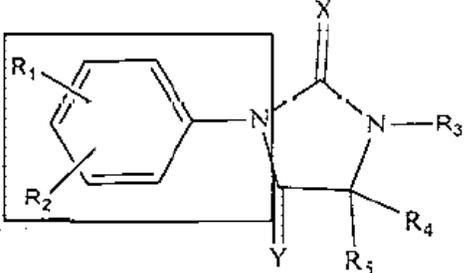
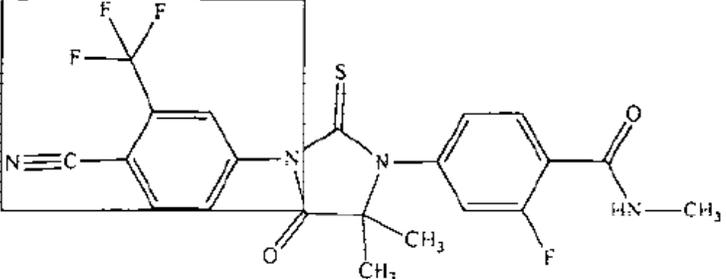


Markush structure of US' 509

The compounds of US 509 are drawn to arylhydantoin compounds. From US'509 it can be seen that in the compounds have a phenyl ring substituted at 4' -position with a cyano group, 3' -position substituted with trifluoromethyl group and 1' -position is attached to a hydantoin ring.

As can be seen from the developments that have occurred in the art, the art has found that aryl hydantoin moiety in the compound confers antiandrogenic effect. The minor toxicity which was observed was removed by replacing the cyano group with phenyl ring. Other compounds/derivatives that have evolved thereafter or developed thereafter have kept and maintained aforesaid aryl hydantoin moiety and made changes to the rest of the compound i.e. modifications were done in the side chain of the hydantoin ring. It is pertinent to note that US'509, which discloses compounds which are similar to enzalutamide maintains the same hydantoin moiety attached to a phenyl ring further substituted by a cyano and a trifluoromethyl group. All these compounds are known for their anti-endrogenic activity.

	<p>Disclosed in background of US4636505 (Flutamide)</p>
	<p>Disclosed in US4097578 (Nilutamide)</p>

 <p style="text-align: center;">Bicalutamide derivative</p>	<p>Disclosed in US4636505 (Bicalutamide Derivative)</p>
	<p>Disclosed in US6087509 (Compounds similar to Enzalutamide)</p>
	<p>Enzalutamide</p>

Thus, it is evident from the progress made in the art that the main anti-androgenic activity lies in this part of the ring. It can be inferred from the above that compounds having a phenyl ring attached to a hydantoin moiety at 1'-position, trifluoromethyl group at 3'-position and a cyano group at 4'-position would be active against androgen receptors. It is submitted that the above position is endorsed by the Applicant in their own patent application. For example; the compounds listed as Tier 1 compounds in Table 5 at Page 102 of Impugned specification all consists of compounds which have a substituted phenyl ring attached to the hydantoin ring as illustrated below:

Compound No.	Structure	IC50 (nM)	
		Reporter	PSA
RD35		147	n/a

RD93		144	158
------	--	-----	-----

Compounds RD35 and RD 93 (both Tier 1 compounds listed in Table 5) of the impugned application share the same structure as they have a common phenyl ring attached to a hydantoin ring, differing only in the substituents attached to the 4' and 5'-position of the hydantoin ring. But the activity exhibited by both the compounds is nearly same with IC50 value of 147 and 144.

The above position that only the hydantoin ring confers antiandrogenic activity is also endorsed by the fact that Tier I compounds of the impugned application all share the same hydantoin ring with difference only in the side chain. It is pertinent to note that the difference in the side chain in case of some compound is vast whereas in case of some compounds is minor and yet the Applicant chooses to group all such compounds under one heading i.e. Tier 1 compounds. Further, compounds RD7 and RD37, which also form part of Tier 1, differ only in a spiro ring and dimethyl group; however, the activity is nearly the same.

All the above illustrations from the prior art and the specification demonstrate that phenyl thiohydantoin compounds were already known and it was a common practice for a person skilled in the art to substitute and add various groups to the side chain.

In the present case, US'505 anyway teaches de-amidified compounds as well as all the substitutions in the side chain. It is pertinent to note that the Markush compounds disclosed by US'505 are fairly limited and therefore, the choice to be made by a person skilled in the art is limited.

It is a settled position of law that in cases where a skilled person has to make limited choices by way of substitution from the prior art, in such cases the compound claim may be deemed to be obvious unless any unobvious effect of the compound claim is demonstrated.

As stated in the foregoing paragraphs, no surprising effect or efficacy of the compound RD 162' has been mentioned or stated or demonstrated anywhere in the specification. Therefore, no unobvious or surprising effect can be read or inferred.

In view of the above, the compound claimed in the impugned application is merely a modification of the compounds already known in the prior art and no inventive step resides in the same.

REJOINDER TO APPLICANT'S ARGUMENTS:

There is no merit or force in the argument of the Applicant that RD162' is the most active compound and that it is inventive, as the prior art does not describe any de-amidified diaryl hydantoin compound.

Nothing is disclosed in the impugned application to show that compound R0162' is inventive. The modifications done in order to arrive at RD162' were taught by the prior art and suggested by US'509 read with US'505 and US'578.

It is pertinent to note that during the rebuttal arguments, the Applicant adverted to example of US' 505 and tried to distinguish the compound of example from the compounds claimed in the impugned application i.e. compound RD162'. However, the Applicant skillfully avoided to comment and rebut the argument of this Opponent whether or not in view of the art already existing, i.e. US'505 read with other prior art, the impugned compound would have been obvious to a person skilled in the art. In view thereof and in view of the prior art, the only conclusion that can emerge is that the invention/compound is obvious to a person skilled in the art.

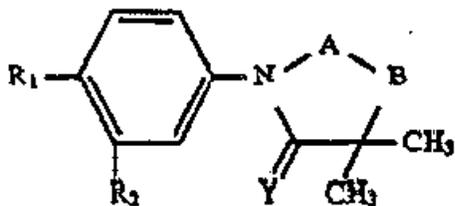
7.3) Arguments given by Opponent 3

Regarding lack of inventive step Opponent 3 has relied on following documents

- a) US5627201 (hereinafter referred to as US'201)

- b) US5434176(hereinafter referred to as US'176)
- c) US5589497 (hereinafter referred to as US'497)
- d) USRE35956(hereinafter referred to as US'956)
- e) US 5656651(hereinafter referred to as US'651)

Opponent 3 argued that documents a-d disclose a compound of the markush structure



Opponent 3 submitted the said compound discloses therein describes various option for substitution, such that, the substitutions as made in the laims of the said patents make the claim1 of said impugned application obvious to person silled in the art. He also submitted that comound of the cited arts have functiona similarity.

Regarding Document US'561 Oponent 3 submitted that the siad document discloses the derivatives of compounds of 4',4'-dimethyi-5'-oxo-2'-thioxo-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile. The compounds claimed in Claim of US'651 merely differ from each other by varying side chains. Therefore, in view of US '651 read along withUS '981, US '201, US '176, US '497 and US '956 the present Claim 1 of the said Impugned Patent Application lacks inventive step.

7.4) Arguments given by Opponent 4: Opponent 4 cited following documents for the discussion on the lack of inventive step

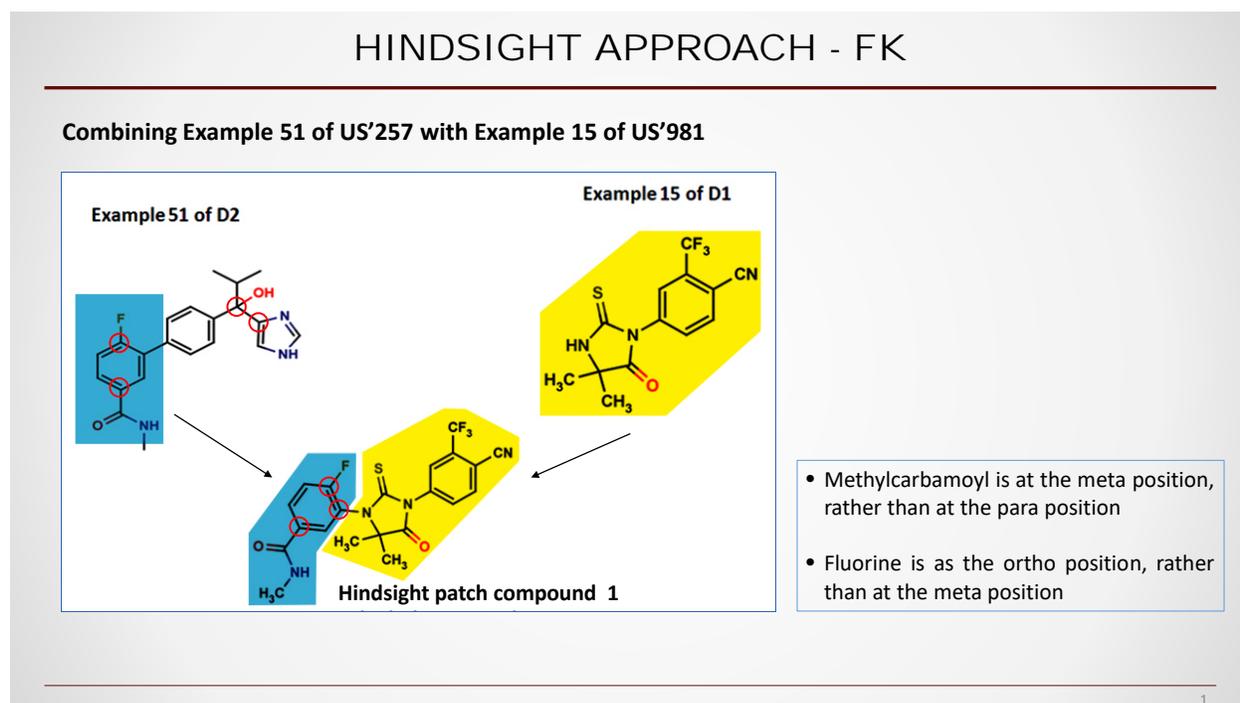
- 1) US 5411981
- 2) US 6087509
- 3) US 5434176,
- 4) US 5750553

Opponent 4 submitted that above mentioned documents disclose compounds of the markush structures and they disclose therein describes various option for substitution, such that, the substitutions as made in the claims of the said patents make the claim1 of said impugned application obvious to person silled in the art.

7.5) Submissions and Arguments Given by the Applicant

In the support of the inventive step the applicant's counsel gave the following arguments.

- I. Opponents fail to provide why a person skilled in the art would select a particular route in the absence of a lead compound. The Opponent have failed to provide a lead compound (a lead compound is a compound having a promising activity / property that would therefore motivate a person skilled in the art to choose it as a starting point and make further points). The lead compound, therefore, cannot be a hypothetical compound, but instead must be a compound which has a promising activity.
- II. None of the cited documents exemplified a compound which would motivate a person skilled in the art (POSA) to make further modification. Opponents have failed to provide any reasoning why a person skilled in the art would make the alleged changes without knowing the structure of Enzalutamide beforehand.
- III. The Opponent have essentially segmented the claimed Enzalutamide compound and then tried to identify prior art documents that disclose each of the moieties through hindsight
- IV. Opponents have tried to cut and paste the prior art compound moieties together like a Jigsaw Puzzle, with no rational guidance provided in the prior art, to allegedly arrive at the compound claimed, Enzalutamide. The applicant also tried to explain by pictorial demonstration how the opponents have tried to chop moieties disclosed in different prior art and combined them to arrive at the claimed Enzalutamide compound



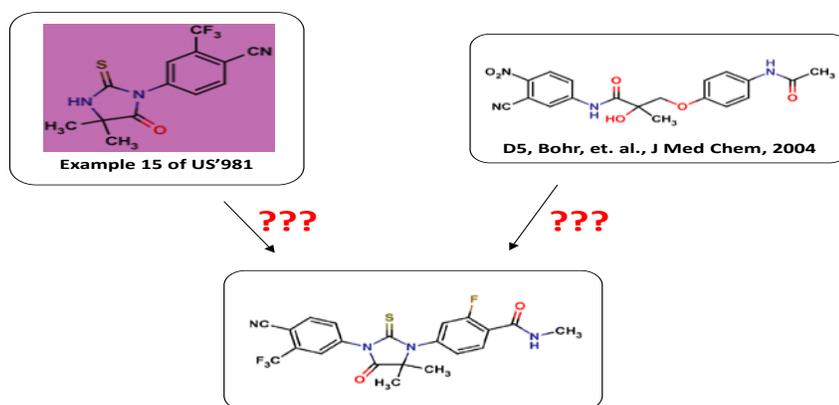
Several other pictorial demonstration were also discussed by the Applicant which were taken into consideration.

The applicant also argued that prior art cited documents are structurally dissimilar and have dissimilar modes of action and also do not provide any guidance for combination with the other documents. And also

The Opponent's suggestions for combination are exclusively based on hindsight.

Regarding Opponent1's citation of US'981 combined additional document D1 the applicant's argued that opponent 1 have taken compound 5 from the document Bohr et al., and have used a hindsight approach to combine it with US'981.

Why POSA would do so many changes in order to arrive at Enzalutamide (KABI)



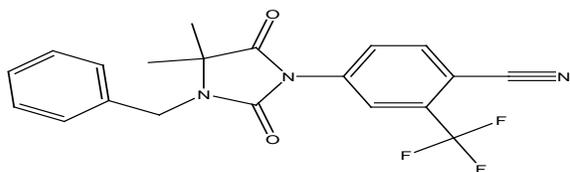
Applicant argued opponent1 has incorrectly equated the acetamido (-NHCOCH₃ in D1) functional group with the methyl carbamoyl (-CONHCH₃ in Enzalutamide) functional group. The teaching of the document D1 is in a direction to make an alternative compound having a bicalutamide core structure wherein the 'SO₂' group is replaced with oxygen 'O' and different substitutions on the phenyl ring are introduced.

8.) Grounds Of Opposition :- Section 25(1)(f)

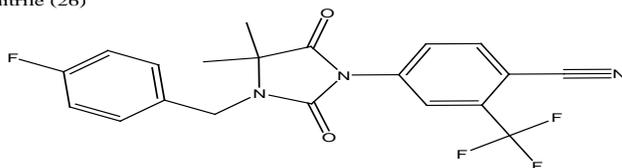
8.1) Not an invention u/s 3(d)

Regarding section 3(d) the opponents 1-4 argued that the compound allegedly claimed in the opposed application is not patentable under Section 3(d) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 as it is a new form of known substances. The compound claimed in the opposed application is derivative of the earlier known compounds disclosed in prior art. Opponents argued that the opposed application has not provided enhancement in the known therapeutic efficacy. The opponent 1

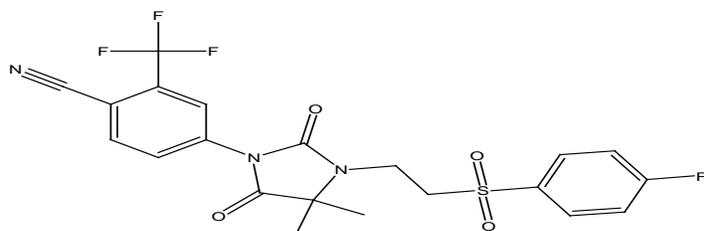
submitted that the applicant fails to provide any comparative data w.r.t the compounds disclosed in US'981. The opponent highlighted that US'981 specifically discloses below compounds which are structurally similar to Enzalutamide. The specific compound similar to Enzalutamide are disclosed in examples 15, 26, 27 and 66 as shown below:



4-(4,4-dimethyl-2,5-dioxo-3-benzyl-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (26)



4-(4,4-dimethyl-2,5-dioxo-3-(4-fluorobenzyl)-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (27)



4-(4,4-dimethyl-2,5-dioxo-3-(2-(4-fluorophenyl sulfonyl) ethyl)-1-imidazolidinyl)-2-trifluoromethyl-benzonitrile (66)

The opponent submitted that the compound of the opposed application is merely a derivative of the known compounds as presented above.

8.2) Applicant's Argument

With regard to section 3(d) Applicant's counsel argued that Enzalutamide is a new chemical entity (NCE) and is not a salt, ester, ether, polymorph, derivative, etc. of a known substance. Therefore, Enzalutamide cannot not be interpreted as the "same substance" in view of the Section 3(d) of the Indian Patent Act.

9) Grounds Of Opposition :- Section 25(1)(f)

9.1) Not an invention u/s 3(e)

Regarding Section 3(e) opponents 1-4 argued that the composition claimed in claims 3-12 of the impugned patent application is a mere admixture of the compound as taught in claims 1 i.e. Enzalutamide as anti-androgens and used in the treatment of hormone refractory prostate cancer without any improvement over

the prior art as evident from the arguments advanced hereinabove. It is stated that there is no demonstrated synergy expected or unexpected provided in the impugned application. Accordingly it is stated that the mere presentation of Enzalutamide with known excipients clearly falls within the mischief of section 3(e) and thus ought to be rejected in view of this section itself.

9.2) Applicants Argument: With regard to section 3(d) Applicant's counsel argued that the claims have been revised and the Applicant has retained a single composition claim as per the practice of the IPO. He also argued that the impugned invention discloses a novel diaryl thiohydantoin compound, Enzalutamide, a new chemical entity, and, therefore, any combinations of Enzalutamide would be new and inventive and cannot be considered as an aggregation of the known properties of the components.

10.1) Grounds Of Opposition :- Section 25(1)(g)

Opponents argued that the complete specification of the alleged invention does not sufficiently and clearly describe the invention or the method by which it is to be performed. The opponent states that it is a well settled rule 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 and it is hereby stated that the applicant has failed to do so. The opponent 2 argued that the specification of impugned application sets out markush structure encompassing several diaryl hydantoin compounds. The patent application provides and lists the IC 50 values as the effect of inhibition of AR hormone refractory profile in respect of various compounds at Table 1 to 3. However no effect of compound RD162' has been provided in any of these table. Table 5 to 11 ranks compounds in the order of their desired pharmacokinetic. In these tables the efficacy of compound RD162' is not illustrated and compared with other compounds including the closest prior art compounds. There is no data in the specification to demonstrate superiority of compound RD162'.

10.2) Applicant's Argument: In response to this applicant submitted that the impugned invention has been sufficiently disclosed in the patent specification in order for a person to work the invention to the fullest extent. So much so that the patent specification provides sufficient working examples, synthetic schemes, and test procedures to determine the biological activity of the disclosed compounds. Enzalutamide (RD162') is specifically disclosed as Example 56 in the complete specification [please see page 80]. Further, the process for the preparation of Enzalutamide is disclosed in the complete specification. Further, it is demonstrated that Enzalutamide is a useful therapeutic agent for the treatment of

Castration-Resistant Prostate Cancer (CRPC). In-vitro efficacy data for Enzalutamide has been provided in the specification, and in-vivo efficacy data for Enzalutamide has been provided in the clinical trials.

11.1) Grounds Of Opposition :- Section 25(1)(h)

It is submitted that the applicant has filed several overseas applications in respect of the invention claimed in the impugned patent application. The details with respect to all the foreign applications in respect of the same/substantially same invention were not disclosed completely in accordance with the requirement of the Section 8(1) and (2) of the Act.

11.2) Arguments given By Applicant: In response to section 8 the applicants counsel argued that the Opponent have not made out a case on Section 8 and does not plead and prove as to how the ground of Section 8 is not met or details of which same or substantially the same invention have not been presented and why any such invention may be considered the same or substantially the same. The ground should therefore be dismissed in-limine based on the decision of IPAB in Glaxo Vs. Fresenius Kabi. It is respectfully submitted that the Applicant has disclosed to the Learned Controller the information related to the corresponding foreign patent applications vide letters dated 13th December 2007, 24th June 2008, 27th April 2009 and 23rd Jan 2014.

Further, the Applicant has complied with the Section 8(2) requirement vide letter dated 16th Aug 2013, within time specified, i.e., six months from the issuance of the FER.

Further Section 8(2) details were also filed on the following occasions:

- a) 10-Jan-2014;
- b) 23-Jan-2014;
- c) 11-Feb-2014;
- d) 23-Jun-2015; and
- e) 26-Jun-2015.

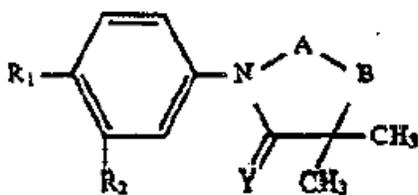
As corresponding applications have been filed in several jurisdictions, the details of which have been provided on the statement and undertaking on Form 3 filed with the Indian Patent Office on various occasions, should the Learned Controller require search or examination reports, including allowed claims issued in any other jurisdictions, the Applicant may be advised of the same.

12) Discussions On Grounds of Opposition:-

Before starting the discussion on the grounds opposition it is to be stated that all the submissions and facts given by the opponents and applicants were taken into the Consideration. It is also to be stated that no representation from the side of Opponent 4 on the date of was made, however pleadings filed by IPA on 12/01/2016 were also taken in the consideration.

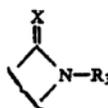
12.1) Grounds Of Opposition :- Section 25(1)(b)

Opponent 1, Opponent 2, Opponent 3 and Opponent 4 cited Document US'981 for the lack of novelty of the impugned application. The said documents discloses a compound of the formula

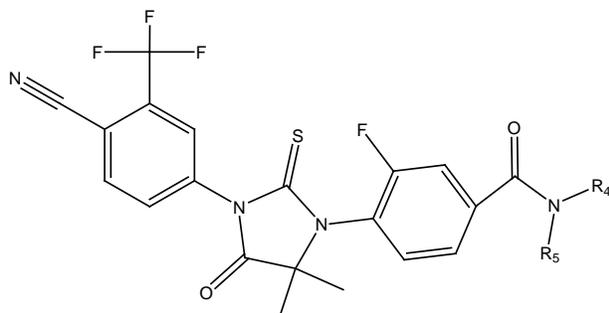


Alongwith the above formula the said document also discloses options for substitutions. The opponents

argued that if we put R₁=CN, R₂=CF₃, Y=O and -A-B- =



R₃=F a compound of the formula below will be formed



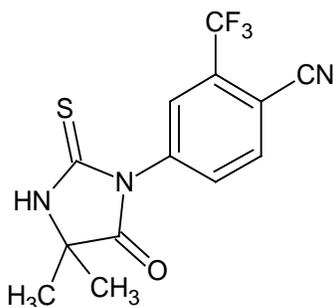
Again if take R₄ and R₅ as discussed in US'981 a compound identical to Enzalutamide would be formed

Opponent 2 cited **US509** for the lack of novelty for the impugned application. The said prior discloses a family of compounds phenyl, phenylimidazolidines represented by a Markush structure which have anti-androgenic activity useful against tumors. Upon making relevant substitutions in the Markush structure as explained above the compound claimed Enzalutamide in impugned application can be arrived. Similar approaches have been taken by the other opponents to explain that the prior art documents disclose the claimed compound Enzalutamide in the impugned application.

It is observed that none of the above cited documents specifically discloses the structure of the compound as claimed in impugned application in either in claim or on example. The claimed compound can only be arrived by suitably substitutions of Different R groups and X,Y, A, B etc. It is my opinion for lacking of the novelty the citing documents should explicitly disclose the claimed compound. But here in this none of cited document discloses Enzalutamide. Rather a person has to pick some suitable substituents from the definition given in markush structure as given in prior art and suitably put them to arrive at the structure of the Enzalutamide. This type of picking and putting is not allowable to ascertain the Novelty of the claimed invention. **In view of above discussion it is found that the claimed compound is novel and not anticipated in view of cited prior art documents**

12.2) Grounds Of Opposition :- Section 25(1)(e)

a) **US' 981 in view of D1:US'981** discloses a compound of example 15 which is represented herein below



US'981 provides data that shows that the compound of example 15 have anti-androgenic activity and is devoid of agonist activity

The difference between the compound of example 15 and Enzalutamide is FLUORO-N-METHYLBENZAMIDE at 1st Nitrogen of thiohydantoin moiety. This moiety is generally disclosed under group R3.

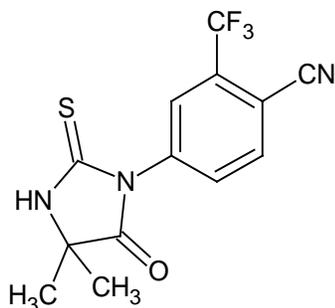
Further D1 suggests that aryl ring substituted with moderately sized groups such as acetamido is required at this position to improve the binding affinity of the compounds for androgen receptors. Therefore, selection of fluoro-N-methylbenzamide is obvious over US'981 in view of D1. Although D1 does not talk about methylcarbamoyl group instead it suggested acetamido group which is different than the methylcarbamoyl group. But D1 at first place suggests that, only a moderately sized group can be accommodated specifically at para position. Further, D1 suggests that groups such as acetamido (molecular formula C₂H₄NO) can be favored. Therefore, in view of teachings of D1 the applicant has selected aryl ring substituted with methylcarbamoyl specifically at para-position.

With regard to fluoro substitution at ortho position to the methylcarbamoyl group, it is to be specified that US'98 clearly suggests that aryl is further substituted by halogen (see column 03, lines 05-09 of US'981).

Further D1 suggests that *"Bulky para substituents and moderately sized meta and ortho substituents, however, would result in unfavorable steric interaction according to the model"* (see page 3772, right hand column, third par, last four lines).

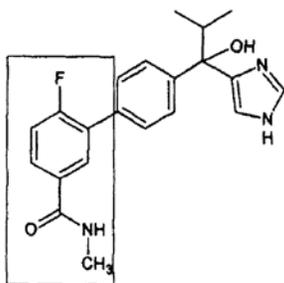
Therefore, D1 clearly mentions that even moderately sized groups are not favoured at ortho and meta position of the aryl ring. Therefore, the only option is halogens out of the disclosure given in D1 at this position. Further the applicant is failed to show in the instant application that fluoro substitution has any effect on the activity as there is no difference in activity of RD153 and compound which has doesn't have fluoro substitution at this position and Enzalutamide.

b) **US'981 in view of US'257 in combination with D1:** The documents D1 discloses a compound of the structure in example 15 as shown below



If we look at the above mentioned structure it is obvious that "FLUORO-N-METHYLBENZAMIDE" moiety is required at 1st N of thiohydantoin moiety to arrive at the structure of Enzalutamide.

As mentioned above, D1 teaches that, aryl ring substituted with moderately sized groups such as acetamido is required to improve the binding affinity of the compounds for androgen receptors (see page 3773, left hand column, first para). Now if we look at the US'257 in column 49 line 30-6, it describes a compound of the formula as shown below.



The FLUORO-N-METHYLBENZAMIDE moiety as shown in the rectangle is clearly taught in US'257. As discussed earlier taking in view of teachings of D1 a person skilled in the art will think of replacing the moiety shown in rectangle of US'257 compound with hydrogen attached to N of hydantoin moiety of the compound 15 of US'981.

In view of above it is stated that claimed invention is lacking inventive step with reference to Document US'981 in combination with D1 AND US'981, US'257 in combination with D1.

c) Grounds Of Opposition:- Section 25(1)(e) (Claim 3 Process Claim):

US'578 discloses a process for preparing 1-(3'-trifluoromethyl-4'-nitrophenyl)-4,4-dimethyl-5-iminoimidazoline-2-one. If we look at the schematic representation for the preparation of above said compound it can be seen that the formation of imidazolidine ring was already known in the art. Further FLUORO-N-METHYLBENZAMIDE doesn't take part in the reaction. **Therefore claimed invention in claim 3 cannot be said to be inventive in view of US'578.**

12.3) Grounds Of Opposition :- Section 25(1)(f)

12.3.1) **Not an Invention u/s 3(d):** From the aforementioned it is clear that the claimed compound Enzalutamide is lacking novelty and inventive step. Therefore the applicant's claim that the said compound is a new chemical entity is not acceptable. Further applicant fails to demonstrate any unexpected improvement in efficacy. Therefore claim 1 is not patentable under section 3(d)

12.3.2) Not an Invention u/s 3(e): Claim 2 is about a pharmaceutical composition containing ...As discussed earlier that Enzulatamide compound used as ingredient used in the composition is not inventive compound. Use of pharmaceutical acceptable carrier or diluents for making a composition is well known in the art. The applicants in the impugned invention fails to show any surprising synergistic effect when the said compound is used as a composition. **Therefore opponent's objection regarding section 3(e) of Patent Act is found to be acceptable.**

13) Lack of Sufficiency 25(1) (g): The impugned invention has been sufficiently disclosed in the patent application. Enzalutamide (RD 162') is specifically disclosed as Example 56 in the complete specification and its process for preparation is also disclosed. In-vivo data for Enzulatamide has been given in the specification and also in-vivo data has been provided in clinical trials. Therefore it can be concluded that specification fully and sufficiently describes the claimed invention. Therefore ground of opposition for lack of sufficiency is refused.

14) Section 8 Compliance Section 25(1)(h):- As stated by applicant the requirement of Section 8(1) and 8(2) was complied on different dates by filing the information about filing detail in other jurisdiction. **In view of this the ground of opposition of section 8 is dismissed.**

15) Discussion on the grounds of opposition by Opponent 5:-

15.1) Section 25(1)(h):-The Opponent submitted that the equivalent PCT Publication bearing No. WO2006/124118 from which the impugned National Phase patent application has been derived recites 51 claims. The Opponent averred while entering the National Phase in India on December 13, 2007, the Applicants were statutorily bound (under Section 10(4A) read with Section 7(1A), Section 138 (4), Rule 20 and Rule 22 of the Act) to file title, description, drawings, abstract and claims (51 claims) filed with original International application (PCT application) to be considered as complete specification in India. However, while entering the National Phase in India on December 13, 2007, the Applicant filed Form 13 which merely mentions that the claims were amended by way of correction and explanation when the fact is that five (5) claims were clearly deleted from corresponding PCT patent application which originally recited 51 claims. The PCT application, on date, recites 51 claims with no amendment with respect to deletion of 5 claims. Hence the Applicant has clearly and intentionally furnished the information (with respect to equivalent / corresponding international / PCT application) which in material particular was false to his knowledge.

The Opponent submitted that the Applicant was duty bound to pay fees (under **Section 142 read with Rules 7, 20 and 22 of the Act**) for all 51 claims originally filed through PCT as on the date of filing or within prescribed time of 31 months from the priority date but the Applicant paid fees for only 46 claims thereby making the Ld. Controller believe that the original PCT application was filed with only 46 claims and not with 51 claims. Hence by paying insufficient/erroneous fees, the Applicant has intentionally furnished the information (erroneous filing of 46 claims instead of 51 claims recited in the equivalent/corresponding PCT application) which was in material particular false to his knowledge. PCT application was never amended under Article 19 or Article 34 of the Treaty for deleting 5 claims from the said application. As on date, PCT application recites 51 claims only.

The Applicant has failed to pay prescribed fees (for entire 51 claims) within prescribed time (31 months from the priority date) required under Rule 20 of the Act. Difference in fees was paid by the Applicant on February 11, 2014 which is far beyond 31 months from the priority date (May 13, 2005). Hence the National Phase Patent Application No.9668/DELNP/2007 ought to be considered not having been filed or withdrawn under Section 142 read with Rules 7, 20 and 22 of the Act.

The opponent further argued that not only false information was provided by the Applicant but also the application is deemed to not have been filed or withdrawn under Section 142 read with Rules 7, 20 and 22 of the Act.

As such, the impugned National Phase Patent Application No. 9668/DELNP/2007 is not valid and does not subsist at all. Hence the impugned National Phase patent application No.9668/DELNP/2007 is opposed under Section 25(1)(h) for furnishing false information and is clearly liable to be rejected under this ground alone.

15.2) Section 25(i):-The Opponent submitted the fact that the National Phase patent application has the same status as that of convention application in India, as accorded under the Patents Act, 1970 since all the sections, rules and regulations prescribed under the Patents Act, 1970 and Patents Rules 2003 for prosecuting convention applications filed in India are equally applicable to National Phase Applications entered in India through PCT. Section 25(1)(i) clearly makes ineligible for grant of patent in case of convention application, if the application is not filed within prescribed time (twelve months from the date of the first application) for protection for the invention made in a convention country by the applicant.

The opponent referred Section 138 of the Act which provides supplementary provisions specifically for convention applications only, however, sub-section 138, viz., Section 138(4) provides mandatory provision

for national phase applications derived from corresponding international (PCT) application also. Opponent argued that the provisions applicable for convention applications are also applicable for national phase applications derived from corresponding PCT applications. The opponent stated that Section 25(1)(i) is a valid ground for opposing the present impugned National Phase Patent Application No. 9668/DELNP/2007 being considered to be not filed within prescribed time of 31 months from the priority date or deemed to be withdrawn as the prescribed national fees were not paid alongwith the documents on the date of filing the said application or within prescribed time (31 months from the date of priority) as mandated under Section 142 read with Rules 7, 20 and 22 of the Patents Act, 1970.

The opponent argued that in view of the similar status of National Phase Application and convention application in India as accorded under the Patents Act, 1970, the impugned National Phase Application is opposed and is clearly liable to be rejected under Section 25(1)(i) of the Patents Act, 1970.

16) Arguments Given By Applicant in Response to Opponent 5

16.1) Section 25(1)(h):- The Applicant's Counsel that the ground provided under section 25(1)(h) is with regard to Section 8 and can be invoked if the Applicant failed to disclose to the Controller the information required under Section 8 or has furnished the information in respect of Section 8 which in any material particular was false to his knowledge. But here in this case the Opponent's averments are not in relation to Section 8 but with regard to insufficient fees, which is not the ground available for pre-grant opposition. He further argued that In fact the Learned Controller was aware of less claims being filed at the time of national phase entry and less fees being paid and therefore raised an objection to pay the insufficient fees in the first examination report. The question of concealment or providing false information therefore, does not arise.

16.2) Section 25(i):-In this regard it applicant's counsel argued that section 25(1)(i) is invoked when a convention application is not filed within 12 months. The PCT application in present case was filed within 12 months from priority, hence is a proper convention application. Applicant further argued that the Indian national phase application was also filed within 31 months from the date of earliest priority along with 46 claims. 5 claims were deleted as they related to method of treatment. The fees paid were also for 46 claims. By way of abundant caution, the applicant also filed a request for amendment on form-13, even when the claims were only being deleted.

17) Discussion Opposition grounds of Opponent and Applicant's argument

17.1) Grounds Of Opposition: - Section 25(1)(h)

The opponent 5 argued that National Phase application of the impugned invention was filed with reduced no of claims (no claims 46) with respect to corresponding Patent application (no of claims 51). While entering as the national phase application less fee for 5 claims were paid. In this regard opponent 5 argued that by not paying the fee for 51 claim and deleting 5 claim applicant has suppressed the fact that application in PCT was filed with originally with 51 claims. But it is to be noted that while entering in the national phase the applicant has given the corresponding PCT application no. Also the applicant has filed Form-13 for the amendment of claims. With the given PCT number the number of claims in international phase can be seen also by the filing of Form-13 the applicant has shown his intention that he his deleting claims in national phase. The ground for opposition under section 25(1)(h) by opponent 5 is not acceptable.

17.2) Grounds Of Opposition :- Section 25(1)(i)

In this regard the opponent argued that at the time of entering in national phase in India the applicant has not paid the entire fee accompanying the document i.e. fee of 51 claims, as per the rule 7 (2)(c). Therefore as per section 142 (3) of the Patent Act the impugned patent application is deemed not to have been filed or withdrawn. But in my opinion at the time of entering in to the national phase the applicant may delete the claims. In this regard reliance on honorable IPAB decision 17 of 2013 submitted by applicant, is made which say:-

*"Therefore the Controller ought to have stated that the fees paid is adequate only for 17 claims and **afford an opportunity to the applicant to delete, remaining 3 claims** if he so desires, as the fees paid by him within the time prescribed under the Act was adequate only for 17 claims. 9. The learned counsel clearly affirmed that the appellants are willing to delete 3 claims and will be satisfied if the application is considered along with only 17 claims. This statement is recorded. In these circumstances, we are not going in to issue whether the Controller should have given the appellant 1 month time under Rule 138. 10. In the European Union where the application is held to be not in order purely on the ground of insufficient fees 1 month time is given, when it was necessary the IPAB may consider that issue but in the circumstance of this case we do not think, it is necessary for us to do so."*

Therefore the applicant claims which an applicant does not want to pursue can be deleted at the time of national phase entry. Moreover as per the amendment Rules 2006 and new rule 20(1) the patent application may be filed by deleting the claims from the claims filed in PCT application. The ground for opposition under section 25(1)(i) by opponent 5 is not acceptable.

18) Conclusion: - from the aforementioned discussion following conclusion is made-

- 1) The claimed compound is novel and not anticipated in view of cited prior art documents.
- 2) The complete specification fully and sufficiently defines the claimed invention.
- 3) Grounds of Oppositions under section 25(1)(h) and 25(1)(i) raised by Opponent 5 is not acceptable.
- 3) Requirement of section 8 has been complied by the Applicant.
- 4) Claimed invention is lacking inventive step with reference to US'981 in combination with D1 AND US'981, US'257 in combination with D1.
- 5) Claimed invention falls under section 3(d) and 3(e) of the Patents Act

In view of above instant application is hereby refused as the claimed invention is lacking inventive step under section 2(1)(ja) and also not patentable under section 3(d) and 3(e). No cost is imposed on either party.

Dated 08/11/2016

Umesh Ch Pandey
(Asst. Cont. Patents & Designs)

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We Claim:

1. A compound having the formula



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or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, for treatment of a hyperproliferative disorder.
3. A pharmaceutical composition comprising a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.
4. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.001 mg per kg body weight per day to about 100 mg per kg body weight per day for treatment of a hyperproliferative disorder.
5. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.01 mg per kg body weight per day to about 100 mg per kg body weight per day for treatment of a hyperproliferative disorder.
6. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of from about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day for treatment of a hyperproliferative disorder.

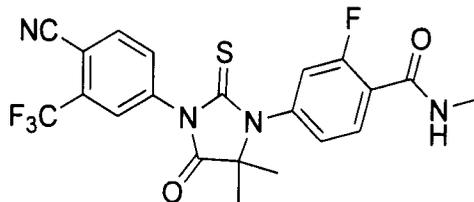
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7. A pharmaceutical composition as claimed in claim 3, wherein said compound is in an amount equivalent to a dosage amount of about 1 mg per kg body weight per day for treatment of a hyperproliferative disorder.
8. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is prostate cancer.
9. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is hormone refractory prostate cancer.
10. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is hormone sensitive prostate cancer.
11. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is breast cancer.
12. The pharmaceutical composition as claimed in any one of claims 2, 4, 5, 6, and 7, wherein the hyperproliferative disorder is ovarian cancer.
13. The pharmaceutical composition as claimed in claim 3, wherein the compound is in a form that can be administered as an intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally.
14. The pharmaceutical composition as claimed in claim 3, wherein the composition has a form selected from the group consisting of a solution, dispersion, suspension, powder, capsule, tablet, pill, time release capsule, time release tablet, and time release pill.
15. A method of synthesizing the compound comprising:

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mixing N-Methyl-2-fluoro-4-(1,1-dimethyl-cyanomethyl)-aminobenzamide and 4-Isothiocyanto-2-trifluoromethylbenzonitrile in DMF and heating to form a first mixture;

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

refluxing the second mixture; and

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

isolating the compound from the organic layer.

Dated this 13th day of December, 2007

Archana Shanker
Of Anand and Anand Advocates
Agent for the Applicant