237678

FORM 7A
THE PATENTS ACT, 1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[see section 25 (1) & rule 55]

1. State names, address and nationality.	I, **Dr. G. Subrahmanyam,** hereby give representation by way of opposition to the grant of patent in respect of application no **854/DELNP/2010** dated **February 08, 2010** made by **Bristol-Myers Squibb Company** and published on **August 13, 2010.**
2. State the grounds taken on after another.	On the grounds **U/S 25 (1) (e), U/S 25 (1) (f), U/S 25 (1) (g) & U/S 25 (1) (h) of The Patents Act, 1970.**
3. Complete address including postal index number/code and state along Telephone and fax number.	My/our address for service in India is with **Dr. G. Subrahmanyam, Kukatpally, Hyderabad, Telangana State, PIN: 500072.**
4. To be signed by the opponent or by his/her authorized registered patent agent.	

5. Name and designation of the natural person who has signed.

Dated this 19th day of November 2015.

G. Subrahmanyam

(Dr. G. Subrahmanyam)

To
The Controller of Patents,
The Patent Office,
Delhi

BEFORE THE CONTROLLER OF PATENTS

DELHI

In the matter of section 25(1) of The Patents Act, 1970 as amended by The Patents (Amendment) Act 2005,

-And-

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

-And-

IN THE MATTER of Patent Application 854/DELNP/2010 dated February 08, 2010 assigned to **Bristol-Myers Squibb Company**, having office at Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, USA.

....APPLICANT

-And-

IN THE MATTER of pre- grant opposition by **Dr. G. Subrahmanyam,** residing in Hyderabad, Telangana State, India.

.....OPPONENT

REPRESENTATION UNDER SECTION 25(1)

I, **G. SUBRAHMANYAM**, residing in Hyderabad, Telangana State, India (hereinafter referred as "opponent') made the following representation under section 25 (1) of the Act in opposing the grant of patent on the application indicated in the cause title.

1 **Locus Standi:**

Locus standi is not a condition precedent for an opposition under Section 25 (1).

2 **Grounds of Opposition**

The application is opposed on the following grounds:

a. **U/S 25 (1) (e):** that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim;

b. **U/S 25 (1) (f):** that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act;

c. **U/S 25 (1) (g):** that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

d. **U/S 25 (1) (h):** that the applicant has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge.

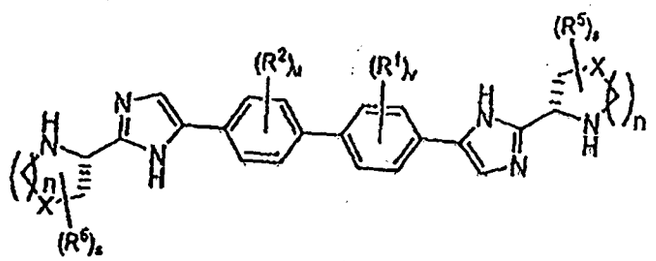
3 **Applicant's Claims:**

3.1 Patent Application No. 854/DELNP/2010 (Hereinafter called as 'impugned patent application) entitled "Process for synthesizing compounds useful for treating hepatitis C" dated February 08, 2010. It is published under section 11A in the Official Journal of Indian Patent Office dated August 13, 2010. There is no notification of grant of patent on this application and it is presumed that a patent has not yet been granted and thus the present pre-grant representation made by the Opponent. The impugned patent application claims a priority of USA dated August 08, 2007, Priority document No: 60/954,595. The

impugned patent application has been nationalized from International Application No: PCT/US08/071696 dated July 31, 2008; International Publication No: WO 2009/020825.

3.2 Applicant filed **amended claims** to the impugned patent application on August 08, 2015 and those claims consists total of 11 claims including 1 independent and remaining are dependent. The complete specification of IN 854/DELNP/2010 is annexed here to as "Annexure A" for ready reference and those amended claims are as follows:

Amended claim 1: A process for preparing a compound of formula (7) or a pharmaceutically acceptable salt thereof;



(7);

wherein,

n is 0, 1, or 2;

s is 0, 1, 2, 3, or 4;

u and v are each independently selected from 0, 1, 2, or 3;

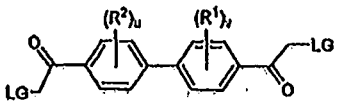
X is selected from O, S, S(O), SO_2, CH_2, CHR^5, and $C(R^5)_2$;

provided that when n is 0, X is selected from CH_2, CHR^5, and $C(R^5)_2$;

R^1 and R^2 are each independently selected from alkoxy, alkyl, and halo; and when s is 2, 3, or 4, each R^5 on the ring is independently selected from alkoxy, alkyl, and aryl, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

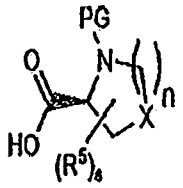
provided that the two heterocyclic rings substituting the imidazole rings are identical; the process comprising:

a) reacting a compound of formula (3)



(3);

wherein
u, v, R^1, and R^2 are as described for formula (7); and
LG is a leaving group;
with a compound of formula (4)



wherein, PG is a nitrogen protecting group;

b) treating the product of step (a) with a reagent selected from ammonium acetate, ammonium formate, ammonium sulfamate, ammonium phosphate, ammonium citrate, ammonium carbamate, and ammonia; and
c) treating the product of step-(b) with a deprotecting agent.

Amended claim 2: The process as claimed in claim 1 wherein

n is 1;
s is 0;
u and v are each 0; and
X is CH_2.

Amended Claim 3: The process as claimed in claim 1 wherein LG is halide.

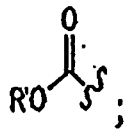
Amended Claim 4: The process as claimed in claim 3 wherein the halide is a bromide.

Amended Claim 5: The process as claimed in claim 1 wherein step (a) is conducted with a base.

Amended Claim 6: The process as claimed in claim 5 wherein the base is diisopropylethylamine.

Amended Claim 7: The process as claimed in claim 1 wherein the reagent used in step (b) is ammonium acetate.

Amended Claim 8: The process as claimed in claim 1 wherein PG is represented by the formula;



wherein

~~~ denotes the point of attachment to the parent molecular moiety; and R' is selected from alkyl, aryl, and arylalkyl.

Amended Claim 9: The process as claimed in claim 8 wherein PG is tert-butoxycarbonyl.

Amended Claim 10: The process as claimed in claim 9 wherein the deprotecting agent of step (c) is an acid.

Amended Claim 11: The process as claimed in claim 10 wherein the acid is hydrochloric acid.

4. **Documents relied on in the present opposition representation:**

D1. US provisional application number 60/836,996, filed on Aug 11, 2006 (US 20080050336)

D2. Tetrahedron, 46(2), 565-76; 1990

5.0 Obviousness/ lack of inventive step–section 25 (1) (e):

Claim 1 of impugned application lacks inventive step and it is obvious over D1. D1 reported a process for the preparation of the compound of formula (8) which is same as the compound of formula (7) in the impugned patent application.

In Scheme-4 of D1, the dibromo intermediate compound of formula 20 is aminated to produce diamino compound of formula 21. The diamino compound of formula 21 is condensed with appropriate amino acid to produce the compound of formula 22. The compound of formula 22 is reacted with ammonium acetate to produce cyclized compound of formula 3 (which is same as the compound of formula 6 in the impugned patent application). Finally, the compound of formula 3 is deprotected using HCl or TFA to produce the compound of formula 8 (which is same as the compound of formula 7 in impugned patent application).

The difference between the prior art D1 and claim 1 of impugned process lies only in the use of diamino compound (21), except 21, the remaining reaction sequences, amino acids, bases (used in condensation), ammonium acetate (cyclization) and acid (deprotection) are similar to the claim 1 of impugned process.
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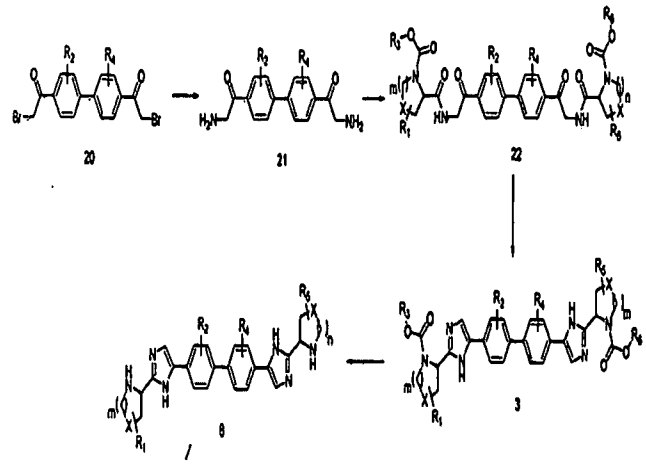
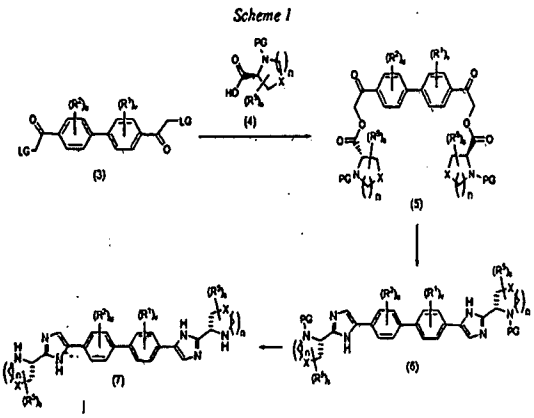
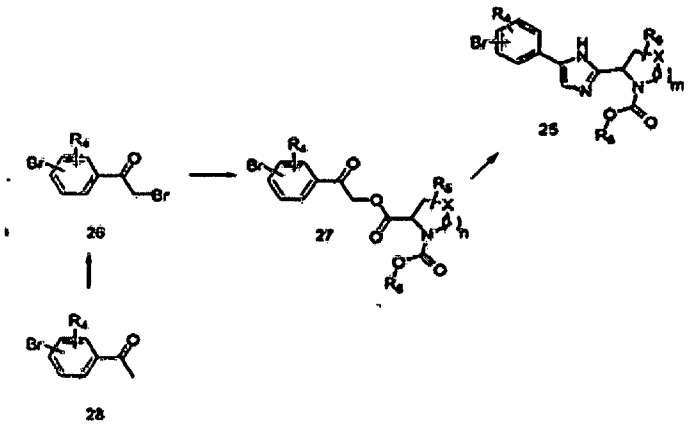
Moreover, D1 also teaches and motivates the person in the art (Scheme-5) to prepare the appropriate imidazole compounds from bromo starting intermediate i.e. the bromo intermediate of formula (26) is condensed with appropriate amino acid (protected) in presence of a base to produce the keto ester of the compound of formula (27) which is reacted with ammonium acetate under thermal condition to provide the appropriate imidazole compound.

The comparative table b/w amended claim 1 and process disclosed in D1 is as follows:

Process disclosed in D1	Claim 1 of impugned application
 Scheme 4: Symmetric Biphenyls Symmetric biphenyl analogs 7 ($R_1 = R_5$; $R_7 = R_8$; m = n) can be synthesized starting from bromoketone 20. Amination by displacement with a nucleophile such as azide, phthalimide or preferably sodium diformylamide (Yinglin and Hongwen, Synthesis, (1990), page 122) followed by deprotection affords 21. Condensation under standard amination conditions such as HATU and Hunig's base with an appropriately protected amino acid provides 22. Heating with ammonium acetate under thermal or microwave conditions results in the formation of 3 which can be deprotected with strong acid such as HCl or trifluoroacetic acid ($R_3 = R_6$ = t-Bu) or by hydrogenolysis with hydrogen gas and a transition metal catalyst such as Pd / C ($R_3 = R_6$ = benzyl). Acylation can be affected with a carboxylic acid ($R_7CO_2H = R_8CO_2H$) in a similar manner to the conversion of 21 to 22. Urea formation can be accomplished by treatment with an appropriate isocycante ($R_7 = R_8 = R_{28}R_{29}N$; R_{29} =H) or carbamoyl chloride ($R_7 = R_8 = R_{28}R_{29}N$; R_{29} is notH). D1 also discloses an alternate method for the preparation of imidazole compound as follows:	 ➢ The compound of **formula (3)** is **reacted with the compound of formula (4)** in presence of a **base** (triethylamine or diisopropylethylamine (Hunig base) **(Condensation)**; ➢ **The compound of formula (5) is reacted with** a reagent selected from **ammonium acetate (cyclization) ....** etc. ➢ The compound of formula (6) is deprotected using acid (HCl) **(deprotection)**

(Scheme-5)



Intermediate 25 is prepared from keto ester 27 via heating with **ammonium acetate (Cyclization)** under thermal or microwave conditions. **Bromide 26 can also be converted to 27 by reacting with an appropriate cyclic or** acyclic **N-protected amino acid in the presence of base (Condensation)** such as K_2CO_3 or $NaHCO_3$.

D2 discloses in its page 574 that:

General procedure for a two step synthesis of N-t-Boc, O-phenacyl esters of proline and secondary aminoacids. N-t-Boc proline phenacyl ester:

N-t-Boc-proline was firstly synthesized as previously reported using t-butyl S-4,6-dimethyl pyrimid-2-yl thiocarbonate[10]. Subsequently, N-t-Boc-proline (0.215 g, 1 mmol) was added to a solution of triethylamine (0.101 g, 1 mmol) in ethyl acetate (10 ml). Phenacyl bromide (0.199 g, 1 mmol) was then added and the mixture was stirred at room temperature for 24 h. The reaction mixture was then treated with a solution of 5% sodium bicarbonate (10 ml) followed by extraction with ethyl acetate (2X20 ml). The ethyl acetate was washed with water (3X10 ml)and dried over anhydrous sodium sulfate; the solvent was removed in vacuo. The crude N-t-Boc-proline phenacyl derivative was obtained in semi-crystallized form. Recrystallization from ethyl acetate/pet.ether (8:2) afforded 0.305 g (91%); m.p. = 80 -82°C; $[a]_D^{25}$ = -93.73 (C1, $CHCl_3$).

Although, D2 explicitly not described about further conversion of N-*t*-Boc-proline phenacyl derivative to required imidazolyl compound, but motivates the person in the art to adopt this technology in the preparation of compound of formula 7 through Scheme-4 (Symmetric Biphenyls) of D1 by not using diamino intermediate.

2(1)(ja) of the Indian Patent Act 1970 states that *"**inventive step**" means a **feature of an invention that involves technical advance as compared to the existing knowledge** or having economic significance or both and that makes the invention not obvious to a person skilled in the art.*

From the above comparison table and page 574 of D2, it is clear that D1 and D2 teaches and motivates the person in the art to reaction of phenacyl bromo intermediate with appropriate amino acid (protected) in presence of a base will yield the keto ester which is further reaction with ammonium reagent to provide the required imidazole compound followed by amino deprotection using acid.

Claim 1 of impugned application is obvious and lack of inventive step in the light of common general knowledge, taken with D1 and D2.

D1 a standard reference work in the chemical arts, teaches that the bromo intermediates are reacted with N-protected L-proline to provide the keto ester which is further reacted with ammonium acetate to produce imidazolyl compound followed by amino deprotection using acid are well-known in the art as protection for amino groups, in particular BOC. One of ordinary skill in that art at the time of the invention would have immediately recognized that the imidazolyl compound could be generated by a simple condensation in presence of a base followed by reaction with ammonium acetate and acid hydrolysis.

In view of the above motivations / teachings from D1 and D2, one skilled in the art would have been motivated to utilize the process as disclosed in D1 to arrive at the impugned claimed process. Therefore, the impugned claimed invention would have been obvious to one skilled in the art.

6.0 Not an invention / Not patentable within the meaning of the Act [Section 25 (1)(f)]:

6.1 Section 2(1) (j) / Section 2(1)(ja)

The opponent states that the claimed invention (claim 1) falls under the mischief of Section 2(1)(j) and Section 2(1)(ja) by virtue of failing the requirements of an 'invention' and also being devoid of inventive step. The opponent states that the invention should be a technical

advancement over the prior art or it should show economic significance or both and should not be obvious to a skilled person in the art.

The Opponent relies on paragraph 5 and the same is not reproduced here for the sake of brevity and states that the applicant has not provided technical advancement over D1. The complete specification of impugned application has not mentioned the advantage of the process of the present invention over the process of D1 in terms of improved yield and purity by way of comparative data.

Thus the alleged invention does not involve any inventive step and hence the invention does not satisfy requirements of 2(1)(ja) and therefore it is not an invention within the meaning of this act.

6.2 <u>Claims not patentable as per section 3(d)</u>

The Opponent states that the claimed invention (claim 1) falls under the mischief of section 3(d) which clearly states that the mere use of a known process which does not result in the enhancement of known efficacy of that substance or the mere discovery of any new property or new use for a known substance of the mere use of known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant is not patentable under this Act.

The opponent relies on paragraph 5 and states that claim 1 of the impugned application claims a mere known process, such known process does not result in a new product or employs any new reactant and thus falls under the mischief of Section 3 (d) and ought to be rejected.

In view of the above, the subject matter as claimed in claim 1 is not patentable as per Section 3 (d) of the Act and ought to be rejected.

Applicant of impugned application allegedly trying to secure the protection (like ever greening) for the already known process by making simple changes in view of known technology which are disclosed in D1 (Ref: Scheme-4 & 5).

7.0 Insufficiency of description (Section 25 (1) (g)):

The Opponent states that the complete specification of the alleged invention does not sufficiently and clearly describe the method of invention 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 states that there is no any sufficient information regarding manufacturing of compound of formula 7. The opponent thus states that the claimed invention is not clear and succinct and is not fairly based on the matter disclosed in the specification as the impugned application does not provide examples for each and every embodiment claimed in the impugned application.

The complete specification of impugned application has not mentioned the advantage of the present invention over the process of D1 and D2 in terms of improved yield and purity by way of comparative data.

8.0 The Applicant has failed to disclose the information to the Controller under section 8 ((U/S 25 (1) (h)):

The applicant has failed to disclose the prosecution details of corresponding foreign patent applications filed under section 8.

Corresponding Peru patent application (PE06112009 A1) withdrawn on March 13, 2012.

Applicant of impugned application failed to furnish all the examination reports of corresponding patent applications in Peru under section 8.2. Hence, the impugned patent application is liable to be rejected.

Accordingly, in view of the above-mentioned factors all the claims of impugned application are needed to be rejected on the various grounds made out by the opponent in the present representation.

RELIEFS SOUGHT

The opponent states that it has established and made out a case on each the aforesaid grounds of opposition and prays to the Ld. Controller for taking on record the present representation and refusal of the impugned application in *toto*.

Dated this the 19th day of November 2015.

G. Subrahmanyam

G. SUBRAHMANYAM
(Opponent)

To

The Controller of Patents

The Patent Office Branch

Delhi

Enclosures:

- Impugned patent application (Annexure A)
- Document-D1 (starting 38 pages of 267 pages);
- Document-D2.