

**The Patents act, 1970
(amended by the patents act 2005)**

**THE PATENT RULES, 2003
(Amended by the Patent Rules 2006)**

In the matter of patent Application no. 5633/DELNP/2006, filed on 27-09-2006, International filing date 24/03/2005, Claiming United States Priority dated 30/03/2004

AND

In the matter of representation by way of opposition U/s 25 (1) dated 8th May 2008 on said application No. 5633/DELNP/2006

The Applicants

M/s MILLENNIUM PHARMACEUTICALS INC., Cambridge, MA, USA.

The opponents

M/s NATCO PHARMA LTD. , Hyderabad, India...

Present:

Ms Reema Arora, Dr. Deepa K. Tiku, Mr. Sukhdev of M/s Remfry and Sagar, Gurgaon, NCR, India.....Attorneys for the Applicant.

Sh. S. Majumdar; Ms A. Majumdar of M/s Majumdar & Co., Kolkata.....Attorneys for the Opponent

Dr. A.K. Bhujangarao, (President); Mr. M. Adinarayan (Company secretary and General Manager) and ; Mr. R. Janaki Ram, (Manager R &D) all from M/s NATCO PHARMA LTD. , Hyderabad, India,(the Opponent)

Hearing held on 06/05/2009

DECISION

(A) The matter under consideration in this decision is the representation by way of opposition filed under section 25(1) by M/S Natco Pharma Ltd., Hyderabad, India through M/S S.Majumdar & Co.,Kolkata (herein after opponent) on 08/05/2008 against the grant of patent on application no. 5633/DelNp/2006 Filed on 27-09-2006, International filing date 24/03/2005, Claiming United States Priority dated 30/03/2004 titled as "Synthesis of Boronic Ester and Acid

Compounds " filed by M/s. Millenium Pharmaceuticals , INC, 40, Landsdowne Street, Cambridge, MA 02139, USA through M/s. Remfry and Sagar, Gurgaon, NCR Region, India(herein after applicants).

(B) The chronology of events(other than mentioned above)in respect of said application and representation is as under:-

- 1.Request for examination on form-19 filed on 22/03/2007
- 2.First examination report (herein after FER) sent on 14/01/2009
- 3.Final date of compliance of all objections raised by patent office-14/01/2010
- 4.Date of reply by the applicant to FER-09/04/2009 (claims finally amended)
- 5.Date of publication- 24/08/2007
- 6.Date of dispatch of notice U/R 55(3) to applicant by patent office -14/01/2009
- 7.Date of filing reply by the applicant U/R 55(4)-14/01/2009 recd. in Patent Office on 15/01/2009 ;

(C) Opposition Grounds: The opponents on the day of hearing relied only on following grounds of opposition:

1. Obviousness and Lack of Inventive Step
2. Not an Invention within the meaning of the Act

(D) To establish the grounds of opposition the opponents have relied upon the following prior art citations on the day of hearing out of several cited in the representation :

S.No	Annexure No.	Cited Document with date of publication
1	III	US Patent No. 4525309, dated 25/06/85
2	IV	US Patent No. 4537773, dated 27/08/85
3	V	Journal of Biological Chemistry Vol. 259, No. 24, Page No. 15106-15114, 1984
4	VI	PCT/US 95/14117

The opponents relied upon following additional citations out of 20 to justify their stand on the day of hearing:

S.No	Annexure No.	Cited Document with date of publication
1	Exhibit 7	Product Catalogue of MTBE (Trade Name Acropure) 1997
2	Exhibit 8	Tetrahedron letters 41 (2000)4335-4338; Xin Wang et.al.
3	Exhibit 9	J.Am.Chem. Soc. 1996,118,11391 to 11398 Donald J. et.al.
4	Exhibit 10	J.Am.Chem. Soc. 022-3263/93/1958-5537-1993 Thomas A. Mulherni et.al.
5	Exhibit 11	Organic letters of ACS publications 2001,3(10), 1575-1577
6	Exhibit 12	J. Org. Chem. 2002, 67(19),6797-6804
7	Exhibit 15	US 6082237, 22/2/2000
8	Exhibit 16	US 6262270; 17/07/2001
9	Exhibit 18	Greener Solvent Alternatives, Aldrich Chemicals No date mentioned

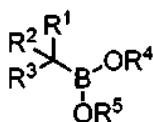
The opponent prayed to take the additional citations on record in accordance with the Decision taken by this tribunal in the case no. IN/PCT/2002/0020/DEL to allow the additional citations in the interest of justice and fair adjudication of the matter.

I hereby hold that the aforesaid additional citations are taken on record in the interest of justice and for the fair adjudication of the matter in consistence with the earlier decision of this tribunal as cited by the opponent above.

(E) The claims of the impugned application

The applicant initially filed 91 claims. However, in response to the First Examination report and to the response to the opposition the applicants amended the claims and refiled reduced number of the claims to Total of 63 claims. The hearing proceeded on the basis of amended 63 claims only. The claim nos 01, 33, 34, 35, 41, 56, and 57 are the independent claims which are reproduced below:

1. A process for preparing a boronic ester compound of formula (I):



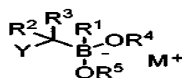
(I)

wherein: R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R² is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R³ is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and each of R⁴ and R⁵, independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S; said process comprising:

- (a) providing a boron "ate" complex of formula (II):



(II)

where

Y is a nucleofugic group;

M⁺ is a cation; and each of R¹ to R⁵ is as defined above; and

- (b) contacting the boron "ate" complex of formula (II) with a Lewis acid to afford the boronic ester compound of formula (I), said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent of the kind such as herein described that has low miscibility with water; or

- (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent of the kind such as herein described, provided that the coordinating co-solvent constitutes 5% v/v to 20% v/v of the reaction mixture; wherein the solubility of water in the ether solvent that has low miscibility with water is less than 5% w/w.

33. A process for preparing a boronic ester compound of formula (I):

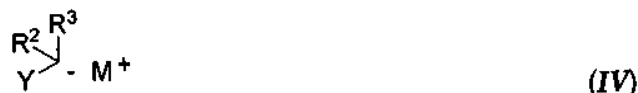
wherein: R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R² is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R³ is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and each of R⁴ and R⁵, independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S; said process comprising: (a) providing a solution comprising: (i) a boronic ester of formula (III):



wherein R^1 , R^4 , and R^5 are as defined above; and (ii) an ether solvent that has low miscibility with water; (b) treating the solution with a reagent of formula (IV):



to form a boron "ate" complex of formula (III): where Y is a nucleofugic group; M^+ is a cation; and each of R^1 to R^5 are as defined above; and

(c) contacting the boron "ate" complex of formula (III) with a Lewis acid to afford the boronic ester compound of formula (I), said contacting step being conducted in a reaction mixture comprising:

(i) a coordinating ether solvent of the kind such as herein described that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent of the kind such as herein described, provided that the coordinating co-solvent constitutes 5% v/v to 20% v/v of the reaction mixture;

wherein the solubility of water in the ether solvent that has low miscibility with water is less than 5% w/w.

34. A process for preparing a boronic ester compound of formula (I):

wherein: R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R^2 is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group; R^3 is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and each of R^4 and R^5 , independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R^4 and R^5 , taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S; said process comprising:

(a) providing a solution comprising: (i) a boronic ester of formula (III); wherein R^1 , R^4 , and R^5 are as defined above; (ii) a compound of formula (V):



where Y is a nucleofugic group, and R^2 and R^3 are as defined above; and (iii) a solvent comprising:

(aa) a coordinating ether solvent of the kind such as herein described that has low miscibility with water; or

(bb) an ether solvent that has low miscibility with water and a coordinating co-solvent of the kind such as herein described, provided that the coordinating co-solvent constitutes 5% v/v to 20% v/v of the reaction mixture; wherein the solubility of water in the ether solvent that has low miscibility with water is less than 5% w/w;

(b) treating the solution of step (a) with a strong, sterically hindered base to form a boron "ate" complex of formula (IV):

where M^+ is a cation derived from the base, and each of Y and R^1 to R^5 are as defined above; and (c)

contacting the boron "ate" complex of formula (IV) with a Lewis acid in a solution comprising:

(i) a coordinating ether solvent of the kind such as herein described that has low miscibility with water; or

(ii) an ether solvent that has low miscibility with water and a coordinating co-solvent of the kind such as herein described, provided that the coordinating co-solvent constitutes 5% v/v to 20% v/v of the reaction mixture;

wherein the solubility of water in the ether solvent that has low miscibility with water is less than 5% w/w.

35. A process for preparing a boronic ester compound of formula (I):

wherein: R^1 is an optionally substituted aliphatic, aromatic, or heteroaromatic group;

R² is hydrogen, a nucleofugic group, or an optionally substituted aliphatic, aromatic, or heteroaromatic group; R³ is a nucleofugic group or an optionally substituted aliphatic, aromatic, or heteroaromatic group; and R⁴ and R⁵, taken together, form an optionally substituted linking chain comprising 2-5 carbon atoms and 0-2 heteroatoms selected from the group consisting of O, N, and S; said process comprising:

- (a) providing a solution comprising:
 (i) a boronic acid compound of formula (VI):



wherein R¹ is as defined above; where M⁺ is a cation derived from the base, and each of Y and R¹ to R⁵ are as defined above; and

- (e) contacting the boron "ate" complex of formula (II) with a Lewis acid in a solution comprising:
 (i) a coordinating ether solvent of the kind such as herein described that has low miscibility with water; or
 (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent of the kind such as herein described, provided that the coordinating co-solvent constitutes 5% v/v to 20% v/v of the reaction mixture; wherein the solubility of water in the ether solvent that has low miscibility with water is less than 5% w/w.

41. A process for preparing an aminoboronic ester compound of formula (VII):



or an acid addition salt thereof, wherein: R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group; and each of R⁴ and R⁵, independently, is an optionally substituted aliphatic, aromatic, or heteroaromatic group, or R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted 5- to 10-membered ring having 0-2 additional ring heteroatoms selected from N, O, or S; said process comprising:

- (a) providing a boron "ate" complex of formula (II):

where Y is a nucleofugic group; M⁺ is a cation; R² is hydrogen; R³ is a nucleofugic group; and each of R¹, R⁴, and R⁵ are as defined above; (b) contacting the boron "ate" complex of formula (II) with a Lewis acid to afford the boronic ester compound of formula (I):

where each of R¹ to R⁵ is as defined above, said contacting step being conducted in a reaction mixture comprising:

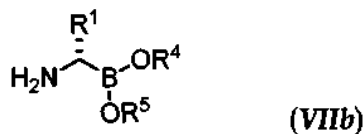
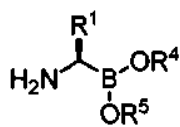
- (i) a coordinating ether solvent of the kind such as herein described that has low miscibility with water; or
 (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent of the kind such as herein described, provided that the coordinating co-solvent constitutes 5% v/v to 20% v/v of the reaction mixture; wherein the solubility of water in the ether solvent that has low miscibility with water is less than 5% w/w;

(c) treating the boronic ester compound of formula (I) with a reagent of formula M¹-N(Si(R⁶)₃)₂, where M¹ is an alkali metal and each R⁶ independently is selected from the group consisting of alkyl, aralkyl, and aryl, where the aryl or aryl portion of the aralkyl is optionally substituted, to form a byproduct of formula M^a-R³ and a compound of formula (VIII):



wherein each G and R¹ to R⁵ are as defined above; and (d) removing the G groups to form a compound of formula (VII): or an acid addition salt thereof.

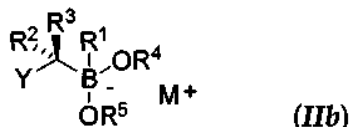
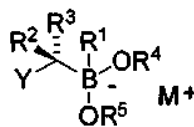
56. A process for preparing an aminoboronic ester compound of formula (VIIa) or (VIIb):



or an acid addition salt thereof, wherein:

R¹ is an optionally substituted aliphatic, aromatic, or heteroaromatic group; and R⁴ and R⁵, taken together with the intervening oxygen and boron atoms, form an optionally substituted chiral cyclic boronic ester; said process comprising:

(a) providing a boron "ate" complex of formula (IIa) or (IIb):

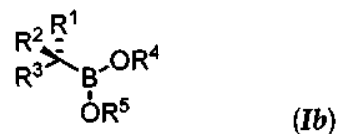
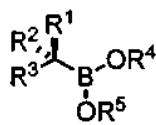


where

Y is a nucleofugic group;

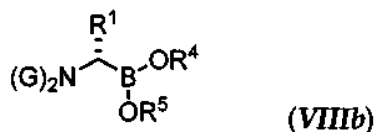
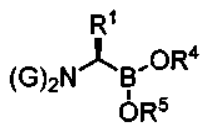
M⁺ is a cation; R² is hydrogen; R³ is a nucleofugic group; and R⁴ and R⁵ are as defined above;

(b) contacting the boron "ate" complex of formula (IIa) or (IIb) with a Lewis acid to afford a boronic ester compound of formula (Ia) or (Ib):



where each of R¹ to R⁵ is as defined above, said contacting step being conducted in a reaction mixture comprising:

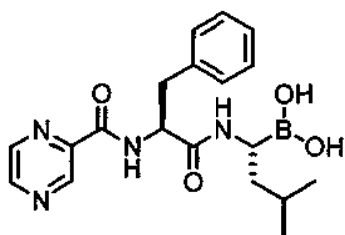
- (i) a coordinating ether solvent of the kind such as herein described that has low miscibility with water; or
- (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent of the kind such as herein described, provided that the coordinating co-solvent constitutes 5% v/v to 20% v/v of the reaction mixture; wherein the solubility of water in the ether solvent that has low miscibility with water is less than 5% w/w,
- (c) treating the boronic ester compound of formula (Ia) or (Ib) with a reagent of formula M¹-N(G)₂, where M¹ is an alkali metal and each G is an amino group protecting moiety, to form a compound of formula (VIIIa) or (VIIIb):



Wherein each G and K¹ to K⁵ are as defined above; and

(d) removing the G groups to form a compound of formula (VIIa) or (VIIb); or an acid addition salt thereof.

57. A process for forming a compound of formula (XIV): or a boronic acid anhydride

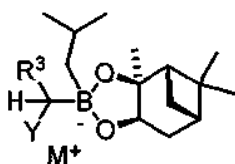


(XIV)

... thereof, said process

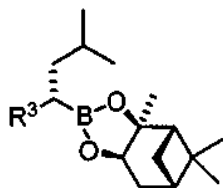
compsmg:

- (a) providing a boron "ate" complex of formula (XV); wherein: M^+ is an alkali metal;



(XV)

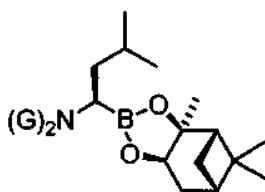
- (b) contacting the boron "ate" complex of formula (XV) with a Lewis acid to afford a boronic ester compound of formula (XVI):



(XVI)

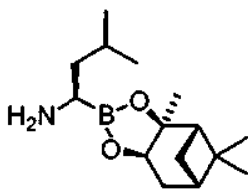
said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent of the kind such as herein described that has low miscibility with water; or
 - (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent of the kind such as herein described, provided that the coordinating co-solvent constitutes 5% v/v to 20% v/v of the reaction mixture; wherein the solubility of water in the ether solvent that has low miscibility with water is less than 5% w/w;
- (c) treating the boronic ester compound of formula (XVI) with a reagent of formula $M^3-N(G)_2$ where M^3 is an alkali metal and each G individually or together is an amino group protecting group, to form a compound of formula (XVII):



(XVII)

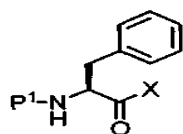
- (d) removing the G groups to form a compound of formula (XVIII):



(XVIII)

or an acid addition salt thereof;

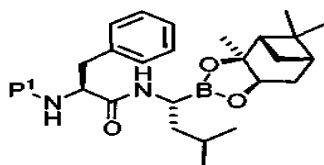
(e) coupling the compound of formula (XVIII) with a compound of formula (XIX);



(XIX)

wherein:

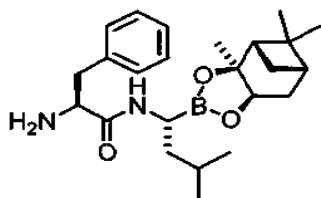
P^1 is a cleavable amino group protecting moiety; and X is OH or a leaving group; to form a compound of formula (XX):



(XX)

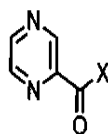
wherein P^1 is as defined above;

(f) removing the protecting group P^1 to form a compound of formula (XXI):



(XXI)

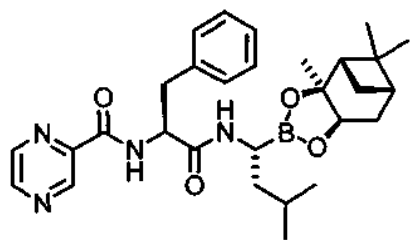
or an acid addition salt thereof; (g) coupling the compound



(XXII)

of formula (XXI) with a reagent of formula (XXII)

wherein X is a OH or a leaving group, to form a compound of formula (XXIII): ist''



(XXIII); and

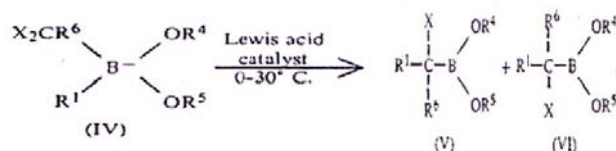
(h) deprotecting the boronic acid moiety to form the compound of formula (XIV) or a boronic acid anhydride thereof.

(F) The applicants in their response to First Examination Report dated 06/04/2009 has admitted that the novelty and the Inventive step of this Invention resides in using a low miscibility solvent " Tertiary Methyl Butyl Ether" in the reaction mixture.

(G) DISCUSSION ON THE GROUND OF OBVIOUSNESS & LACK OF INVENTIVE STEP:

(G-1) OPPONENTS ARGUMENTS: The opponents first of all discussed the prior arts which they have relied upon:

Annexure 3 -The US Patent teaches preparation of α -halo boronic ester by using Lewis acid as catalyst at temperature of 0-30⁰C (column No: 1, line numbers 34-42). The said patent preparation of α -halo boronic ester of formula NO; V and VI, by way of intermediate boronate anions of formula-IV.



On carefully observing it can be seen that the structure of intermediate of formula – IV is identical to compound of formula – II and structure of formula-V and VI same as that of formula – I of present Indian application.

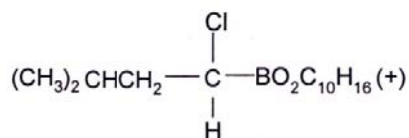
The suitable ether solvents as mentioned in lines 47 to 49 includes solvents of broadly three categories: highly miscible ethertetrahydrofuran; low miscibility ether – diethyl ether and a immiscibility solvent petroleum ether. Therefore, preparing boronic esters using ether solvents having low miscibility is clearly taught in this documents. All the applicant had to do was to carry out a few experiments to verify the amounts of the solvents needed to get the alleged optimum yield.

Example 2 provides process for the preparation of (+) – pinanaediol (IS) – 1-chloro – 3- methylbutane-1-boronate of the following structure, which corresponds to the compound of formula I as claimed in the impugned application.

It is prepared by reacting (+) – pinanaediol 2-methylpropane-1-boronate with dichloromethyl lithium in the presence of anhydrous zinc chloride (Lewis acid) and solvent tetrahydrofuran (THF) and ether (4 ml and 2 ml respectively). The metal complex identical to intermediate of formula-II of present Indian application is formed insitu.

Table 1 at column 8 provides the yields and diastereoselectivities of the compounds produced in the invention, the 6th compound in the table is of particular relevance as it is compound I of the impugned invention and it is seen that both the yield and the diastereosectivity of the compound is 89 and 99.5 respectively which goes to show that the compound as prepared in prior art has significantly high yields and better purity.

Annexure 4



US 4537773 pertains to alpha amino boronic acids. Example 1 of US 4537773 teaches a process for the preparation of 4, 4, 5, 5 tetramethyl-2 (2-methylpropyl) – 1, 3, 2 – dioxaborolane by reacting the solution of 2-methylpropylboronic acid (Corresponds to specific compound of formula – VI with appropriate substitutions as disclosed in the impugned invention.) in ether with Pinacole hexahydrate (falls under markush structure of HO-R₄-R₅-OH). At the end of reaction the resulting reaction mass was diluted with hexane and water layer was separated.

Example 4 deals with a solution of hexamethyl disilylhydrazide in tetrahydrofuran treated with n-butyl lithium to form lithio hexamethyl disilazane (which is identical to M²-N (si (R₆)₃)₂) of the present Indian application) is treated with 2- (1-chloro-3- methylbutyl) – 4, 4, 5, 5 –tetramethyl – 1, 3,2-dioxaborolane (which falls under markush structure of formula – I of present Indian application) at 78⁰C TO GIVE 2 (1-BIS(trimethylsilyl) amino]-3- methylbutyl) – 4,4,5,5, - tetramethyl – 1, 3,2-dioxabrolane (which falls under markush structure of formula – VIII of present Indian application)

This 2-(1-bis(trimethylsilyl)amino]-3 methylbutyl) – 4, 4, 5, 5 – tetramethyl – 1, 3, 2 – dioxaborolane is treated with trifluoroacetic acid in methylene chloride at 0⁰C to give the desilylated compound 3-methyl) – 1, 4, 5, 5- tetramethyl – 1, 3,2-dioxaborolane-2yl) -1-butanaamine, trifluoro acetate (which falls under markush structure of formula – VII of present Indian application). (Example 5)

Therefore, it is quite clear that the method of preparation of the alpha boronic acid ester as claimed in the impugned application is same excepting the use of low miscibility ether solvent in the impugned invention, as admitted by the applicant in its reply statement, which is nothing but obvious in light of the documents referred here.

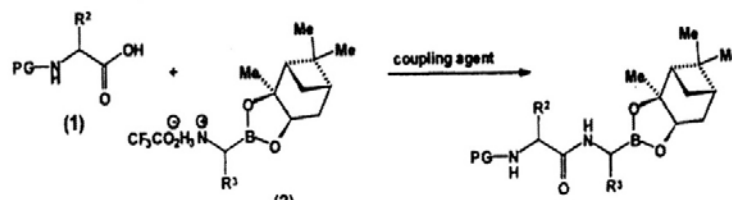
Annexure 5

Similar type of processes for the preparation of α-amino boronic ester of formula – VII is taught in this publication. The last paragraph in right column at page 15112 teaches the preparation of amino boronic acid wherein a solvent system comprising tetrahydrofuran and ether (Diethyl ether) of 125 mL and 75 mL has been used respectively.

It is seen that a combination of highly miscible ether with a lowly miscible ether has been use din prior art for same class of compounds thus providing enough motivation to try and optimize the amount of solvents to obtain alleged high yield and superior purity.

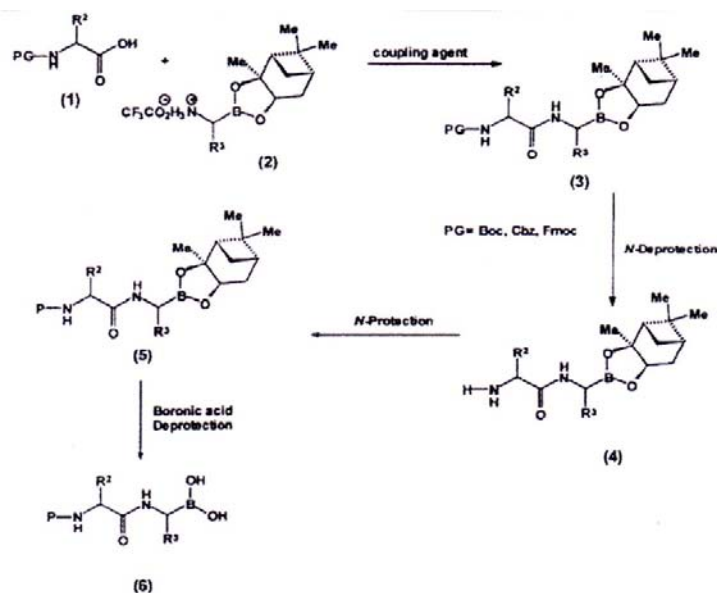
Annexure 6

It teaches coupling of N-protected amino acid of formula 1 (identical of formula – IX of present Indian application) with α-amino boronic ester of formula 2 (identical of formula – VII of present Indian application) to give the N-protected mono-peptide compound of formula 3, which is identical to compound of formula – X of present Indian application (Scheme I, page no. 46).



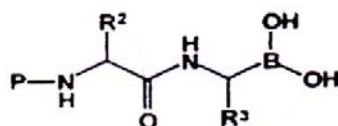
It further teaches the deprotection of protecting group (PG) of formula 3 (Identical to formula – X of present Indian application) to give the compound of formula 4 (Identical of formula –IX) of present Indian application). The amino group formula 4 is protected with N-protecting group P to

give the compound of formula 5 (Identical to formula –X II of present Indian application). Finally deprotection of boronic acid moiety from compound of formula 5 affords compound of formula 6 which is identical to compound of formula XIII of present Indian application (Scheme I, page no. 46).



Step No. (a) to (d) of claim No. 57 is same as that of process claimed in claim No. 41, wherein step (d) can be done by art known methods and steps (e) to (h) of claim No. 57 is same as the process claimed in claim No. 53 & 55.

The said PCT application number PCT/US95/14117 discloses process for the preparation of compound of formula 6 which as following structure (Scheme I, page no. 46)



(6)

The table no. 2 of PCT application discloses various boronic ester and acid compounds which falls under the markush structure of formula 6. The P has been mentioned as (2-pyz)-C (O) on page no. 85 in table 2 under compound MG-341. The chemical components disclosed under compound MG-341 in table 2 confirms the structure of bortezomib (Compound corresponding to compound of formula I)

Annexure 7

This is the product catalogue of MTBE (trade name Acropure). This publication teaches as well as discuss the advantages of MTBE over other ether solvents, some of which have been mentioned below:

- ❖ Higher stability of MTBE, specifically a 4-7 times higher stability than other ether solvents.

- ❖ Cost effective alternative to other solvents thereby making it commercially favorable.
- ❖ Its purity contributes to the process consistency and product quality.
- ❖ It is a routinely used solvent.
- ❖ It can also function as a purification or crystallization solvent in the syntheses of certain peptide compounds (the compound of formula I of the impugned application is a dipeptide), thereby producing purer final products.
- ❖ Limited solubility helps in better separation from aqueous phase.
- ❖ Oxidative stability of MTBE is most significant, unlike other ether solvents which tend to decompose over a period of time to produce peroxides are at a risk of detonating.
- ❖ It is preferred for ortholithiation of aromatics (Such processes have been used in the impugned application).
- ❖ It more specifically teaches that desired products are obtained **in better yields by changing the solvent from THF to MTBE** (THF was used either alone or in combination with other ethers in art known processes for the preparation of boronic acids and esters).

This document makes it quite clear that using MTBE as a solvent in an industrial process would not only prevent the use of hazardous but also increase the product yield and purity. Being a cost effective solvent makes the same industry-friendly. A person skilled in the art ought to be aware of such superior properties of MTBE over other ether solvents and is motivated to substitute THF and MTBE used in the known reactions. Such verification/trial and error that too with the most obvious alternative clearly demonstrates the lack of inventive ingenuity.

Annexure 8

This article deals with the monolithiation reactions which has been carried out in the impugned invention. The table at page 4336 exemplifies the product distribution (yield) using various solvents which include THF and MTBE (1st and 5th entry respectively). The product yield with THF as solvent is around 66% on an average and around 75%.

Albeit the compound in this article is different it definitely provides a certain degree of motivation to try the alternate solvent in anticipation of better yields. The increase in yield is almost 10% which is very significant in chemical sciences thus using MTBE in the impugned application instead of THF is obvious to try with an reasonable expectation of better yields and purity.

Annexure 9

This research paper relates to structure and reactivity of beta lithiated beta phenylcarbozamides. At page 11397, under the experimental section few experimental examples have been taught. The third paragraph in the left column on the same page teaches the use of THF and MTBE in a ratio of 1:1, the final product so obtained has an enantiomeric excess of 91:9.

Such teachings show that the use of ether solvents viz THF and MTBE in combination produce products with high purity and a skilled person ought to be led or motivated by such prior art to try the combination of the solvents at various ratios and select the one which gives the optimum yield. Such selection does not require any inventive ingenuity which would render the invention nonobvious.

Annexure 10

This journal publication relates to ortholithiation based synthesis of 2-chloro-6-methylaniline. In the right hand column on the first page of the article, the criticality of solvent selection has been discussed, after the experiments were conducted it was seen that on using diethyl ether and

MTBE, the highest yield of the desired product was obtained whereas on using THF the undesired product was obtained whereas on using THF the undesired product was predominant. Therefore, even this article corroborates the fact the using MTBE would lead to better product yields and a person aware of such teaching would merely replace THF with MTBE to test the expected increase. Thus, the inventive concept of the impugned invention is nothing but obvious.

Annexure 11

Page 1576 of this article in the second column teaches that using THF in a lithiation reaction did not give satisfactory result and was in fact was teaching away.

Thus in view of such document and Annexure 3, a person skilled in the art would replace THF with other ether solvents. MTBE being the most commercially used ether solvent was an obvious alternative.

Annexure 12

This article relates to enantioselective synthesis of a certain compound by lithiation substitution reactions. At page 6798, the very first paragraph mentions teaches that the lithiation reaction was carried out in 3:1 MTBE/THF solvent system which gave both better yield and high enantiomeric ratios of 91:9.

This document provides enough impetus to try such a solvent system in lithiation reactions to get similar results. The applicant has simply followed such teaching of combining the two ether solvents namely, MTBE and THF to obtain a final product with high purity. There are umpteenth teachings regarding the use of MTBE and THF as a solvent system, out of which a few have been relied upon, to produce products with higher yields and better purity. Thus the applicant being a skilled person in the art has merely in view of these teachings went ahead and tried such combinations to obtain the desired results.

Annexure 15

US 6082237 at column 7 lines 9 to 25 some commonly used suitable solvents which may be readily selected by one skilled in the art. The relevant passage reads as under:

The reactions of the synthetic methods claimed herein are carried out in suitable solvents which may be readily selected by one of skill in the art of organic synthesis, said suitable solvents generally being any solvent which is substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, i.e. temperatures which may range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction may be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step may be selected.

Suitable ether solvents include: **tetrahydrofuran, diethyl ether**, diethoxymethane, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, **or t-butyl methyl ether**.

It would be evident from the above passage that the skilled person being aware of these ether solvents (only 10 in number) would easily and readily select any one of these ethers alone or in combination depending on the need of the particular process.

Out of these 10 commonly used ether solvents, the applicant has merely carried out a job of verifying the suitable solvent as a skilled person ought to do being aware of such teaching.

And it is well established in Patent Law that routine experimentation does not render an invention nonobvious unless associated with some surprising finding.

Annexure 16

The most relevant passage from US 6262270 reads as under

“Under the **prior art conditions which include use of methyl magnesium halides in THF or ether** (see U.S. Pat. Nos. 5,395,842, OR 5,407,947 and J.Med. Chem, 1990, a p 32163222), **VIII and Q are obtained in a ratio of about 7:1 and are normally separated by chromatography. Mixtures of VIII and Q are also obtained with MeLi in THF alone (See J.Med. Chem., 1997, 40 p. 2117-2122) and chromatography is normally required to separate these mixtures into pure compounds. WE have found that under certain conditions chromanones of formula IX can be methylated such that less than about 3% of compounds of formula Q are formed the (Ratio of IX to Q is greater than about 27:1).** No chromatography is required as small amount of Q is conveniently removed in the next step i.e. Step E during crystallization of XI. *To achieve this low level of Q, methylation is carried out in a non-polar acyclic ether solvent using methyllithium as the methylating reagent and a non-polar ether solvent such as diethyl ether, t-butylmethl ether, dimethoxyethane or diethoxymethane under anhydrous conditions. The preferred acyclic ether solvent is t-butylmethyl ether.* Use of a cyclic ether, e.g. THF, as the sole solvent normally leads to larger quantity of compounds of formula Q. Other non-polar solvents such as toluene or cumene may be used but are not as convenient since they have relatively high boiling points and are difficult to remove. Mixtures of the above-listed anhydrous acyclic ethers with anhydrous aromatic hydrocarbons such as cumene or toluene: preferably a mixture of cumene and THF may also be used. Preferred aprotic solvents are neat anhydrous ethers, especially, diethoxymethane (“DEM”) and t-butyl methyl ether (“TMBE”). At least about 2.8 equivalents, preferably about 3 equivalents of MeLi are required in Step D; lesser amounts of MeLi lead to larger amounts of Q. The preferred methylation reagent is methllitium as an 8% solution in Dem. Other commercially available sources ofmethyllithium such as methyllithium 1.4M in diethyl ether or methyllithium 1.0M in cumene / THF (9:1, v/v) may be utilized but are less preferred as methylation reagent, and they also give more of Q. the methylation is preferably run under a dry, oxygen-free inertatmosphere such as dry nitrogen or argon. The methylation reaction temperature is normally in the range of about – 20 degree. 20 degree C, and most preferably in the range of about 0 degree C. to about 50 degree C under anhydrous, inert atmosphere conditions. The prior art methylation was run at a temperature of -78 degree C”

US 6262270 pertains to a commercial process for the efficient enantioselective synthesis of non-steroidal antistrogen. This process is divided into 5 steps namely steps A to E. Step D relates to the step of resolution of the racemic compound obtained form the previous steps. Compound Xi is the desired compound and Q is the undesired one. The inventors in this patent document states that prior art process employing tetrahydrofuran or ether as solvent gave a poor yield of the desired compound, namely IX. Whereas the inventors found that using MTBE have them higher yield of IX having higher purity as well. The preferred ether solvent as mentioned in this patent is MTBE which provides a clear teachings to use such solvent in order to achieve higher yields and better purity. A skilled person working out ways to increase the efficiency of a known process would use such teaching in expectation of achieving the increased yields and better purity. Applying such sound teachings of prior art to known processes does in no way make an invention nonobvious rather clearly shows that use of MTBE in place of THF is obvious to try with reasonable expectation of success for the same purpose.

Annexure 18

This was only cited for the table which is present on the last page of the exhibit, which puts forth the miscibility index of various ether solvents.

The opponent submitted that the prior art as annexed to the statement of opposition deal with products and processes related to boronic acids and ester formed the basis of the present invention and the teachings of the other exhibits clearly motivated a skilled person to carry out such alterations in solvent to achieve the desired yield and purity. Annexure 3 taken with each of annexures 7,8,9,10,11,12,15,16 alone or in combination makes the present invention obvious. Annexure 3 teaches a process similar to the process claimed in the impugned application only with THF as the ether solvent. Annexure 15 teaches commonly used 10 ether solvents which can be readily selected by one skilled in the art and includes MTBE, thus a skilled person aware of such disclosure would try the commonly used solvents to achieve the desired results. Annexure 7 which is the product catalogue of MTBE clearly teaches the commercial as well as stability benefits of using MTBE as a solvent over other ethers viz. THF has made it a routinely used solvent in the chemical industry. It even specifically teaches that THF is being replaced by MTBE in several processes and that ortholithiation reactions are favoured using MTBE due to its stereospecific utility. A skilled person would definitely have knowledge of such superior properties of MTBE and would try MTBE instead of THF to achieve the desired results utilizing the superior properties of MTBE. Thus the applicant has done nothing more than routine experimentation/optimization to verify its expected results. And an invention does not involve an inventive step when it is obvious to try even with a reasonable expectation of success. Annexure 8 and 10 though relating to some other compounds exhibit that on using MTBE as solvent the product yield and purity is higher than what was obtained with THF. Such teaching in view of the known process of production of boronic esters would provide motivation to a skilled person to try MTBE in order to increase the yield of boronic esters. Annexure 9 and 12 teaches the use of a solvent system comprising MTBE and THF in combination in a ratio of 1:1 and 3:1 and exemplifying a higher purity. These teachings clearly make the combination as claimed in alternate step (ii) of Claim 1 obvious. Annexure 16 too teaches that on replacing THF with MTBE the desired product was obtained in better yields. Moreover, it is also to be noted that Annexure 3 itself taught the use of an acyclic ether solvent, namely diethyl ether, having low miscibility of 6.8 % w/w, which the applicant conveniently failed to deal with in its reply. The opponent further submits that the applicant amending the claims to incorporate the 5% w/w miscibility ought to have shown the superior effects of ethers having miscibility of less than 5% w/w (MTBE) over diethyl ether, which is also a low miscibility ether solvent, to assert its statements on inventive step. It is well settled law that when an invention is prima facie obvious, the burden lies on the applicant to show some surprising or unexpected result which would render the invention nonobvious. The specification lacks such comparative data or any surprising effect, whatsoever. In the absence of such data the impugned invention is devoid of any inventive feature.

The opponent further submitted that annexures 3 to 6 teach processes of preparing the alpha amino boronic esters and acids. There too the only difference lies in the solvent used as admitted by the applicant. Therefore, Annexures 4 to 6 read with each of Annexures 7,8,9,10,12,15 and 16. The opponent further submitted the applicant in its reply on the ground of inventive step stated that none of the documents as cited in the statement of opposition teach or suggest the selection of MTBE as a solvent, thereby admitting the fact that the impugned application claims nothing more than a mere selection. Such selection too is not supported by any data corroborating the superior effects of the selected ether solvent "MTBE" over the others. Thus the impugned application is totally devoid of an inventive step.

The opponent submitted that the applicant's expert evidence contained no extra information than what is already there in the applicant's reply statement.

Furthermore, it is to be noted that the expert did not consider the prior art cited by the opponent to show the nonobviousness associated with the invention, not even Annexure 3 which was also cited with the FER. The expert ought to have distinguished between the low miscibility of less than 5% w/w as claimed in the amended claims of the impugned application and diethyl ether (taught in Annexure 3) for fairly commenting on the inventive feature of the impugned invention.

Thus, the impugned invention is obvious and clearly lacks an inventive step and ought to be rejected.

A few case laws were relied upon for obviousness:

EPO Board of Appeals Case Number: T 1034/01 Date of decision: 29 January 2004

From the teachings of documents E3 and E8 the skilled person learns that a fluorine scavenger can be made of different materials as long as they consume the fluorine radicals. The possible materials comprise inter alia Si and SiC, although a source of carbon would also react with the fluorine radicals producing CF₄. Moreover, the location of the scavenger can be below the substrate to be treated, as done in document E8, or above the substrate, as in document E3. It is, therefore, obvious for a skilled person to locate a fluorine scavenger made of silicon above the substrate to be treated, since by locating the scavenger above the substrate the scavenger's surface exposed to the plasma increases and the scavenging of free fluorine radicals is improved with respect to the apparatus disclosed in document E8 in which a portion of the scavenger is covered by the substrate and the scavenging action only takes place at the substrate's periphery. Accordingly option (i) of claim 1, ie the use of an article of silicon as fluorine scavenger mounted between the window and the substrate, does not involve an inventive step having regard to the combined teaching of documents E1, E3 and E8. A finding of lack of inventive step with respect to one alternative of the invention as claimed, however, renders the whole claim including different alternatives not allowable. For this reason, it is not necessary to discuss the presence of an inventive step of the other options provided in claim 1. The patent, moreover, does not disclose any technical effect that is achieved by locating the scavenger above the substrate when it is formed by an article of silicon that is not achieved by a scavenger formed by an article of graphite. Such a limitation in the claim renders the claimed subject-matter new with respect to the state of the art, but is hardly suitable to render it inventive.

The Board, moreover, does not concur with the respondent's argument that the teachings of documents E1, E3 and E8 cannot be combined with one another, since they are directed to different kinds of plasma etch apparatus. Although it is true that these apparatus differ e.g. in the gas distribution system and the pressure ranges used, the skilled person learns from documents E3 and E8 that the presence of free fluorine radicals is the main cause for a poor etch selectivity of the oxide layers and that the free fluorine radicals have to be removed from the reaction gas. For the skilled person it is, in consequence, obvious to apply these teachings also to the plasma etch apparatus disclosed in document E1.

For these reasons, in the Board's judgement, the apparatus according to claim 1 does not involve an inventive step in the sense of Article 56 EPC.

From the above underlined passage it is quite clear that if one alternative of a claimed invention is found to be obvious, the other alternatives of the claim are also rendered obvious. Thus, in the present case, the relevant part of claim 1 reads as follows:

" (b) contacting the boron "ate" complex of formula (TT) with a Lewis acid under conditions that afford the boronic ester compound of formula (T), said contacting step being conducted in a reaction mixture comprising:

- (i) a coordinating ether solvent that has low miscibility with water; or (ii) an ether solvent that has low miscibility with water and a coordinating co-solvent. Since (i) and (ii) of step (b) are alternatives, if any one of the reactions is shown to be obvious the other is also rendered obvious. In view of the citations as mentioned above use of each of such solvent as recited in I) or ii) for the given purpose has been shown to be obvious. Accordingly the claim is rendered obvious. Similarly the alternatives present in the other independent claims no longer stand if the other alternative is found lack inventive step.

EPO Board of Appeals Case Number: T 0139/04 Date of decision: 26 January 2007

Moreover, the Board considers that the passage in D1 at column 5, lines 62 to 65, stating that it is a unique feature of the invention that the labels are produced throughout a production process rather than at the beginning of an identification process, explicitly discloses the claimed feature as an alternative. The appellant considers that D1 teaches away from the latter. However, in the Board's view, it does not teach

away, but rather discloses that both alternatives are possible, but that one was preferred for the invention of DI. There is no actual disclosure that teaches away, e.g. **by saying that producing labels at the beginning would not work, or would suffer from drawbacks.**

The above passage construes "teaching away", it was held that unless a prior art specifically directs viz. producing labels at the beginning that using a particular solvent would not work or would produce some negative results it would not be considered as teaching away. In this case too, none of the documents actually taught away from using MTBE specifically mentioning that it would not work or would be disadvantageous, rather there was teaching/motivation for trying MTBE as exhibited by the annexures with reasonable expectation of success. Therefore, the applicants merely followed what prior art taught which renders the invention obvious.

In re Richard E. Woodruff 919 F.2d 1575: *Nor can patentability be found in the difference in carbon monoxide ranges recited in the claims. The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. See, e.g., Gardner v. TEC Sys., Inc., 725 F.2d 1338, 220 USPQ 777 (FedCir.), cert. denied, 469 U.S. 830, 105 S.Ct. 116, 83 L.Ed.2d 60 (1984); In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980); In re Ornitz, 351 F.2d 1013, 53 CCPA 716, 147 USPQ 283 (1965); In re Aller, 220 F.2d 454, 42 CCPA 824, 105 USPQ 233 (1955). These cases have consistently held that in such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range. Gardner. 725 F.2d at 1349, 220 USPQ at 786 (obviousness determination affirmed because dimensional limitations in claims did not specify a device which performed and operated differently from the prior art); Boesch, 617 F.2d at 276, 205 USPQ at 219; Ornitz, 351 F.2d at 1016-17, 147 USPQ at 286; Aller, 220 F.2d at 456, 105 USPQ at 235. Woodruff has made no such showing in the present case. The only test results presented by Woodruff are the results reported by Mr. Bell, comparing Woodruff's claimed invention to the commercial embodiment of McGill's method. While Woodruff's invention certainly showed superior fungi-inhibiting effect in these tests, the critical comparison is not with the commercial embodiment of McGill's invention, but with the method taught in his patent. According to Mr. Bell's declaration, the carbon monoxide concentration in the test group representing the commercial embodiment of McGill's invention was allowed to drop to 0% after 4 days. The McGill patent does not teach allowing the concentrations of any of the gases to fall out of the suggested ranges.*

CONCLUSION

In the absence of adequate evidence showing that ranges of carbon monoxide concentration recited in claims 27-34 are critical, the Board correctly affirmed the rejection of the claims under 35 U.S.C. Sec. 103. In the present case, the applicant has failed to provide any comparative data which is necessary to support the inventive step as claimed by the applicant. The applicant has amended its claims to incorporate the cut-off for the lower miscibility range at 5% w/w. the applicant has not provided any data to show the superiority of using ethers having less than 5% miscibility over diethyl ether which is taught in prior art and has low miscibility of 6.8% w/w. for a correct determination of inventive step, the applicant ought to have provided the comparative data to establish criticality if any in the choice of range. Without such data no inventive step can be acknowledged in the impugned application. EPO Board of Appeals Case no. T 0228/98 Date of decision: 7 August 2001

2.14 For certainty as to whether a lipase obtained from Pseudomonas fluorescens would be effective to resolve the chroman now claimed, an experiment admittedly would be necessary. But such an experiment would be a routine matter, and not involve anything like the research with uncertain outcome that would have been necessary in cases considered by the Boards of Appeal where reasonable expectation of success has been denied. As acknowledged even by the Respondent's expert at the oral proceedings, based on prior art document (6) it was definitely worth running the experiment. There have been no indications here

that the conditions suggested in document (6) would not serve to resolve the chroman whose resolution is now claimed, so the Board must presume that the skilled person would find that the method of document (6) works for this chroman. Checking up, by performing a relatively simple experiment, whether or not the most promising line suggested by the prior art solves a problem or not, is something that the skilled person can be presumed to carry out as a matter of routine. The absence of certainty cannot in such circumstances mean that there was no reasonable expectation of success.

Consequently, the Board comes to the conclusion that the claimed process does not involve an inventive step in the sense of Article 56 EPC.

In the present case, the applicant being a skilled person is aware of the commercially used ethers which includes MTBE, THF, Diethyl ether. Depending on the reaction to be performed in the particular process the solvents selected to get the desired results in the end product. Therefore, the applicant looking for an alternative ether to THF, which was being used in similar reactions to get boronic esters, merely tested and tried the other commercially used ether solvents available which would give the expected better properties. In the above decision it was held that by performing an experiment whether or not the most promising line suggested by the prior art is something which a skilled person is presumed to carry out as a part of routine experimentation. Moreover, in the present case, there was several teachings regarding the superiority of MTBE over THF as a solvent.

EPO Board of Appeals Case no. T 0051/97 Date of decision: 24 August 2000

As a skilled person, he would be struck by document (6) which aims at improving the dispersion stability at high temperatures of the d-modification of a particular azo dye (page 2, lines 1 to 6). Moreover, he would take that document into consideration since it is particularly relevant for the reason that it is directed to an azo dye having the formula (1) of the claimed dye apart from the exclusive structural difference of substituting the allyl for the ethyl groups on the amino substituent. Document (6) teaches to transform the d-modification of that particular azo dye into the d-modification thereof for improving its dispersion stability at high temperatures (page 2, lines 8 to 14; page 4, lines 19 to 24). The dispersion stable d-modification of that particular azo dye is prepared by heating the d-modification thereof dispersed in water (page 2, lines 16 to 24). Furthermore, the Respondent conceded that numerous azo dyes exist in different modifications and that therefore the teaching of document (6) is embedded and not unique in the field of azo dyes.

The Board concludes from the above that the state of the art, in particular document (6), gives the person skilled in the art a concrete hint as to how to solve the problem underlying the patent in suit as defined in point 2.3 above, namely by transforming the d-modification of the azo dye of formula (1) known from the closest prior art document (cf. point 2.2 above) into the d-modification thereof thereby arriving at the solution proposed by the patent in suit. In the Board's judgement, it was obvious to try to follow the avenue indicated in the state of the art with a reasonable expectation of success without involving any inventive ingenuity.

The Respondent also argued that the person skilled in the art could predict with certainty neither the existence of different modifications of the azo dye of formula (1), nor the successful preparation of the d-modification thereof, nor its improved dispersion stability. Due to that lack of predictability of success and the possibility of failure, the claimed invention was not obvious.

However, when assessing inventive step it is not necessary to establish that the success of an envisaged solution of a technical problem was predictable with certainty. In order to render a solution obvious it is sufficient to establish that the skilled person would have followed the teaching of the prior art with a reasonable expectation of success (see decisions T 249/88, point 8 of the reasons; T1053/93, point 5.14 of the reasons; neither published in EPO).

In the present case, the Board cannot agree with the Respondent's argument that due to some uncertainty about the predictability of success the skilled person would not have contemplated transforming the known d-modification of the azo dye of formula (1) into the d-modification thereof in order to improve

the dispersion stability at high temperatures. The skilled person has a clear incentive from document (6) to do so (see point 2.6 above). Nothing was submitted by the Respondent from which the Board could reasonably conclude that the skilled person has been deterred from following the straight teaching of the art. It was only necessary for him to confirm experimentally by routine work that the obvious d-modification of the azo dye of formula (1) is in fact obtained and that it successfully shows an improved dispersion stability, thus arriving at the claimed invention without inventive ingenuity.

2.8 Therefore, in the Board's judgement, the subject-matter of claim 1 represents an obvious solution to the problem underlying the patent in suit and does not involve an inventive step. Since a decision can only be taken on a request as a whole, none of the further claims need to be examined.

In the present case, the applicants were aware of the superior properties of MTBE over THF vis-a-vis product yield and purity and Annexures 7,8,9,10,12 and 16 provided ample motivation to use MTBE or a combination of THF and MTBE instead of THF alone and it was obvious to try. And as held by Courts across the world, a reasonable expectation not a guarantee of success renders an invention obvious.

EPO Board of Appeals Case no. T 0948/01 Date of decision: 8 April 2004

In accordance with the "problem-solution approach" applied by the Boards of Appeal to assess inventive step on an objective basis, it is in particular necessary to establish the closest state of the art forming the starting point, to determine in the light thereof the technical problem which the invention addresses and successfully solves, and to examine the obviousness of the claimed solution to this problem in view of the state of the art.

The "closest state of the art" is normally a prior art document disclosing subject-matter aiming at the same objective as the claimed invention and having the most relevant technical features in common. In particular, where the background of the invention lies in difficulties encountered in known processes for preparing known compounds, the documents to be considered when determining the closest state of the art are those which describe these compounds and their preparation (T 713/97, point 4.2 of the reasons). Since document (5), which is cited on page 2, lines 42 to 45, of the present application, is the only cited document describing the preparation of the allophenylnorstatin derivatives according to Claim 1, document (5) represents the closest state of the art, which was no longer contested. As set out in the application in suit, document (5) effectively discloses, indeed, the syntheses of optically pure cyclohexylnorstatin and of (2S,3S)-phenylnorstatin and their isopropyl ester by oxidizing an alcohol to the corresponding aldehyde and adding hydrogen cyanide to the aldehyde (page 2709, left-hand column, second paragraph to right-hand column, last but one paragraph).

3.2 The Appellant submitted that the use of isopropanol as the solvent in the asymmetric hydrogenation-step provides a significant and unexpected enhancement, as follows from comparing the yields in example 1 for preparing (2S,3R)-2-chloro-3-hydroxy-4-phenylbutyrate in methanol or isopropanol. However, according to the jurisprudence of the Boards of Appeal of the EPO, in order to show a superior effect, the nature of the comparison with the closest state of the art must be such that the effect is convincingly shown to have its origin in the distinguishing feature of the invention (see T 197/86 OJ EPO, 1989, 371, Reasons for the Decision 6.1.3). However, since by comparing the yields in example 1 of the application in suit comparison has not been made with the closest state of the art, such comparison is not suitable for making any effect plausible, let alone a surprising one. As alleged but unsupported advantages cannot be taken into consideration in respect of the determination of the problem underlying the application, the said problem must rather be seen as described on page 2, lines 46 to 48, of the present application, namely that the known synthesis of (2S,3S) allophenylnorstatin derivatives, as described in document (5), raises problems due to an oxidation reaction, the use of harmful cyanide and a step of steric inversion. Furthermore, since the intermediate aldehyde is very labile and ready to racemize, it is difficult to obtain the desired compound at high optical purity. Therefore, the Board concurs with the statement on page 2, lines 48 to 50, of the present application, that the problem to be solved consisted in providing a process for preparing (2S,3S)-allophenylnorstatin at high optical purity, easily, safely and in high yield.

The Appellant argued that, due to the different conformations of the cyclohexyl group, which has a chair form, and the phenyl group, which has a planar form, a skilled person could not predict that the ruthenium-phosphine complex would have the same stereoselectivity in the asymmetrical hydrogenation of the 2-phenyl-2-halogeno-3-oxybutyric acid ester as of the 2-cyclohexyl-2-halogeno-3-oxybutyric acid ester. However, the correct approach in assessing inventive step is not whether a skilled person would derive from given information in the prior art a sure predictability of success, but rather whether it would be obvious to try something with a reasonable expectation of success, which implies the ability of a skilled person to reasonably predict, on the basis of the existing knowledge, a successful conclusion of an experiment (see point 28.5 in the Reasons for the Decision of T 694/92. OJ EPO 1997. 408. and point 7.4.4 in the Reasons for the Decision of T 296/93 of 28 July 1994).

In the present case, the Appellant did not provide any evidence that the stereoselectivity of the rutheniumphosphine complex would be so different in the asymmetrical hydrogenation of phenyl-substituted compounds and their cyclohexyl analogues that a skilled person would not have considered the reaction sequence proposed in document (1). On the contrary, document (5) suggests strongly that in the stereoselective synthesis of norstatins the phenyl group and the cyclohexyl group ave an analogous behaviour and, thus, that a skilled person would indeed have every reason to look to documents, such as document (1), treating the stereoselective synthesis of norstatin having acyclohexyl group for readily applicable methods for making the norstatin analogue with a phenyl, and thustry the asymmetric hydrogenation of 2-phenyl-2-halogeno-3-oxybutyric acid and the reaction sequence known from document (1) for the preparation of (2S,3S)-cyclohexylnorstatin ester.

Therefore, Claim 1 and, thus, the only request cannot be considered to meet the requirement of inventive step.

In the above case, the ability of a skilled person to predict with certainty that MTBE is superior vis-a-vis yield, purity and amenable for industrial production than THF is not required, only a reasonable expectation of achieving the desired results is what is required for showing obviousness. The applicant also failed to provide comparative data with the closest prior art "annexure 3" which also taught the use of low miscibility solvents viz. diethyl ether. Therefore, the present application was not only obvious to try but it also failed to corroborate the alleged unexpected enhancement.

Pfizer v. Apotex Fed. Cir 2007

Reasonable Expectation of Success

*As noted above, the district court found that the skilled artisan would have had no expectation of success in making a besylate salt of amlodipine because there was no reliable way to predict the influence of a particular salt species on the active part of the compound. We cannot reject the district court's finding that in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be. The problem with the district court's ultimate conclusion of non-obviousness based on that factual finding, however, is that case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success. See *In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985) ("Although [the inventor] declared that it cannot be predicted how any, 229 F.3d 1120, 1125 (Fed. Cir. 2000); *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989); *In re Merck & Co., Inc.* candidate will work in a detergent composition, but that it must be tested, this does not overcome [the prior art's] teaching that hydrated zeolites will work."); see also *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). Indeed, a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt—including those specifically listed in the '909 patent itself—would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute. *Merck*, 874 F.2d at 809; *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).*

"Obvious-to- Try "

To be sure, "to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. " *Medichem. S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (internal quotations omitted). Pfizer argues that, if anything, amlodipine in its besylate salt form would at most be "obvious to try, " i.e., to vary all parameters or try each of numerous possible choices to see if a successful result was obtained. *O'Farrell*, 853 F.2d at 903.

First, this is not the case where there are "numerous parameters " to try. Rather, the only parameter to be varied is the anion with which to make the amlodipine acid addition salt. Although we recognize some degree of unpredictability of salt formation, see, e.g., *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1379 (Fed. Cir. 2006), the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious. This is especially true here, where (1) as noted above, the skilled artisan had a reasonable (although not guaranteed) expectation that amlodipine besylate would form; (2) Pfizer conceded in prior litigation that the type of salt had no effect on the therapeutic effect of the active ingredient, amlodipine, and was practically interchangeable, *Pfizer v. Dr. Reddy's Labs.*, 359 F.3d at 1365-66; and (3) numerous other publications (described above) clearly directed the skilled artisan to a pharmaceutically-acceptable acid addition salt made from benzene sulphonate, including, significantly, the *Carabateas* patent which taught the besylate acid addition salt form of another dihydropyridine pharmaceutical compound.

Second, this is not the case where the prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903; *Medichem*, 437 F.3d at 1167. Here, as admitted by Mr. Davison, in selecting an acid addition salt formulation, one skilled in the art looked to pharmacopoeias and compendia to find a salt that was previously approved by the FDA and used successfully within the pharmaceutical industry. Berge clearly pointed the skilled artisan to 53 anions that, as of 1974, were pharmaceutical[^] acceptable. As Dr. Wells' testimony and the *Carabateas* patent demonstrated, one of ordinary skill in the art was capable of further narrowing that list of 53 anions to a much smaller group, including benzene sulphonate, with a reasonable expectation of success.

("[W]e do not agree that 'routine experimentation' negatives patentability. The last sentence of section 103 states that 'patentability shall not be negated by the manner in which the invention was made.' To support the board's decision that 'routine experimentation within the teachings of the art' will defeat patentability requires a primary determination of whether or not appellants' experimentation comes within the teachings of the art. Whether the subsequent experimentation is termed 'routine' or not is of no consequence. ")

However, on the particularized facts of this case, consideration of the "routine testing" performed by Pfizer is appropriate because the prior art provided not only the means of creating acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing. *Merck*. 874 F.2d at 809. The evidence shows that, upon making a new acid addition salt, it was routine in the art to verify the expected physicochemical characteristics of each salt, including solubility, pH, stability, hygroscopicity, and stickiness, and Pfizer's scientists used standard techniques to do so. These type of experiments used by Pfizer's scientists to verify the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to discover a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success. This is not to say that the length, expense, and difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably "routine " to one of ordinary skill in the art. Rather, our conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation. Cf *Velander v. Garner*, 348 F.3d 1359, 1368 (Fed. Cir. 2003) (that one skilled in the art would

view variability in producing fibrinogen in transgenic mammals as evidence that "expense, time and effort" would be involved did not equate to a conclusion that success was unlikely). Simply put, to conclude that amlodipine besylate would have been obvious, "the prior art, common knowledge, or the nature of the problem, viewed through the eyes of an ordinary artisan " merely had to suggest reacting amlodipine base with benzene sulphonic acid to form the besylate acid addition salt, and that that acid addition salt form would work for its intended purpose. DyStar 464 F.3d at 1361. They did. See O'Farrell. 853 F.2d at 904

In the present case too, the applicants had a reasonable expectation of success of achieving the desired properties of higher yields, purity on using MTBE as a solvent instead of THF in the light of the relevant teachings in prior art as exemplified by exhibits 3,7,8,9,10,12, 15 and 16. Here, too prior art documents Ex. 8, Ex. 10 and 16 taught that on using MTBE instead of THF produced compounds with higher yields and better purity. Ex.9 and Ex.12 taught the combination of MTBE and THF giving better results. Therefore, the applicants had to reasonable expectation of success given these documents and merely had to verify that expectation. Such verification does not render an invention nonobvious.

In the matter of application no. 396/DEL/96 between Gilead Sciences Inc and Intermed Lab, the Ld. Deputy Controller of Patents held:

(c) Lack of inventiveness or inventive step; In support of this ground, as stated earlier the opponents have relied upon three(3) documents namely (i) I'CT Ihibition NO.WO91 /16320, **marked as D1** entitled "derivatives and analogues of 2-Deoxy 2.3-didhydro-N accetyl neuraminic acid and their use as Antiviral agents", (ii) I'.M.Colman article entitled "influenza virus neuraminidase: structure, antibodies and inhibitors" accepted on July 2b, 1994 which was published in Protein science (pages 1687-1697), **marked as D2** and (iii) W.Thornber, article titled "Isosterism and Molecular Modification in Drug Design", published in Chem. Soc. Reviews 18 (1979), 563 580, **marked as D3**. During the hearing the agent for the opponents apart from the above documents also referred to some of the decisions of El'O Board of Appeals namely, T 0467/97(closest prior art) T 0712/92, T 0252/9.T 1110/03(Post published document) and T 0128/897 (obvious to try).

In T 0467/97 the IfiPO board of appeal held that for deciding whether or not a claimed invention involves inventive step, the board has consistently applied the problem and solution approach which consists essential in (a) identifying the closest prior art (b) assessing the technical results or effects achieved by the claimed invention when compared with the closest state of the art, (c) defining the technical problem to be solved as the object of the invention to achieve these results and (d) examining whether or not a skilled person starting from the closest prior art would arrive at something falling within the claimed invention by following the suggestions made in the prior art. [f the technical results of the inventions provide some improvement over the closest prior art, the problem can be seen as providing such improvements provided this improvement necessarily results from the claimed features for all that is claimed If, however there is no improvement, but the means of implementation are different, the technical problem can be defined as the provision of the alternative to the closest prior art. The board also held that technical progress shown in the comparison with the commercial products could not be a substitute for demonstration of inventive step.

In T 0712/92, the EPO, Board held the recognition of the inventive step presupposes the absence in the prior art of hints at the proposed solution. In T 0252/9, the EPQ, Hoard held that when a person skilled in the art arrives at a subject matter of the claims by selecting the knowledge from prior art with a reasonable expectation of success and carrying out routine experiments, this could render the invention obvious. In T 128/897, the board of appeal had similar opinion. In T 1110/03 IfiPO, Board discussed about the issue relating to indirect evidence on novelty and lack of inventive step when the document is post, published.

The decisions cited in the one of the Decisions passed by the Delhi Patent office in the matter of Patent application no. 396/DEL/96, goes to show that when a skilled person achieves a result by performing a

routine experiment from prior art with a reasonable expectation of success, the invention is rendered obvious. In the present case too, the applicant had cognizance of the teaching of the enhanced yields and purity associated with using MTBE over THF and had a reasonable expectation of achieving the desired results. As MTBE is cost effective, it is a suitable solvent for industrial scale ups. Thus, the present invention is completely devoid of any inventive ingenuity.

EPO Board of Appeals Case number: T 0369/94 Date of decision: 3 December 1996

Appellant has not provided any evidence that the alleged drawbacks are of such a nature that it would be impossible to carry out the process according to D4. The argument that the reactor of D4 contains dead volumes wherein reactive gas is in contact with the catalyst without sufficient cooling which might trigger a runaway reaction is not convincing

According to the patent in suit there is nowadays an increasing demand for larger capacity equipment, but the upscaling of classical reactors of the externally cooled multitube type such as disclosed in D8 causes cooling problems. The Board accepts that temperature control is a general problem in upscaling reactors since in indirect cooling systems the cooling capacity increases with the cooling surface (to the square) whereas the heat development increases with the volume (third power).

The skilled person encountering cooling problems in upscaling the reactor of D4 will first look for solutions in the field of ethylene oxide reactors.

The choice in this field is very limited, probably only the reactor types disclosed in D6 and D8, which suffer from the same kind of cooling problems. D6 is cited in D4. In fact, the reactor disclosed in D4 is a further development of the reactor of D6; see D4, page 1, lines 4 to 13. The skilled person is taught in D6 that internally cooled reactors suitable for the production of ethylene oxide are also suitable for other chemical exothermic reactions such as the synthesis of methanol, methane and formaldehyde (page 8, lines 73 to 114). The skilled person trying to improve the reactor capacity will also take into consideration available reactors used in other exothermal reactions. The skilled person will certainly look for the more recent developments in the field of isothermal reactors and should be aware of the Linde reactor and the publications D2 and D15 both relating thereto. The skilled person knows from D2 (point 2) that by using cooling tubes in a helical pattern the cooling capacity can be increased and the heat exchange on a large technical scale can be improved. D2 also teaches that the reactor, developed for the synthesis of methanol, can also be used for other exothermal catalytic reactions such as for the preparation of higher alcohols or methane by the expression "partial oxidation" in D15. this indication will encourage the skilled person to use the Linde reactor for the synthesis of ethylene oxide too. In view of the positive indication in D2 that the capacity can be increased by using the Linde reactor and the general character of the cooling problems in isothermal reactors for exothermic reactions it must be considered obvious to the skilled person to use the Linde reactor, one of the most recent developments in reactor technology, to solve the above mentioned problem.

3.5 D15 discloses in a very general statement that the reactors with helically bent cooling tubes can also be used for reactions which are not determined by equilibrium reactions such as hydrations or partial oxidations. This statement comprises most, if not all, of the large scale synthesis reactions and reinforces the general statement at the beginning of the article that the newly developed reactors are for use in exothermal catalytic processes. There is no indication that some partial oxidation reactions were to be excluded therefrom. The Appellant's reference to D16, relating to the synthesis of formaldehyde is, therefore, of no relevance to this decision.

3.7 In summary, the claimed solution of the technical problem as defined above in point 3.2 results from applying recent developments in reactor technology for the preparation of a known compound with a

known catalyst under known reaction conditions, which required no more than ordinary technical skill, without involving an inventive step in the meaning of Article 56 EPC.

The applicant at the hearing contended that the examples of annexure 3 are all lab scale experiments and the impugned invention has made a process which is amenable for industrial scale up. In that regard the opponent would like to rely upon a decision of the EPO Board of appeals where it was held that using convenient starting material and selective reaction made the lab scale process suitable for scale up. In the present case, MTBE being of such high commercial interest both in terms of efficacy and cost-effectiveness, therefore being the most suitable alternative as an ether solvent. Even the product yield and purity of the final products of processes employing MTBE as solvent is better than when using other solvents especially THF as taught in Ex. 7.

It is further stated, since Bortezomib is required in low dosages and has highly specialized application thereby having a low requirement. In reply to such assertions of the applicants, it is to be noted that the annual requirement of Bortezomib in USA is 1 Kg and a global requirement of 2 Kg, thus, a commercial batch at a time produces around 25 to 50 gm of the product. Therefore, the contentions relating to large scale applicability do not hold good. Such information is available from the IMS database, the relevant page has been annexed herewith and marked as EX. A.

Thus, in view of the above case-laws it is clear that an invention which made with reasonable expectation of success cannot be regarded to involve an inventive step and thus is obvious.

(G-2)APPLICANTS ARGUMENTS

The Opponent's Counsel relied on **Annexures 3-6** as annexed to their statement of Opposition and further on additionally submitted documents - i.e., **Annexures 7-12,15,16** and **18** to argue lack of inventive step. The Applicant humbly submitted that such precedents of submitting further prior art during the hearing should not be encouraged as it renders the entire purpose of the hearing meaningless. The Learned Tribunal, while taking the documents on record, kindly ordered the Opponent to submit written arguments in respect of the additional documents and serve a copy to the Applicant to enable it to respond.

The problem faced by Applicant at the time of the invention was that the reaction required the rigorous exclusion of water to avoid epimerization at the alpha-carbon center. Thus, as stated in paragraph [028] of the description of the present application, failure to employ rigorously dried equipment, solvents and reagents, which is particularly difficult on a large scale, resulted in dramatic reduction of diastomeric ratio. As discussed in the forthcoming paragraphs, the problem solved by each of the references cited by Opponent is entirely different than the problem solved by Applicant's invention.

Opponent contends that in the light of the Annexures submitted by them, it would be clear that "*MTBE or a combination of a lowly and a highly miscible solvent (MTBE and THF) instead of THF is known to show better results vis-a-vis yield and purity.*" The Applicant denied the above and submitted that they would be able to comment in this regard only once all the newly submitted documents are reviewed.

Opponent argued that selecting solvents to extract the desired product during work-up can readily be done by a person skilled in the art, and that solvents having low miscibility with water are preferred for convenient recovery of the desired product. Applicant submitted the standard procedure in the prior art is to concentrate the THF reaction mixture and then add a solvent for extraction. However, as discussed in paragraph [029] of the description of the present application, "*attempted scale-up of the prior art process frequently resulted in a further deterioration in diastomeric ratio during work-up and isolation of the product.* Overcoming this problem was not obvious for the reasons discussed herein.

The Applicant argued as follows against the Opponent's allegations based on the prior art relied upon in the opposition:

Annexure 3: The Applicant denied the Opponent's allegation that this document renders the present invention obvious. It was reiterated that where the said document teaches use of diethyl ether, it is

present in a very low amount as compared to the primary solvent THF, which has high miscibility with water. Thus, the skilled person would not have been motivated to use diethyl ether in an amount of 80% v/v to 95% v/v of the total reaction mixture. By contrast, the process of the present invention requires the use of solvents having low miscibility with water, such as MTBE, as the primary solvent. The choice of a primary solvent having low miscibility with water is critical to the present invention and is not a mere optimization of the solvent ratios. Accordingly, the Opponent's contention that disclosure of using diethyl ether in Annexure 3 renders the present invention obvious, does not stand and is liable to be rejected.

Annexure 4: The Applicant reiterated the submissions made hereinabove and asserted that the use of solvent having low miscibility in water is an inventive aspect as it obviates the problem of water exclusion as posed by the prior art and results in obtaining high yield and purity in a large scale production. The use of a solvent having low miscibility with water as the primary solvent in the formation of the boron "ate" complex is an inventive feature leading to technical advancement and not obvious as alleged by the Opponent.

The process disclosed in Annexure 4, employs THF and dimethoxyethane as solvents, both of which have high miscibility with water (as evident from Annexure-1 submitted with our reply statement). Thus, in view of the submissions presented above, the present claim is inventive in view of the teachings of Annexure 4.

Annexure 5: The Applicant denied the Opponent's allegation that, *"a combination of highly miscible ether with a lowly miscible ether has been used in the prior art for the same class of compounds thus providing enough motivation to try and optimize the amount of solvents to obtain the alleged high yield and superior purity."* The Applicant reiterated that where Annexure-5 teaches use of diethyl ether, it is present in a lower amount as compared to the primary solvent THF, which has high miscibility with water. Thus, the skilled person would not have been motivated to use diethyl ether in an amount of 80% v/v to 95% v/v of the total reaction mixture based on the disclosure of Annexure 5. On the contrary and as admitted by the Opponent, analogous to the process of Annexure 4, the process disclosed in example (3b) of Annexure 5 (page 15113) employs THF, which has high miscibility with water, as primary solvent. Thus, the present claim is inventive in view of the teachings of Annexure 5.

Annexure 6: The Applicant denied the Opponent's allegation that this document discloses the same process as claimed in the present invention. As stated above, the process of the claimed invention requires the use of a solvent having low miscibility with water as the primary solvent.

The (1S,2S,3R,5S)-Pinanediol leucine boronate trifluoroacetate salt of Annexure 6 was synthesized as reported in Annexure-5 (see e.g., page 44, line 28 to page 45, line 2 of Annexure 6). The arguments submitted with respect to Annexure 5, above, were reiterated and the same are not reproduced here for sake of brevity. Accordingly, the present invention is inventive over the said document. The following documents were submitted during the hearing but not explicitly argued upon. Accordingly, we present arguments on the basis of the Opponent's comments on these documents as presented in their written arguments:

Annexure 7: The Opponent's allegation, that the product catalogue of MTBE discusses the advantages of MTBE over other solvents, is not relevant in assessing the inventive step of the present invention. This reference does not teach or suggest that MTBE may be used in reactions where the problem faced is the requirement of rigorous exclusion of water. Opponent points out that some desired products in the directed ortho-lithiation of aromatics are obtained in better yields by changing the solvent from THF to MTBE. However, it is pertinent to note that the product catalogue does not refer to any problem that was solved to produce the desired products in better yields with MTBE, nor does it mention the role of water. Therefore, this document fails to teach or motivate the skilled person to arrive at the present invention. Accordingly, the present claim is inventive in view of the teachings of Annexure 7.

Annexure 8: The Applicant denies the Opponent's allegation and submits that the document describes use of coordinating solvents such as diethyl ether, MTBE and THF in increased production of lithiated bromopyridine at the 5'- position. This reference does not mention what problem was being solved by using a coordinating solvent versus a non-coordinating solvent. Moreover, the reference does not distinguish between MTBE and THF. Opponent points to Table 1 at page 4336, in which THF results in a yield of 66.5% after 40 min and 65.6% after 2 h, while MTBE results in a yield of 80.7% after 40 min, 76.4% after 2 h and 68.5% after 7.5 h and alleges that this would motivate a person skilled in the art to use MTBE to achieve higher yields. The Opponent's arguments are denied and it is submitted that there is no mention of the role played by water in the said document. Accordingly, even if a skilled person would note from this reference that MTBE exhibits better yields than THF in the production of lithiated bromopyridine at the 5'- position, he would not have been motivated to use MTBE instead of THF to overcome any requirement of rigorous exclusion of water. Thus, he would not have arrived at the solution obtained by the present invention by looking into this reference. Accordingly, the present invention is not obvious in the light of this document.

Annexure 9: The Opponent's contention is denied. The Applicant submits that this document shows that use of sec-butyl lithium and a chiral ligand in equal amounts of THF and MTBE produces enantioenriched p-lithiated P-phenylcarboxamides. Opponent argues that *"a skilled person ought to be led or motivated by such prior art to try the combination of solvents at various ratios and select the one which gives the optimum yield."* This reference, however, does not discuss the effects of solvent on the reaction, nor does it compare different solvents or different ratios thereof. There is no mention of the role played by water or that changing the amount of THF relative to MTBE would eliminate the requirement of rigorous exclusion of water. In fact, all reactions in this reference involving organometallic reagents were carried out under a nitrogen or argon atmosphere in dried glassware, which indicates rigorous exclusion of water was necessary for these reactions. Thus, this document also does not render the present invention as obvious.

Annexure 10: The Applicant denies the Opponent's contention and submits that in this document, lithiation occurs at the meta position when THF is used as the solvent because butyl lithium exists as a less aggregated, more reactive species in THF, whereas the use of MTBE favors lithiation at the ortho position because in MTBE, butyl lithium is highly aggregated and thus, less reactive. There is no mention of the role played by water or that changing the solvent from THF to MTBE would solve the requirement of rigorous exclusion of water. Thus, this document also does not render the present invention obvious.

Annexure 11: The Applicant denies the Opponent's contention and submits that this document describes lithiation of fluorinated hydrazones with various alkylolithiums. This reference discloses that for n-butyl lithium, using diethyl ether as the solvent results in higher yields and increased diastereoselectivities as compared to THF. There is no mention in the said reference, of the role played by water or that changing the solvent from THF to diethyl ether would eliminate the requirement of rigorous exclusion of water. Thus, this document also does not render the present invention as obvious.

Annexure 12 describes lithiation of iV-(2-phenylethyl)isobutyramide in 3:1 MTBE/THF and subsequent reaction with various electrophiles to yield substituted products in enantiomeric ratios of 72:28-91:9. The authors hypothesize that this selectivity is based on whether or not the electrophile has the ability to coordinate to the lithiated species. This reference, however, does not discuss the effects of solvent on the reaction, nor does it compare different solvents or different ratios thereof. There is no mention of the role played by water or that 3:1 MTBE/THF would eliminate the requirement of rigorous exclusion of water. In fact, all lithiation-substitution reactions in this reference were carried out under nitrogen atmosphere in dried glassware, which indicates rigorous exclusion of water was necessary for these reactions. Accordingly, this document does not render the present invention as obvious.

Annexure 15 is a patent directed to the synthesis of cyclopropylacetylene. Opponent cites this reference for a list of suitable ether solvents in column 7, lines 21 to 25. The lithiations in the examples of this

patent all occur in THF. There is no mention of the role played by water in this synthesis or that choosing from any of the ether solvents listed in the patent would eliminate the requirement of rigorous exclusion of water. Thus, there is no teaching in this document to render the present invention as obvious.

Annexure 16 is a patent directed to a synthesis including the step of methylating chromanones. The problem addressed is formation of undesired compounds of formula Q, which must be separated out by chromatography (see *e.g.*, Column 11, line 51). However, if methylation is carried out in a non-polar acyclic ether solvent, such as diethyl ether, MTBE, dimethoxyethane or diethoxymethane under anhydrous conditions, a low level of compounds of formula Q are formed. When polar solvents, such as THF are used as the sole solvent, a larger quantity of compounds of formula Q is formed. There is no mention of the role played by water or that using a non-polar solvent would eliminate the requirement of rigorous exclusion of water. In fact, the methylation is preferably run under a dry, oxygen-free inert atmosphere (Column 12, lines 14-16). Moreover, there is no distinction in the reference between non-polar acyclic ether solvents having hi eh miscibility with water (*e.g.*, dimethoxyethane) as compared to non-polar acyclic ether solvents having low miscibility with water (*e.g.*, diethyl ether, MTBE, or diethoxymethane). Rather using diethyl ether, MTBE, dimethoxyethane or diethoxymethane under anhydrous conditions produces the same result. Thus, this reference does not render the present invention obvious.

Annexure 18, as admitted by the Opponent, was cited to put forth the miscibility index of various ether solvents including that of diethyl ether. Accordingly, this reference does not require any comment.

Opponent alleges that Annexure 3 taken with each of the newly cited Annexures alone, or in combination, makes the present invention obvious. Applicant reiterates that none of the newly cited Annexures overcome the deficiencies of Annexure 3 in addressing the problem of the requirement of rigorous exclusion of water. In fact, many of the newly cited references also require the rigorous exclusion of water which is evident by the experimental conditions and setups used in the said references.

Opponent argues that the "*specification lacks such comparative data or any surprising effect.*" In view of what has been argued hereinbefore, it is reiterated and submitted that it is important to note that diethyl ether is not used in Annexure 3 as the primary solvent. The appropriate comparison is rather between MTBE and THF (both used as primary solvents). The surprising effect is that using an ether solvent in which the solubility of water is less than 5% w/w. such as MTBE, as the primary solvent obviates the requirement for the rigorous exclusion of water. Therefore, a combination of any of the documents with Annexure 3 does not teach or motivate the skilled person to arrive at the present invention and accordingly, the present invention is inventive.

The Applicant denies the Opponent's allegation that "*the impugned application claims nothing more than a mere selection.*" Applicant reiterates that none of the newly cited Annexures overcome the deficiencies of Annexure 3 in addressing the problem of the requirement of rigorous exclusion of water. Moreover, the present invention does not involve a mere selection of solvents for optimum use, but rather solves a long-existing problem which was never addressed in any of the documents relied upon by the Opponent. Accordingly, the present invention has achieved a technical advancement and clearly involves inventive step.

The Opponent alleges that the Applicant's expert should have "*distinguished between the low miscibility of less than 5% w/w as claimed in the amended claims of the impugned application and diethyl ether.*" It is reiterated that a comparison between diethyl ether and MTBE is not appropriate as diethyl ether is not used in Annexure 3 as the primary solvent. The appropriate comparison is rather between MTBE and THF. The surprising effect is that using an ether solvent in which the solubility of water is less than 5% w/w, such as MTBE, as the primary solvent obviates the requirement for the rigorous exclusion of water, gives high yield and purity even in large scale operations and thus, clearly involves an inventive step.

As regards the case laws cited by the Opponent on inventive step, it is submitted that they do not advance the case of the Opponent and the Opponent's submissions in this respect are merely vague allusions and

comparisons which are not substantiated and terminate with abrupt and forced conclusions, as will be evident from the forthcoming paragraphs:

* EPO BOARD OF APPEALS CASE NO. T 1034/01

The Opponent relied on this judgement to advance the argument that if one alternative of a claimed invention is found to be obvious, the other alternative(s) of the claim are also rendered obvious. Thereafter, the Opponent went on to abruptly conclude that in view of the prior art citations, the alternatives (i) or (ii) of step (b) in Applicant's claim 1 is obvious and accordingly the invention is obvious. The Applicant reiterates the submission on inventive step in this regard which is not being repeated here for the sake of brevity. The Applicant has clearly illustrated how both alternative (i) and (ii) of step (b) in claim 1 are individually inventive. In view of the foregoing, where the facts of the present case have been clearly distinguished, it is submitted that the Opponent's reliance on this case law stands flawed and misplaced and ought not be considered.

* EPO BOARD OF APPEALS CASE NO. T 0139/04

The Opponent relied on this judgement to emphasize that the prior art should actually 'teach away' from the invention. However, the particular facts of the case on which Board of Appeals applied this concept have to be appreciated. A portion of the passage relied on by the Opponent is reproduced below:

"The appellants considers that DI teaches away from the latter. However, in the Board's view, it does not teach away, but rather discloses that both alternatives are possible, but that one was preferred for the invention of DI."

It is clear from the above that in the particular case, the alleged invention was an alternative which was disclosed in the prior art DI. The Applicant's process invention requires the use of a solvent (*e.g.*, MTBE) having low miscibility with water as the primary solvent. None of the prior art documents relied upon as primary references (Annexures 3-6) disclose the use of a solvent having low miscibility with water as the primary solvent. Moreover, none of the prior art documents address the same problem as the Applicant's invention and accordingly it should not be expected that the prior art documents should teach away from using MTBE to solve this problem. In view of the foregoing, where the facts of the present case have been clearly distinguished, it is submitted that the Opponent's reliance on this case law stands flawed and misplaced and ought not be considered.

* IN Re RICHARD WOODRUFF 919 F2d 1575

The Opponent has relied on this case law to argue on the premise that when the difference between the claimed invention and the prior art is in some ranges or other variables within the claims, the Applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range. The Opponent has unsurprisingly failed to appreciate the Applicant's invention and has equated the use of diethyl ether in the prior art to the use of MTBE in the Applicant's invention which is incorrect. The Applicant reiterates that none of the prior art documents provide a solution to the problem of the requirement of rigorous exclusion of water. It has to be appreciated that diethyl ether has been used in the prior art only as a secondary solvent and accordingly the comparison, if any, has to be between MTBE and THF (prior art). The unexpected result or surprising effect in the Applicant's invention over the prior art is that the use of MTBE obviates the requirement for the rigorous exclusion of water. In view of the foregoing, where the facts of the present case have been clearly distinguished from the case relied upon, it is submitted that the Opponent's reliance on this case law stands flawed and misplaced and ought not be considered.

* EPO BOARD OF APPEALS CASE NO. T 0228/98

* EPO BOARD OF APPEALS CASE NO. T 0051/97

* EPO BOARD OF APPEALS CASE NO. T 0948/01

* PFIZER VS APOTEX Fed.Cir 2007

* 396/DEL/96 INDIAN PATENT OFFICE

The Opponent relied on these case laws to argue that routine experimentation with a reasonable expectation of success renders an invention obvious. The Opponent's reliance on these case laws is inappropriate given the particular circumstances of the Applicant's invention. As explained earlier, prior art processes for preparation of boronic esters, including the process disclosed in the prior art ('309), required rigorous exclusion of water, and were difficult to perform on a large scale. The Applicant's invention stems from the premise that rigorous exclusion of water is not required when the reaction is conducted in a solvent system in which the primary solvent is an ether solvent that has low miscibility with water. The use of a solvent having low miscibility with water as the primary solvent is an entirely new and inventive solution to the problem of the deleterious effects caused by the presence of water in the reaction mixture. Moreover, as stated at paragraph [029] of the specification, when following the prior art processes, even if water is successfully excluded during the reaction, deterioration in diastereomeric excess is often observed during workup and isolation of the product.

By contrast, the Applicant has discovered that rigorous exclusion of water is not required before, during, or after the reaction, when the reaction is conducted in a solvent system in which the primary solvent is an ether solvent that has low miscibility with water. In fact, as stated at paragraph [052], water actually can be intentionally added to the reaction, without deleterious effect.

In the process disclosed in '309, THF is employed as the primary solvent. THF is an ether solvent, but it has high miscibility with water. In examples 1, 2, and 3 of '309, diethyl ether is present as an additional solvent. However, THF is always present in greater amount. By contrast, the process of the present invention requires the use of a solvent having low miscibility with water as the primary solvent.

In view of the above, it is submitted that none of the documents cited by the Opponent provide a reasonable expectation of success in selecting an alternative to THF. Moreover, the superior properties of MBTE demonstrated in some entirely unrelated chemical reactions would not in any way lead the ordinary person skilled in the art to use MBTE to overcome the problem of the requirement of rigorous exclusion of water. In view of the foregoing, it is submitted that the Applicant's reliance on these case laws is misleading and ought not to be considered.

* EPO BOARD OF APPEALS CASE NO. T 0369/94

The Opponent's reliance on this case is flawed and inaccurate. The Applicant reiterates that the use of MTBE as a primary solvent in such processes has not been taught in the prior art. Moreover, the skilled person, from the knowledge of the superior properties of MTBE, would not have been motivated to use it to overcome the problem of the requirement of rigorous exclusion of water. It should be appreciated that, while the fact that the Applicant's invention is suitable for large scale production of bortezomib is certainly a critical point which distinguishes it from the prior art, it is not the only point on which the Applicant's invention hinges on, as explained hereinabove.

Moreover, the Opponent's assertion that "... a commercial batch at a time produces around 25 to 50 mg of the product" is denied as it is unclear as to how they have advanced such baseless contentions. It is submitted that it is clear that such a product (bortezomib) which generates huge revenues worldwide is produced in commercial batches of a much larger scale than that asserted by the Opponent.

Without prejudice to the above, the Learned Tribunal's attention is respectfully invited to the specific language of Section 25(1 Xe) which is as reproduced in part as under:

*"the invention so far as claimed in any claim of the complete specification is obvious and **clearly** does not involve an inventive step.... "*

It is most respectfully submitted that **refusal of a patent in opposition proceedings should be 'only in clear cases'*** where it is evidently clear that no inventive step is present. This interpretation has been consistently followed in all established patent jurisdictions. In this context, the patentee draws the attention of the learned Tribunal to the following excerpt from the text book 'Patent Law' by P. Narayanan (page 213-214, 4th Edition) (**Enclosure A**) which unambiguously elucidates this concept: *"Refusal only in clear cases. Under s.64 (1)0 obviousness and lack of inventive step is also available as a*

ground for revocation of a patent by petition before the High Court. In opposition proceedings under s. 25(1)(e) and 25(2)(e) it must be shown that the invention "clearly" does not involve any inventive step while there is no such qualification under s. 64(1)(f). This shows that if the matter is in doubt, the Tribunal may allow the grant leaving the question to be finally decided, when an occasion arises, by the High Court.

Referring to the corresponding provisions of the U.K. Act, Diplock, L.J. observed: "This difference in phraseology of the corresponding paragraphs in s. 14 and s. 32 reflects the difference in the character of the proceedings upon opposition to the grant of a patent and in an action for the revocation of a patent. The effect of the former is to dismiss the Applicants' Claim in limine in pursuance of the public policy, inherent in the adoption of a system of granting only 'examined patents', that the register shall not be cluttered up with patents which would be certain to be revoked by the court in a revocation action. To allow such patents to be granted would not only place Applicants for such patents in a position to threaten unmeritorious and costly infringement proceedings against persons exercising their common law rights to engage in manufacture and trade, but would also reduce the status and value of valid 'examined patents' to little better than deposit patents is apparent both from the wording of s. 14(1)(e) and from the comparison of the procedure under that section with the procedure in an action for revocation, that the jurisdiction to refuse the grant of a patent on the ground specified in that paragraph should be exercised only in clear cases. This does not mean that it should only be exercised in cases which are on the face of them simple cases. The right principle is that if on the face of the written evidence filed there appears to be a bona fide conflict of fact or credible expert opinion upon a question on the answer to which the existence or non-existence of the ground for refusal specified in s. 14(1)(e) depends, the Tribunal should not exercise his jurisdiction to refuse the grant unless, after cross examination of the witnesses if he thinks fit to order it, the conflict is clearly resolved in favour of the party opposing the grant. "

In *General Electric Co. (Cox's) Patent*, Buckley, L.J., observed. "It seems to me that the test can be stated, perhaps more simply, in these terms: Is it clear on the evidence before the Comptroller that, if the issue of obviousness (assuming that to be the ground relied on) were fought out in a full scale revocation action, the claims would be held bad for obviousness? If the answer is affirmative, then it is right that the patent should be killed in its infancy. If the answer is negative, the patentee should not be deprived of his patent without the protection of a full scale action. In other words, s. 33, like s. 14, is designed to clear the register of patents which are manifestly untenable. It is not intended to provide a method of disposing of truly contentious cases". In opposition, proceedings, at that stage in the life of a patent, one has to be quite satisfied, so far as the question of obviousness is concerned, that there is not really any case left at all upon the application. "

It is submitted in view of the exhaustive and detailed arguments presented in the reply statement, at the hearing and the written arguments herewith, the Applicant has advanced a strong case of inventive step in its favour. Consequently, it follows that a clear case has been established that the subject patent application has inventive step and it is humbly submitted that this ground of opposition cannot be maintained and should be decided in favour of the Applicant.

(G-3) DECISION ON OBVIOUSNESS AND INVENTIVE STEP:-

According to section 2(1) (j) of the Patents act 1970 (as amended) the "inventive step" has been defined as a feature of an invention that involves technical advancement as compared to the existing knowledge and having economic significance or both that makes the invention not obvious to a person skilled in the art . Therefore, to have " inventive step" the subject matter of the invention must possess.

(a) technical advancement compared to existing knowledge ; or Economic significance; or both;

(b) to such an extent that it does not become obvious to a person skilled in the art.

In general according to various case laws as discussed above following approach is adopted to assess the technical advancement compared to existing knowledge :

- (a) Identifying the Closest Prior Art;
- (b) Assessing the technical results or effects achieved by the claimed inventions when compared with the closest prior art;
- (c) Defining the technical problem to be solved by the impugned invention;
- (d) Examining whether or not a skilled person starting from the closest prior art would arrive at something falling within claimed invention by following the suggestion made in the prior art.

If the technical results of the impugned invention provide reasonable improvements over the closest prior art and such technical results in ordinary course of the activity by the person skilled in the art cannot be achieved, the subject matter of the invention may be said to have an inventive step. The invention can be understood as providing the improvements if such improvements necessarily result from the claimed features of all that is claimed. If however there is no improvement but the means of implementation are different, the technical problem can be defined as provision of the alternative to the closest prior art. The technical progress shown in comparison with the commercial products could not be a substitute for demonstration of inventive step.

The opponents have brought into the notice the prior art citations as mentioned in the para "D" .

The closest prior art with respect to the claims or impugned application are annexed as 3,4,5,6, 7,8,9,10,12,15,16, and 18.

Annex 3 discloses process for preparation of α -halo boronic ester by using Lewis acid as catalyst at temperature of 0-30°C (column No:1, line numbers 34-42) which is similar to impugned invention using the solvent THF and acyclic ether solvent diethyl ether having low miscibility of 6.8% w/w.

Annex 10 discloses ortholithiation process for synthesis of 2-chloro-6-methyl aniline which discussed criticality of the solvents used in the reaction and, discloses that if lowly miscible ether solvent MTBE and or diethyl ether is used , results in obtaining good product yield and purity as compared to using THF as major solvent. This indicates to a person skilled in the art that using lowly water miscible solvent like MTBE or diethyl ether would lead to better product and the skilled person in the art would be motivated

to replace THF with MTBE with the reasonable expectation of success of expected increase in yield and purity of the final product.

Annex 8 discloses monolithiation reaction discussed in preceding Para. This uses solvent mixture including THF and MTBE which results in increase of yield almost 10%.

The annex 9 & 12 teaches the use of solvent system comprising lowly water miscible ether (particularly MTBE) and THF in ratio of 1:1 and 3:1 and resulting into higher purity of the final substance.

The applicant claims that the ether of low miscibility having less than 5% w/w miscibility with water (like MTBE) would be capable of affording good results. However the applicant failed to prove that how the very low miscibility ethers (eg. MTBE) shows better results compared to bit higher miscibility ether like diethyl ether. There is no comparative data which could compare between these two kinds of ethers to show the unexpected or improved results in using ethers of miscibility less than 5%.

The applicant evidence of expert matches with the reply statement of applicant therefore adds nothing to justify the inventive step.

From the teaching of prior art citation annex 9 and 12 a person skilled in the art could gather the knowledge that by increasing the ratio of low miscible ether in solvent system or completely replacing the THF the better results are expected. In such circumstances a person skilled in the art would carry out the routine experimentation to optimize the % age of each solvent (polar and non polar or H₂O immiscible ether and THF) to obtain the best results.

Annex 7 wherein prior art discloses that MTBE is the superior solvent over the THF.

The economic significance has not been pleaded by the applicants and opponents, therefore applicants appear to base inventive step of this invention only on technological advancement . This technological aspect is well known before the priority date as is evident from the above discussed prior art.

The MTBE is being of high commercial interest both in terms of efficacy and cost effectiveness, therefore being the most effective alternative as ether solvent. The yield of final product of processes similar to the present impugned invention , where rigorous exclusion of water takes place ,employing MTBE as solvent is better than the other solvents like diethyl ether and THF if used.

The applicant has pointed out that the solvent systems of impugned invention when used in the process obviates the requirements for the rigorous exclusion of water, gives high yield and purity even in large scale operation and then clearly involves inventive step.

This contention of the applicant is not agreeable as it is always expected to obviate the said requirement if higher amount of water immiscible solvents like MTBE which has less than 5% water miscibility is used in the solvent system, therefore the same is not unexpected phenomenon therefore does not contribute to inventive step.

Finally in view of all the above discussion the impugned invention lacks inventive step and is obvious to a person skilled in the art as the person skilled in the art would arrive at the conclusion of the present invention with a reasonable expectation of success by following the teachings of the prior art citations presented by the opponents.

(H) NOT AN INVENTION/NOT- PATENTABLE

(H 1) OPPONENTS ARGUMENTS

Since the impugned application lacks inventive step and is obvious in light of the cited documents, it does not qualify as an invention under Section 2(1)(j) and ought to be rejected. In view of the above the patent application may be rejected in toto as it is in breach of the various provisions of the Act as placed before the Ld. Controller with the representation as well as at the hearing.

(H-2) APPLICANTS ARGUMENTS:

Applicants argued that they have established that the present invention is non obvious and involving the Inventive Step, therefore, the argument of the opponents is not maintainable and therefore should be rejected.

(H-3) DECISION ON NON PATENTABILITY:-- in view of the discussion in para G above the impugned invention lacks inventive step therefore the is not patentable u/s 2(1) (j).

(I) FINAL CONCLUSION: In view of my findings and discussions above after considering the submissions made by both the parties,their evidences,arguments and all the documents submitted and all circumstances of this case, I conclude that the claims 1 to 63 of the instant application are not allowable as being obvious to person skilled in the art and lacking an inventive step. Therefore, the claims do not constitute an invention u/s 2(1)(j) of the Patents(Amended) Act,2005.

(j) ORDER:- Therefore, in view of my findings and observations I hereby order to refuse the grant of the Patent on this application.

No order for cost.

Dated: 24/07/2009

sd/-

**(DR. NILANJAN MUKHERJEE)
ASSTT. CONTROLLER OF PATENTS & DESIGNS**