The Patents (Amendment) Act, 2005

And

The Patents (Amendment) Rules, 2006

In the matter of Patent No. 209251

(Application No. IN/PCT/2002/00785/DEL)

In the matter of opposition u/s 25(2)

M/s Sugen Inc., USA and Pharmacia and Upjohn Co., USA……..The Patentee

M/s Cipla, Mumbai, India……The Opponent

Hearing held on 18-21, December 2012

Present

Mr Praveen Anand, Ms Archana Shankar, Mr Devinder Singh Rawat and Mr Aditya Gupta
Of M/s Anand and Anand, Gurgaon……Agent of the patentee

Mr Sanjeev K Tiwari and Mr Amrish Tiwari
Of M/s K & S Partners, Gurgaon……Agent of the patentee

Mr S. Majumdar, Ms Sanchita Ganguly, Ms Mythil Venkatesh and Mr Abhishek Sen
Of M/s S. Majumdar and Co., Mumbai…….Agent of Opponent

Mr Kleiman, Mr Roy F Woldron and Mr Fadi Haddadin ……..Representative of the patentee

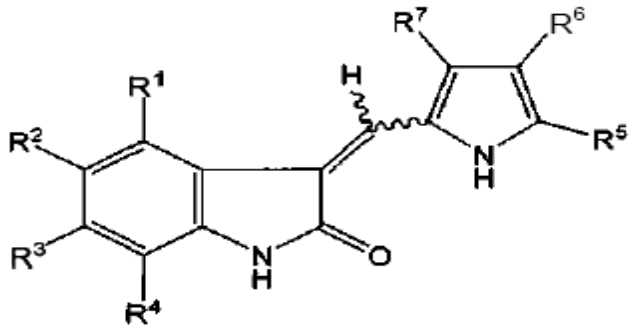
Mr Manjinder Singh……Representative of the opponent

Dr Sunil Gautam, Examiner of Patents and Designs, Patent Office, Delhi

Decision

(A) The application No. IN/PCT/2002/00785/DEL (Pyrrole substituted 2-indolinone protein kinase inhibitors) was filed on August 9, 2002 (national phase entry) for grant of patent by M/s K & S Partners, Gurgaon on behalf of M/s Sugen Inc., USA and Pharmacia and Upjohn Co., USA. International application no. was PCT/US01/04813 and international filing date was February 15, 2001. The application claimed priority of three US applications viz. 60/182,710 dated 15/02/2000, 60/216,422 dated 06/06/2000 and 60/243,532 dated 27/10/2000. The application was published u/s 11A on January 19, 2007. Request for examination was filed on September 8, 2005. First examination report (FER) was issued on May 17, 2006. Response to FER was filed on June 1, 2006. The application was granted as IN 209251 on August 23, 2007. The application was published u/s 43(2) on October 5, 2007.

(A1) The application related to 3-pyrrole substituted indolinone compounds of formula I, which modulate the activity of protein kinases. The application as granted consists of 11 claims. Claim 1 to 6 are directed towards formula.

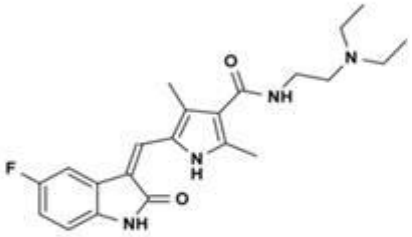


(I)

Claim 7 and 8 are directed to sunitinib and its maleate salt respectively.

Claim 7:

A compound as claimed in claim 1 having formula



or a pharmaceutically acceptable salt thereof.

Claim 8:

A compound as claimed in claim 1, wherein the compound is L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide.

Claim 9 relate to a specific compound.

Claim 10 related to the pharmaceutical composition comprising the compounds of the previous claims.

Claim 11 is omnibus claim.

(A2) A post-grant opposition was filed by M/s S. Majumdar and Co., Mumbai on behalf of M/s Cipla on September 1, 2008. After all the proceedings were over, hearing u/r 60 was held on February 21, 2012. Decision revoking the patent 209251 was issued by the controller on September 24, 2012. The patentee filed writ petition against the said decision. On November 27, 2012, the Hon'ble Supreme Court set aside the decision of Controller with directions to Controller to dispose of the opposition afresh after giving opportunity to each party to raise contentions for and against the Joint recommendation of the opposition board.

(A3) Under such directions, hearing u/r 60 was held afresh from December 18-21, 2012.

(A4) All the submissions and evidences put forward by both the parties have been taken on record and duly considered. For the sake of brevity and to avoid repetition and conciseness of the decision, the detailed contentions taken in the written statement of the opponent and reply

statement of the patentee has not been reproduced here. The main contentions raised by both the parties during hearing have been noted below.

(B) Arguments of Patentee

(B1) The patentee made four preliminary objections which are as follows –

(a)That the documents numbered Dl, D2 and D3 and cited by the opponents as prior art are inadmissible since Section 25 (2) (b) of the Patents Act has not been taken as a ground either in Form 7 or in the written statement. The patentee submitted that the opponent has relied upon prior public knowledge and use but not on prior publications.

The patentee placed the following cases to support their argument –

-Court of Appeal in General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd., t19727 RPC 457

-Union of India vs Ibrahim Uddin & Anr.

(b)That the reply evidence by the opponent was time barred. The patentee submitted that they have filed the reply statement along with evidence on the 29th October 2008 and consequently the cutoff date for the filing of evidence in reply by the opponent was admittedly 5th December 2008.

(c) That Dr. Cui's affidavit dated 3d June 2009 was not supplied to the Opposition Board and hence the Board's recommendation stood vitiated or at the very least could not be taken into account by the hearing officer. The patentee submitted that the recommendations were made by the board without looking at all relevant material.

(d)That the reply evidence has been filed beyond the scope of Rule 59 according to which the said evidence is to be "strictly confined" to the evidence of the patentee. The patentee submitted that the affidavits of Dr. Rao and Dr. Phull contain extensive references to the reply statement (as opposed to the patentee's evidence) and that the mandatory requirement of Rule 59 has been violated.

(B2) On the above mentioned preliminary objections, I opine the following –

(a) I rely on paragraph 16-48 from Patent law by P. Narayanan

“An invention may have become “publicly known” through documents or books published prior to the date of the patent. It is not necessary that the invention should be used by the public as well as known to the public. If the invention and the mode in which it can be used

have been made known to the public by a description in a work which has been publicly circulated, or in a specification duly enrolled, it avoids the patent, though it is not shown that it ever was actually put in use"

I observe that D1, D2, and D3 are published before the priority date of the impugned patent and therefore are considered as "publicly known".

(b) For filing the reply evidence, petition was filed by the opponent which was considered by the office. Therefore, the said evidence by opponent is not time barred.

(c) Any document which is not a part of the pleadings under Rules 56 to 60 cannot be sent to the Opposition Board in accordance with the Rules. It is observed that the affidavit of Dr. Cui has not been filed in accordance with rule 60. However, at the time of hearing the said affidavit has been taken on record.

(d) I observe that Mr. Rao has responded to the technical issues raised. By looking at the essence of Rule 59, the Evidence as filed by the opponent after the Reply statement and evidence of the patentee can refer to the Reply statement and the same has been considered. If the opponent is not allowed to rebut the reply statement of the patentee it would be inconsistent with the principles of natural justice.

I rely on the judgment of the Hon'ble Delhi High Court (Division Bench) (Phonographic Performance Ltd. through it authorized representative Debasrita Das Biswas Vs. Radio Mid Day (West) India Ltd. (2010(43)PTC377(Del)

'it is clear that constitutional tribunals and statutory bodies are entitled to adopt suitable procedures which are just and fair and compliant with the principles of natural justice. *'*

(C) Arguments of the opponent during the present hearing

(C1) The opponent has pleaded the following four grounds out of which u/s 25(2)(d) has been dropped by opponent. Therefore the discussion will be restricted to the grounds of Section 25(2)(e), 25(2)(f) and 25(2)(h) –

Section 25(2)(e) – That the invention is obvious,
Section 25(2)(f) – That the subject matter is not an invention and;
Section 25(2)(h) - That there has been a failure to disclose information required in Section 8.

(C2) The opponent has relied upon the following prior art documents –

Document	Assignee	Priority date	Publication date
D1 (US5886020)	Sugen, Inc	June 7, 1995	March 23, 1999
D2 (WO9850356)	Sugen, Inc	May 7, 1997	November 12, 1998
D3 (WO9961422)	Sugen, Inc	May 29, 1998	December 2, 1999.

The opponent has presented a detailed comparison of the three prior art documents with the instant specification in a tabular format.

(C3) Opponent submitted that development of Sunitinib, (the compound as claimed in Claim 7) took about 16 years and this has been corroborated in the Cui affidavit of October 2008. The patentee filed D1 (US5886020) in 1995 on finding that indolinones with pyrrole substitution could be useful in inhibition of several important tyrosine kinases. Then patentee filed D2 (WO 98/050356) which was published in November 1998. Then patentee filed D3 (WO 99/06142) which was published in December 1999 claiming earliest priority of May1998. Both D2 and D3 identified a large number of tyrosine kinase inhibitors. In the instant patent, the patentee indicated about 204 compounds while claiming several thousand by way of markush structure. Application for drug approval for particular compound Sunitinib was made in 2005.

(C4) The opponent submitted that the entire three prior art originated from the patentee and involved common inventors and, therefore, the list of the compounds in each of the three prior art are all known to the patentee. The background, prior art, the objects, the utility of the compounds and method of formation of the markush structure of the instant patent are same as those of D1 to D3. D1, D2, D3 and the instant patent did not specify problem being solved. The background of the instant patent application talks about protein kinase inhibitors and their role in cancer. There is mention of attempts been made to identify small molecules that are protein kinase inhibitors. Thus there was parallel research in the field as no prior art is added to the background from 1995 to 2000.

(C5) The opponent submitted that there is no data to show that the compound Sunitinib is better than other compounds covered in markush. Hence Sunitinib is one of the alternatives of the compounds covered in the Markush structures. It is known jurisprudence if one alternative is obvious in the group covered by markush the others also are rendered obvious.

(C6) The opponent submitted that the Cui affidavit (at para 6 f) points out that when both SU 5416 (compound of D1) and SU6668 (compound of D3) failed in the clinical trials (which admittedly occurred much after the filing of the impugned patent) "*leading Sugen to almost abandon the project. However on the insistence of one of the inventors Sugen continued its research efforts and eventually after lot of effort they developed Sunitinib."* . The patentee did not provide comparison in the instant patent application over the concurrently developed compounds of D1to D3. There is overlap of compounds (compound 132 of the instant patent with D3). The molecule Sunitinib was developed over period of 16 years but the attributes of the product as a drug became known only in 2005. . The opponent stated that D1, D2 and D3 when read by a person of average skill in the art would know that he has to go forward in the same path traced by D1, D2 and D3 and in the process try to arrive at alternative compound suitable for a similar purpose by following the teachings of each of such documents individually and in combination. This is the motivation in the present case.

(C7) The opponent submitted that Dr.Cui stated in her affidavit (paragraph 6f) that it was only "per chance" (which admittedly means "accidentally"), found that the basic amide substituent on the R6 position of the pyrrole ring increased the kinase inhibition generally and more particularly improved solubility and metabolic stability. There is no data in the Cui affidavit to show comparison with the similar known compounds disclosed in prior art. Though the markush structure is claimed only one compound has been described in the specification of the instant patent with respect to both in vitro and in vivo activities and it is mentioned in the specification that the compounds are expected to have therapeutic activity. This indicated further trial and error with the compounds of the instant patent to find the best compound. Having arrived at best compound in 2005 (increased kinase inhibition effect in general and improved solubility and metabolic stability) by chance, the patentee made voluntary amendments in 2005 where unlike in the as- filed document claiming 6 specific compounds (claim 49 of PCT claims) only 2 specific compounds were claimed (as in claim 7 and claim 9). Such findings were therefore admittedly not arrived at on the priority date of the invention but only after five years of the priority date.

(C8) The opponent submitted that the patentee has stated in the instant specification under the sub-heading *"State of the art - The following is offered as background information only and is not admitted to be prior art to the present invention."*

In this regard, reference was made by the opponent to Article 54 of the EPC which states –

"1) An invention shall be considered to be new if it does not form part of the state of the art.

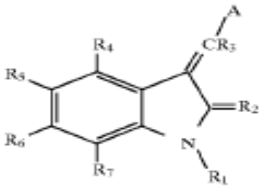
(2) The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application."

The opponent submitted that the patentee admits state of art as background information and not prior art. Even in that case it forms existing knowledge against which the technical assessment ought to be done.

(C9) The opponent submitted that in page 7 of the instant specification as filed, the substituents R1, R2, R3, R4, R5 and R6 are defined. R6 is stated to be selected from the group consisting of hydrogen, alkyl and –C(O)R10. Later R6 was amended to be only –C(O)R10 at the time of prosecution. At the time of filing there was no specificity about the group R6(H, alkyl or –C(O)R10, which is now the diethyl amide group). This amide group of Sunitinib is allegedly the activity imparting group according to the patentee. The opponent referred to Table 1 in the instant specification wherein a list of 204 compounds stated to be representative compounds of the invention is provided. All compounds which fall in this list do not possess an amide group at the R6 position. These compounds are 1, 2, 3, 4, 5, 41, 90 upto 104. The opponent submitted that the claim of the patentee and the statement of Dr. Cui stating that amide substituent at the R6 position increase kinase activity cannot be taken to reflect the alleged inventive merit of the instant invention as the same was never found at the priority date of the impugned patent.

(C10) The opponent submitted that Dr. Cui has stated in her affidavit at paragraph 6(e) that "*we generally ignore markush structure set out in patents; since these are merely a generalization of the possible compounds generated"*. At paragraph 6g the Cui affidavit mentions "*I would expect the compounds that could be formed within the scope of claim 1 to be effective in treatment of solid tumors*….." . The opponent submitted that the compounds of the markush structure are hypothetical and their function is speculative i.e only expectation.

(C11) The opponent drew attention towards compound of Formula III at column 10 of D1



(III)

wherein the values of substituents when read as R1 – H; R2 = O, R3 = H; R4 = R6 = R7 = H; R5 = Halogen and A = Pyrrole ring such that the pyrrole group is substituted at two positions by alkyl groups and at one position by –CONRR' wherein R' is alkyl and the definition of an alkyl group includes $N(CH3)_2$ amino (at column 7, line 12 of D1).

(C12) The opponent submitted that R, R' is H and alkyl respectively. The specification as filed contemplated R6 to be C(O)R10 wherein R10 includes the group –NR13R14 amongst others, and R13, R14 may be independently hydrogen or alkyl. This would amount to R6 being C(O)NR13R14. This definition of R6 falls within the ambit of disclosure of D1, thereby encompassing certain compounds that fall in the markush claim 1 of the instant specification. The opponent submitted that an amendment effected to disclaim prior art cannot change the invention as a whole.

(C13) The opponent submitted that the compound that is arrived at by making the aforesaid substitutions differs from Sunitinib in two aspects viz:

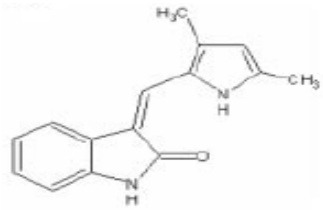
i. the dimethyl group on the terminal amino N atom on the amide group instead of the diethyl group; and
ii. absence of disclosure of the point of the attachment on the pyrrole ring to the doubly bonded carbon connected to the indolinone ring.

(C14) The opponent drew attention to Table 1 at para 8 of Dr. Cui's affidavit which gave a comparison of Sunitinib with D1 compounds viz SU5408, SU5463 and SU5455. The opponent submitted that these compounds chosen by Dr.Cui for comparison of activities with sunitinib do not possess an amide group at the R6 position and thus will not qualify as the closest prior art. The opponent submitted that since the other substituents in the said compounds of D1 also differ from those of Sunitinib, the difference in degree o f activity cannot be attributable to presence of the R6 amide linkage alone. thus comparison of the unlikes have been carried out.

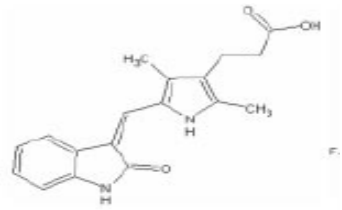
(C15) The opponent submitted that at paragraph 6(e), Dr. Cui while discussing the synthesis of the title compounds has stated that the construction of indolinones with various substituents is a challenge. However when the process disclosed at page 87 of the instant specification is the same as the process disclosed in D3. Thus the basic process conditions used are the same as disclosed in the prior art and the substituents may be selected from the list disclosed in the prior art D1, D2 and D3.

(C16) The opponent relied upon the statements made at paragraph 5.20 of the evidence in reply of Mr. D.R. Rao filed under rule 59 wherein it stated that *"I am aware of article namely "Sunitinib: a novel tyrosine kinase inhibitor. A brief review of its therapeutic potential in the treatment of renal carcinoma and gastrointestinal stromal tumors (GIST)" by Christophe Le Tourneau et al). From the said article it would be apparent SU102662 is a metabolite of Sunitinib and in fact a N-desmethyl metabolite. This clearly indicates that the metabolization is at the N-ethyl position and not at the intervening alkyl position as stated by the applicant and in the Cui affidavit in paragraphs 12-13. Accordingly there was apparently no specific draw-back with the compound of D3 and that formation of a similar compound with a slight modification in structure is but mere trial and error and within purview of a skilled worker. Without prejudice to above even if the skilled worker while trying to develop further compounds might find that the said alkyl position led to easy metabolization and reduced half life of the compound, he would obviously try to overcome the same by removing the alkyl group from position R9 so that the substituent CONR13R14 are directly on the R9 of the pyrrole ring as this would least disturb the known compound of D3 so that the activity is not compromised. I say that even this is mere trial and error within the purview of regular experiment of skilled worker, and in the course if another compound with similar biological activity evolves it cannot be regarded as innovative but mere verification of result so that the known compound with known activity is retained with least modification."* The opponent submitted that this disclosure makes it clear that the metabolization occurs at the terminal N atom and not at the position of the (Alk1) group.

(C17) The opponent submitted that as mentioned in paragraph 16 of Cui affidavit SU5416 exhibited low potency, very limited aqueous solubility, and low biological exposure whereas SU6668 exhibited very high protein binding resulting in lack of efficacy in humans.



SU5416



SU6668

The opponent submitted that the failure of SU 5416 and SU 6668 admittedly occurred in clinical trials which were around 2005, which is much later than the priority date of the instant patent. Hence at the priority date the patentee would not have known the outcome of the research with the compound of D1-D3. The opponent submitted that finding of the role of C-amido group at R6 position came after failure of SU5416 and SU6668.

(C18) The opponent submitted that paragraph 17 of Cui Affidavit says that SU6668 has a propionic acid at R6 which provides an excessively strong protein binding interaction whereas in SU5416 this additional binding is absent. The opponent submitted that the optimal polarity of the group at R6 plays a key role. An acid group been highly polar and the hydrogen been highly non-polar cause improper interactions. Therefore finding a group with polarity in between the extreme ends is a matter of trial and error.

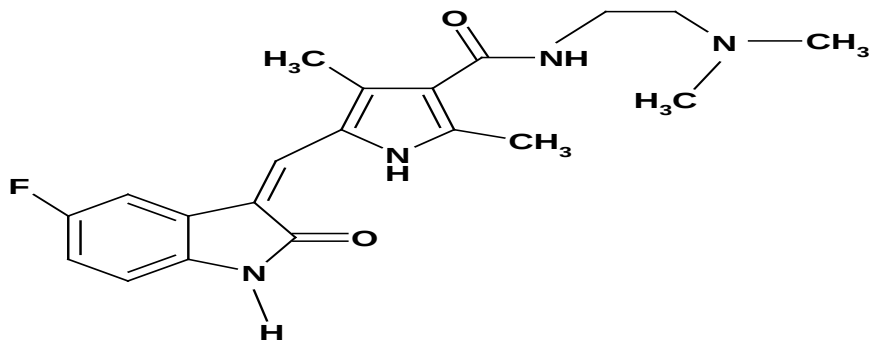
(C19) The opponent submitted that disclosure of D3 in the paragraph bridging pages 9 and 10 makes it obvious for a person skilled in the art to combine the teachings of D1 and D3 to formulate a compound which does not possess the (Alk1) group but retains the protein tyrosine kinase inhibitory activity.

(C20) The opponent submitted that the patentee has not provided comparative tests between compounds that possess the intervening (alk1) group vis-à-vis the compounds lacking the same to demonstrate that they are not efficacious and also are susceptible to metabolization.

(C21) The opponent submitted that reference 39 of the article "Anti-angiogenesis agents – published 2006" which is annexed to the patentee's reply statement makes it evident that dose finding studies of SU6668 were conducted around 2005.

(C22) The opponent submitted that there is teaching paragraph 2 at page 23 of D3 to combine the oxindole and the aldehydes in all possible combinations. Amongst the various oxindoles and aldehydes in the combinatorial library, the compounds 5-fluorooxindole (line 10, page 24), 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylaminoethyl) amide lines 31, 32 at page 27 of D3 are disclosed. Thus following the teaching of above portion of D3 forming a compound combining these two oxindole and aldehyde namely the compound 132 of the impugned patent which is *"5- (5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-lH-pyrrole-3-carboxylic acid (2-dimethylaminoethyl)amide":* The said compound is synthesized by taking -5-Fluoro-1, 3-dihydro-indol-2-one and condensing with 5-formyl-2, 4-dimethyl-lH-pyrrole-3-carboxylic acid (2- dimethylaminoethyl) amide. This compound is therefore clearly motivated and derivable from D3 without the need for any innovative work.

(C23) The opponent submitted that when 5-fluorooxindole (line 10, page 24), 5-formyl-2,4-dimethyl-1Hpyrrole-3-carboxylic acid (2-dimethylaminoethyl) amide are reacted under the conditions specified which is same as the conditions in the impugned patent, a compound of the following structure is obtained;



(C24) The opponent submitted that the above compound differs from sunitinib at only the terminal N atom in as much as the former bears a dimethyl group instead of a diethyl group in the latter. This compound is compound 132 at page 147 of the impugned patent. *"Example 132: 5- (5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-lH-pyrrole-3-carboxylic*

acid (2-dimethylaminoethyl)amide -5-Fluoro-1, 3-dihydro-indol-2-one was condensed with 5-formyl-2, 4-dimethyl-lH-pyrrole-3-carboxylic acid (2- dimethylaminoethyl) amide to give the title compound."

(C25) The opponent submitted that the reaction conditions for the synthesis of the compounds of the impugned invention is discussed at page 85 (lines 5 to 15) of the instant specification. These conditions are same as that of D3.

(C26) The opponent submitted that D1 discloses compounds bearing a –CONRR' substituent directly attached to the pyrrole ring. D3 generically discloses the diethylamide substituent at the R6 position but with an intervening alkyl group and specifically discloses the dimethylamide substituent at the R6 position without the intervening alkyl group. A person skilled in the art will test and verify the physical, chemical and biological activity of both the compounds and would find out as to which is the best candidate to be taken for further clinical studies. The opponent submitted that minimum structural modifications need to be carried out in the compounds disclosed in D3 which is a matter of routine experimentation for a person skilled in the art. The compounds allegedly claimed in the instant patent specially Sunitinib is obvious over the combined teachings that flow from D1 and D3.

(C27) The opponent submitted that in view of the *structural and functional similarity* of the compounds of D1 to D3 (as observed by the opposition board page 55) and the difference being obviously made by interchangeable substituents, the compounds of the patent under opposition are very much obvious to the skilled person.

(C28) The opponent submitted that D2 teaches compounds with pyrrole substituted indolinones compounds which possess the C-amido substituent on the pyrrole ring at the 4-position of the indolinone nucleus. When such disclosure is read along with the compounds disclosed in D3, Sunitinib is obvious to a person skilled in the art.

(C29) The opponent submitted that at paragraph 18 of Dr. Cui's affidavit, the expert has stated *"the inventors discovered that this substituent provides a very favourable balance of compound properties, while retaining excellent potency."* This statement is indicative of the fact that the

selection of substituents is a mere process of verification of results which exercise is obvious to try. This point was demonstrated by considering the activities of compounds 3 and 19 of D3 which are the chloro and bromo derivatives of SU6668 respectively. The opponent submitted that compound 19 shows IC50 of 0.006µM against FLK whereas compound 80 of the impugned specification which is Sunitinib shows FLK activity with IC50 of 0.13µM. This comparison is noteworthy since the expert has stated that Sunitinib is a potent inhibitor of FLK1. The opponent submitted that such tests can be conducted on each of the compounds disclosed in the prior art with a permutation combination of the various substituents disclosed therein since the backbone or the basic structure is a pyrrole substituted indolinones.

(C30) The opponent submitted that Cui affidavit at paragraph 19 has mentioned that to produce preferred compounds of claim 7 and 9 , which are the Z configuration unnecessary exposure to light which can promote isomerism is avoided. The opponent submit that there is no such mention in the specification about avoiding exposure to light. This thus is a later day development and was not available at the time of invention.

(C31) The opponent submitted that para 21 of the Cui affidavit mentioned that it requires hard work and that the success and failure of various substituents at various position provide more directions towards more experiments. Thus there is mention of the further experiments based on failure and success of the substituents. Moreover it also hints to failure of SU5416 and SU6668 after which Sunitinib got approval.

(C32) The opponent submitted that at paragraph 21 Dr CUI says that the 209251 appears to disclose and claim 3-pyrrole substituted indolinone compounds. Thus even to the expert it appears to be 3-pyrrole substituted indolinone compounds with preferred substituents at various positions and not conclusive.

(C33) The opponent submitted that the Cui affidavit is not binding on Court and it assists the Court. It is not the opinion but the reasoning of the opinion based on knowledge and qualification which has to be used. (ORDER (No.166 of 2012) (IPAB).

(C34) The opponent submitted that Sunitinib is prepared by a similar process (Table 3 annexed to show the overlap of the chemical process), has the same effect, acts on the same receptors in the same pathway as the compounds disclosed in the prior art D1, D2 and D3.

(C35) The opponent drew attention towards paragraph 5 of Cui affidavit dated June 8, 2009, paragraph 23 of the Reply Statement of the patentee, Mr Rao's affidavit at paragraph 5.5, Mr. Rao affidavit at paragraph 5.10. The opponent submitted that the said paragraphs make it clear that certain compounds from the prior art were modified by incorporating substituents which were previously disclosed generically and testing such newly formed compounds for their activity.

(C36) The opponent submitted that when D1 is read with D3, the difference merely lies in the presence of the diethyl substituent and the absence of the alk1 group in markush structure in general and Sunitinib in particular. Such difference can be easily overcome by trial and error techniques i.e. testing compounds with the -CONRR' group at the R6 position and testing compounds with the exact diethylamide substituent but with an intervening alkyl group and recording their various properties. Thus the impugned invention is obvious to try and does not involve any inventive ingenuity.

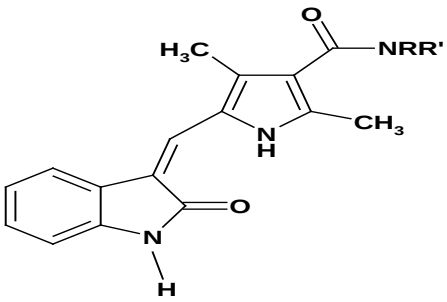
(C37) The opponent submitted that paragraph 20 of Dr. Cui's affidavit stated that D1 – D3 essentially outline the "structure activity relationship" associated with this core. The opponent submitted that though preclinical trials were not available, all applications were running parallel. Therefore the behavior of compounds was known in general. The opponent submitted that the patentee has failed to provide appropriate comparison with closest prior art demonstrating inventive step, if any either in the specification or during the opposition.

(C38) The opponent submitted that from the EP prosecution it is seen that a number of compounds have been deleted and R10 value has been limited. Amendments have also been done in the present case. Form 13 filed on September 22, 2005 has been given without proper reasoning. Form 13 filed on September 22, 2005 has been given without proper reasoning. Amendment may change the claims / scope of protection but the invention does not change. In

other words, if two elements are interchangeable and in case one element is deleted, it does not change the nature of invention as made at the time of filing.

(C39) The opponent submitted that the selection of prior art compounds for the comparative tests is arbitrary. Comparative study is provided with some compounds which are structurally different on the plea that these are indicated in ISR. No comparison with SU 5416 and SU6668 which are the most effective compounds, though structurally different.

(C40) The opponent submitted that D1 teaches pyrrole substituted indolinones compounds and this is evident from the structures of compounds 5.100 and 5.101. However the presence of the –CONRR' substituent at the R6 position is clearly taught at column 10 of D1 and admittedly –CONRR' is the C-amido group. Thus there is no dispute that the generic structure (shown below) is disclosed and taught in D1.



(C41) The opponent submitted that with regard to the interpretation of the structure of the group –N(CH3)2 amino, if the structure as contemplated by the patentee were considered to be the actual structure of –N(CH3)2 amino, the same will work out to be a substituted hydrazine (monograph 4770 from The Merck Index – 14th edition). The opponent submitted that no scientific literature would ever refer to the hydrazine group in the manner as projected by the patentee. Therefore a comma has to be present in between –N(CH3)2 and amino. However even if it were to be considered that R' is an unsubstituted alkyl, then it will be a group of the formula –CONH(alkyl). It is submitted that the application as filed contemplated R6 = -CO(R10) wherein R10 = NR13 R14 and R13, R14 could be H, akyl, etc. Such a group in the instant specification will squarely fall in the definition of the compounds taught in D1. The patentee ought to have differentiated such compounds from Sunitinib in terms of stability and activity to demonstrate

the allegedly claimed unexpected potency of Sunitinib due to the diethylamide substituent at the R6 position.

(C42) The opponent submitted that D2 discloses pyrrole substituted indolinone compounds. D2 is INPADOC family member of D1 and is much broader in its disclosure. The opponent submitted that the 'Q' group is the equivalent of the 'A' group in D1. Upon perusing D2, it is evident that 'Q' is defined by 5 generic structures. On the other hand, 'A' in d1 is specifically stated to be a five membered ring with different values assigned to it. Thus D1 is narrower prior art but originates from D2.

(C43) The opponent submitted that according to the teaching at page 23 of D3 – each oxindole can react with each aldehydes, all oxindoles can react with all aldehydes, some oxindoles can react with all aldehydes and all oxindoles can react with some aldehydes. Thus the oxindoles and aldehydes from the combinatorial libraries can react with one another in different ways.

(C44) The opponent submitted that the referring to substitutions R13 and R14 on the –Z moiety, it is submitted that claim 10 at page 228 of D3 is worded as "-----R13 and R14 are independently selected from the group consisting of: ……. And combined, a five-member or a six-member unsubstituted heteroalicyclic, and ….." From the said claim terminology, it is evident that R13 and R14 may be independently one of the substituents specified and if and only if they are combined, they would be a five or six membered ring. The opponent submitted that these are two independent conditions for R13 and R14 and cannot co-exist in any particular compound.

(C45) The opponent submitted that claim 7 of the impugned patent is one amongst the various compounds claimed in claim of the impugned patent. In other words one will arrive at the structure of Sunitinib (claim 7) only after attributing specific values to the variants described in the Markush structure and claim 7 till date is dependant on claim 1 and derives its patentability from claim 1.

(C46) The opponent submitted that any structural modification of a pharmaceutically active compound is expected to disturb the pharmacological activity. However the expert Dr. Cui has

stated that D1 to D3 teaches the structure activity relationship of the compounds with pyrrole substituted indolinone backbone. This knowledge coupled with the journey through D1 to D3 provides impetus to make sequential structural modifications and test the activities of the resulting compounds.

(C47) The opponent submitted that D3 teaches structurally similar compounds and the motivation to remove the intervening alkyl group comes from D1 which teaches compounds without the intervening alkyl group. Upon improper results with compounds with the intervening alkyl group, the person skilled in the art will verify results of D3 substituents at the R6 position which in effect will be close to the D1 compounds. This cannot be said to be a teaching away as nothing is taught against removal of the intervening alkyl group. Moreover there is no particular problem in the prior art which the patentee sought to solve.

The opponent submitted the judgment of T1060/99

"…….. *the merit of what is presented as an invention is not to be assessed per se but as opposed to the prior art. In that sense, a technical effect resulting from a combination of compounds, plays no role until it is acknowledged as non-obvious having regard to the state of the art. Therefore, it is only in comparison with the closest state of the art that the technical problem must be determined and, on this basis, the inventive step to be assessed*."(page 12 last paragraph).

(C48) The opponent submitted that in absence of comparative data to show improved activity, it cannot be said that the claimed compound is unobvious by mere statement that the modifications made by inventors to reach the claimed compounds are unobvious.

(C49) The opponent submitted that the patentee filed the following documents on December 17, 2012 to show commercial success of Sunitinib –

-Sutent and Nexavar put brakes on renal cell carcinoma,
-Kidney cancer patients should get Sutent on the NHS, says Nice,
-Sutent significantly increases progression free survival for patients with advanced pancreatic islet cell tumors, study stopped early,

-Pfizer hopes to keep Sutent successes coming, Pfizer's Sutent boosts survival, slows tumors in cancer cases all of them represent the factor of secondary consideration.
-The complete responsive Expert report of Sean Nicholson filed in the Pfizer v/s Mylan pharmaceuticals

The opponent submitted that commercial success cannot overshadow or render non obviousness to an otherwise obvious invention. Reference is made to Patent Law by P. Narayanan (4th edition) at page 418 section 16-93 which states that "If an invention is obvious from a technical or practical point of view, it will be invalid even though it was commercially successful and the step taken was not an obvious commercial step to take."

(C50) Not an invention

The opponent submitted that the instant patent suffers from lack of inventive step and the submissions with regard to obviousness and inventive step are adopted for the present ground

(C51) On opposition board recommendations

-The opponent submitted that the board has categorically mentioned that the comparison with compounds of D1 not appropriate.
-The opponent submitted that the board has appropriately observed that compounds of D1, D2 and D3 being structurally and functionally same, comparative tests are necessary.
-The opponent submitted that the board has recommend in favour of lack of inventive step specially when cited prior art shows structural and functional similarity with that of the impugned patent and lack of appropriate comparison with the closest prior art to demonstrate technical advancement, if any.

(C52) Section 8

The opponent submitted that the patentee has failed to comply with the requirements of 8(1) and also 8(2). The details of the corresponding applications as regards the substantially same or substantially same invention have not been furnished. The opponent submitted that the INPADOC family shows 48 applications and all of the same are not provided to the controller even on demand (para 14 and 15 of first examination report).
The opponent submitted the following documents filed on December 17, 2012 .

-Copy of E-Register showing date of grant of IN 209251 i.e. 23.08.2007

-FER-dated May 17, 2006.

-Form-3 (3 Nos.)- filed on August 9, 2002, December 16, 2002 and June 7, 2006.

-The INPADOC patent family list as downloaded from the espacenet. This shows the presence of 48 family members (Exhibit 8A).

-EP 1914376.7 was granted as EP 1255752 on August 8, 2007 which is before the date of grant of the Indian patent i.e. August 23, 2007. This status change is not filed at the Indian Patent Office, which is in breach of section 8(1). The office actions (dated 14.03.2003, 09.01.2004, 10.04.2006, 14.11.2006, and responses (dated 16.02.2006, 24.05.2006, 08.12.2006, 18.01.2007) have not been filed at the Indian Patent Office, which is in breach of section 8(2) (Exhibit 2A)

-US7125905 granted on 24.10.2006 – filing particulars dated 04.01.2005 is not filed at the Indian Patent Office, which is in breach of section 8(1). The office actions (dated 10.11.2005, 07.02.2006) and responses (dated 17.11.2005, 05.05.2006) have not been filed at the Indian Patent Office, which is in breach of section 8(2) (Exhibit 3A)

-US'2004063773 published 01.04.2004- filing particulars dated 14.04.2003 is not filed at the Indian Patent Office, which is in breach of section 8(1). The office actions (dated 16.08.2004, 04.10.2004, 19.04.2005) and response (dated 13.09.2004) have not been filed at the Indian Patent Office, which is in breach of section 8(2) (Exhibit 4A)

-US'2007010569 published 11.01.2007 - filing particulars dated 06.09.2006 is not filed at the Indian Patent Office, which is in breach of section 8(1). (Exhibit 5A)

-US6573293 granted on 03.06.2003 is the counterpart US patent. The office actions (dated 07.03.2002, 22.04.2002, 20.08.2002) and responses (dated 03.04.2002, 22.10.2002) have not been filed at the Indian Patent Office, which is in breach of section 8(2) (Exhibit 6A)

-US7211600 granted on 01.05.2007 – Orange Book listed patent claims a method of treatment and no information regarding this patent has been furnished. Filing particulars dated 16.08.2005 is not filed at the Indian Patent Office, which is in breach of section 8(1). The office action

(dated 15.12.2005) and response (dated 14.03.2006) have not been filed at the Indian Patent Office, which is in breach of section 8(2) (Exhibit 7A)

(D)Patentee's arguments during hearing

(D1) The patentee has placed the following points for analysis of obviousness –

(a)The "Long Jump" test

The patentee submitted that the question to ask is whether the jumper would jump from the prior art line to the inventive concept line. In other words: is it obvious for the person of ordinary skill to take a step from the prior art to the inventive concept given the common general knowledge in a specific industry.

The patentee submitted that the plain meaning of the word obvious according to The Oxford English Dictionary (Second Edition, Volume X) is "the quality of being clearly perceptible, the state or condition of being easily seen or understood; plainness or openness to the eye or mind".

(b)Identifying the person of ordinary skill and his characteristics

The patentee submitted that the onus to define a person of ordinary skill in the art is on the opponent but the opponent failed to offer any evidence on this aspect. The patentee submitted that paragraph 5 of Dr. Cui's affidavit dated October 27, 2008 defined the educational and other qualifications of such a person.

The patentee placed the following cases in support of their arguments–

-*General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd., t1972 1 RPC 457.*

-*Genentech/ Boehringer Manheim, T O455l9l (Volume B, pages 169 - 208, see page 197)*

(c)The subjective test of obviousness

The patentee submitted that in the present case the Assistant Controller of Patents and Designs, during the examination of the case, took the view on the same documents Dl, D2 and D3 that the invention disclosed an inventive step and it would not be appropriate to interfere with that decision without the strongest evidence.

The patentee placed the following cases in support of their arguments –

-*Kirsch Manufacturing Co. v. Gould Mersereau Co,, 6F. 2d 793*

-*Deller's Walker on Patents,2nd edition*

-*Georgia Pacific Corporation v. United States Plywood Corporation, 258 F.2d 124*

-Picard u United Aircraft Corporation, 128 F.2d 632

-Warren Telechron Co. v, Waltham Watch Co., 91 F.2d 472

-Dickey John Corporation u international Tapertronics Corporation, 710 F.2d 329

-Wander v. Antox India Pvt. Ltd., 1990 Supp (1) SCC 727

(d) Burden of proof in post - grant oppositions

The patentee submitted that the opponent's written statement accuses the patentee of not showing or demonstrating or convincingly substantiating some property or the other, but the onus to do all those things was on the opponent.

The patentee placed the following case law –

-F,H, and B. Corporation v. Unichem Laboratories, AIR 1969, Bom 255

(e)The tests of inventive step in different jurisdictions

The patentee placed the following case laws –

-Eli Lilly v. Zenith

-The Yanamouchi Pharmaceutical Co. Ltd. V. Danbury Pharmacal Inc., 231 F.3d 1339

-Otsuka Pharmaceutical Co. Ttd. V. Sandoz Inc., 678 F.3d 1280

-Unigene Laboratories v. Apotex, 655 F.3d 1352 (2011)

-Windsurfing International Inc. v. Tabur Machine (GB) Ltd., 1985 RPC 59

-Pozzoli SPA v BDMO SA (2007) FSR 37

-F. Hoffmann La Roche and Anr. V. Cipla Ltd., CS (OS) No. 89 of 2008

(f) Hindsight analysis impermissible

The patentee placed the following cases in support –

-In Re Fitch, 972 F.2d 1260

-Grain Processing Corporation v. American Maize Products, 840 F.2d 902

-Ortho-McNeil Pharmaceutical Inv. V. Mylan Laboratories Inc., 520 F.3d 1358

(g) Teaching away

The patentee submitted that if the prior art "teaches away" or prejudices the person of ordinary skill in the art from embarking on the path chosen by the inventor, then the invention is non - obvious. The patentee submitted that, the prior art D3 taught against the direct linking of the pyrrole ring with the polar group and taught the skilled person to mandatorily use an intervening "alk" linker or bridge. The patentee submitted that they have worked against this prejudice and have shown that removal of this "alk" bridge is merely a "paper tiger" and thus their invention is non - obvious.

The patentee placed the following case in support –

- *Pozzoli SPA v BDMO SA (2007) FSR 37*

(h) Objective indicia of non – obviousness

The patentee submitted that the court stated that such secondary considerations as commercial success, long felt but unresolved needs, failure of others etc. might be utilized to give light to the circumstances surrounding the origin of the invention and may have relevancy as indicia of non - obviousness.

The patentee placed the following case in support -

-Extract from Chisum on Law of Patents

-Graham v. John Deere Company, 383 US 1

The patentee has provided evidence of eight such objective guideposts in the present case which are as follows –

1. The drug SUTENT was a huge commercial success as per Sean Nicholson's affidavit.

2. Long felt need - the FDA release said that the drug had been simultaneously approved for two indications and has been given the expedited approval within the six months. Also marketing approval for SUTENT has been granted in over 105 countries.

3. The failure of other drugs including drugs invented by the patentees themselves including compounds 5416 and 6668 and many others throw light on the inventiveness of SUNITINIB.

4. Copying by multiple parties

5. The amount of money spent on R&D is huge for the SUTENT project.

6. The amount of time spent on R&D from 1990 to 2006 is another factor.

7. The unexpected results achieved by SUTENT are demonstrated by the FDA release. SUTENT is now regarded as the standard of care.

8. Corresponding patents have been granted in over 91 countries.

Technical submissions on Obviousness by the patentee

(D2) The patentee submitted in paragraph 6(d) of Dr. Cui's affidavit dated 27thOctober 2008, (hereinafter referred to as the first affidavit) states that the pyrrole substituted indolinone chemistry involves two challenges comprising:

(a) The construction of indolinone with various substituents

(b) The construction of pyrrole with different substituents

(D3) The patentee submitted that Dr. Cui further states that the substituents on the indolinone core play a key role in terms of kinase selectivity profile. The kinase selectivity profile has been discussed by Dr. Cui in paragraph 6(b) of her affidavit. She further states that the substituent on the pyrrole rings also play a very important role in potency, kinase selectivity profile and pharmaceutical properties.

(D4) The patentee submitted that during prosecution of the application, they have limited R6 in claim 1 to C(O)R10and R10 to N(R11)(CH2)nR12. The patentee submitted that the scope of the patent is not determined by the description but by the claims and therefore what has not been claimed is disclaimed.

(D5) The patentee submitted that on Pages 30 to 53 disclose the example compounds and pages 97 to 159 disclose the best method for preparing these compounds. It is further submitted that the patent specification from pages 195 to 209 have a complete and fair disclosure of compound 80 which according to the patentee is the best compound and was later developed and subjected to pre-clinical studies and clinical trials and eventually marketing approval obtained thereof.

(D6) The patentee submitted that compounds from D1 and D3 were tested and went right uptil the stage of clinical trials but eventually failed. Regarding verbatim language used in the specifications of D1 to D3 and the instant patent, the patentee submitted that it is common and desirable to have similar language for the background information and need not be originally written particularly if it is from the same applicant or inventors.

The patentee submitted the following case law in support –

-F. Hoffmann La Roche and Anr. V. Cipla Ltd., CS (OS) No. 89 of 2008

(D7) The patentee submitted that in D1 all the claimed compounds namely claims 1, 5, 10, 13, 17, 22, 25 & 30 comprise of a substituent, amino-benzylidenyl at the 3 position of the indolinone compound. Therefore, the teaching of this document is clearly directed towards "Aminobenzylidenylindolinone compound**s**" and not pyrrole substituted indolinone compounds.

(D8) The patentee submitted that D1 discloses millions of compounds represented by the five different Markush formulae in (i) (Col. 9), (ii) (Col.9), (iii) Col. 10), (iv)(Col.11), and (v) (Col. 12). Markush formula III in Col. 5 of D1 is the only compound which includes amongst several other 5-membered hetero-aryl rings such as thiophene, pyrazole, imidazole etc., a pyrrole substituent as well.

(D9) The patentee submitted that Markush formula III is the only compound that has not been claimed in the claims by the Document D1 and therefore there is no teaching in D1 to work or modify Markush formula III leave alone identifying selecting and substituting pyrrole at the 3' position on the indolinone compound.

(D10) The patentee submitted that the preferred compounds of each of the Markush formulas were provided in Columns 9 to 12 of D1 and comprise the following:

MARKUSH FOMULA	**PREFERRED COMPOUND**
I	SU4932
II	SU4312
III	SU5416
IV	SU5204
V	SU4942

(D11) The patentee submitted that D1 discloses the following number of specific compounds:

Example compounds	129
Test compounds	128
Preferred compounds	5
In vivo activity data compounds	6
Claimed compounds	19

(D12) The patentee submitted that Dr. Cui in her affidavit compared the IC50 values of the following compounds with the preferred compound of IN209251, compound 80. The compounds of D1 that were compared to claimed compound80 (SU11248) were SU5408, SU5463 & SU5455 (some of which were identified by the ISR).

(D13) The patentee submitted that SU5408 and SU5455, both had an ethoxy carbonyl substitution at the 4' position on the pyrrole ring. SU5408 has a dimethyl substitution on the pyrrole ring and SU5463 has one-methyl substitution. SU5455 had carboxylic acid on the 5' position and ethyl group at the 3' position and the methyl group at the 2' position. None of the said compounds had carboxyamide substitution at the 4' position leave alone a diethyl aminoethyl carboxyamide substitution (CONHCH2CH2N(CH2CH3)2].

(D14) The patentee submitted that approach of the Opponent as provided in Para 5.4 of the written statement and 3.12 of the reply evidence demonstrate that a minimum of 5 changes had to be effected in order to arrive at a compound structure and not compound closest to the claimed compounds.

(D15) The patentee submitted that the opponents have attempted to reconstruct the claimed compounds of IN209251 through impermissible hindsight. The probability of selecting the substituents on each of the position of the compounds disclosed in D1 results in infinite number of choices to be made before arriving at the compound structure closest to the claimed compound. The patentee submitted that no explanation or evidence has been filed by the Opponent to demonstrate as to why a person of ordinary skill in the art will select or be motivated to select the substituents from a laundry list of substitutions to arrive at the alleged closest compound/structure.

(D16) The Patentee submitted that the substitution is not of dimethylamine as alleged by the Opponent but is [–NH-N(CH3)2[N(CH3)2amino].

(D17) The patentee submitted that D1 is an irrelevant document for the purpose of an inventive step enquiry for the following reasons:

(1) D1 relates to amino benzylidenyl indolinone compounds.

(2) All the claimed compounds have an amino benzylidenyl substitution (6-member ring) on the 3rd position of the indolinone structure and not a pyrrole substitution. The claims with 6-member substitution include claims 5, 10, 13, 17, 22, 25, 30, 35 & 41.

(3) Even Markush formula III does not provide the connection point of the substitution such as CONRR'on the pyrrole ring. In this regard, Dr. Cui (in her second affidavit) clearly states that even the connection point at the hetero aryl ring is critical and that the biological activities will be largely different with different action points.

(4) Col. 10 envisages a pyrrole substituted indolinone but has not been claimed. It contemplates substitution at R1 position which if alkyl would lead to loss of potency (Dr. Cui's first affidavit, Para 13 & 15).

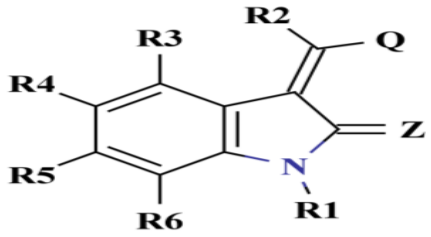
(5) If R2 is sulphur, the compound is not indolinone.

(6) D1 does not teach where the methylene has to attach to the pyrrole ring.

(7) In D1 there is no exemplified compound that has a carboxyamide substitution on the pyrrole ring

(8) Compounds 5.100 and 5.101 identified by the Opponent are irrelevant compounds as both have a "nitro" group at the 5' position of the indolinone core.

(D 18) The patentee submitted that D2 is directed to 2 indolinone derivatives of formula:



(D19) The patentee submitted that D2 discloses almost 800 test compounds. As the opponent did not identify any specific compound as being the lead compound, the patentee provided the Patent Office with the necessary comparative data with respect to the compounds that were selected by International Searching Authority.

(D20) The patentee submitted that D2 is an irrelevant prior art document for the purpose of inventive step enquiry for the following reasons:

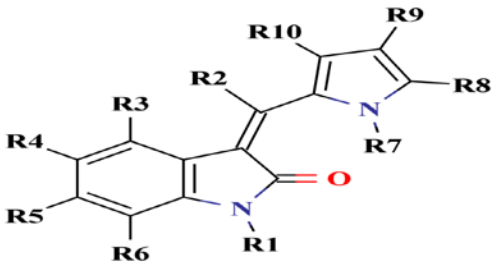
(1) It relates to indolinone substituted compound.

(2) The opponents have failed to identify any lead compound in the said document.

(3) The closest compound structure identified after several manipulations is a hypothetical compound structure for which no disclosure in terms of a specific compound or test data available is provided.

(4) The Opponent seems to suggest that the hypothetical compound structure that is the closest compound structure should first be synthesized and then for the purpose for securing grant of a patent, the patentee should conduct in vitro and in vivo studies

(D21) The patentee submitted that D3 is directed to pyrrole substituted indolinone compoundsfor formula.



(D22) The patentee submitted that D3 was not cited as even a relevant prior art by the International Searching Authority. The patentee submitted that the teaching of D3 is that the substitutions of R8, R9 and R10 on the pyrrole ring have to have (alk1)Zgroup. Further it is also essential that at least one of R8, R9 or R10 have to have an (alk1)Z group. In other words, the compound of Markush formula of D3 can have more than one (alk1)Z substitutions at the R8, R9 and R10 positions (Page 11, Line 23, 24).

Z is a polar group and definition of polar group has been provided on the following pages of the specification: Page 20, Lines 30 to Page 21, Line 4, Page 33 and Page 21, Lines 1 to 7, Page 21, Lines 28 to 33 and Page 22, Lines 1 to 8

The patentee submitted that in none of the instance, the polar Z group contemplate to the di-ethylaminoethylcarboxamide group [-CONHCH2CH2N(CH2CH3)2].

(D23) The Patentees drew the attention of the learned Controller to Table 1 on Page 38 to 41 of the patent specification.

i. Each of the said exemplified compounds in Table 1 teaches in one direction namely
i. Have an ethyl group as an "alk" substituent between the pyrrole ring and the polar group and
ii. The polar group should be an acidic side substituent preferably a carboxylic acid.
iii. Each of the compounds in Table 1 namely from compounds 1 to 41 have a propanoic acid (acidic side substituent) at the 4' position of the pyrrole ring.
The patentee submitted that there are 22 compounds which also have an alk(ethyl intervening group) between the pyrrole ring and the Z group.
There is no disclosure or teaching in the D3 document to even suggest a C-amido group being directly linked to the pyrrole ring at the 4' position.

(D24) The Patentee at the hearing further drew the Controller's attention to Pages 213 to 218 of D3.

The patentee submitted that in vitro and in vivo tests were conducted on the exemplified compounds of Tables 1 & 2. On page 214, Lines 15 to 23, D3 document stated that compound 5 was the best compound that surprisingly stood out from the rest and inhibited tumor growth by

80 to 85% than compounds 3, 19 and 21 which showed only 40 to 45%inhibitions.This further establishes that small structural changes have a dramatic effect on the biological activity including pharmacological properties of a drug product

(D25) The patentee submitted that compound 5 (SU6668) is a compound that has no substitution on the indolinone structure and has a propanoic acid on the 4' position of the pyrrole ring.

(D26) The patentee submitted that D3 further supports that small structural changes have a dramatic effect on the biological activity including pharmacological properties of a drug product. Toestablish this proposition, the Patentee drew the learned Controller's attention to Page 218, Lines 11 to 15 which clearly states that despite structural similarities of the close analog compound 71 and compound 5, compound 71 showed only 57% inhibition of tumor growth as opposed to 80 to 85% inhibition demonstrated by compound 5. Therefore, a person skilled in the art, if for any reason would be motivated to modify the compound, the lead compound would be compound 5 (SU6668).

(D27) The patentee submitted that D3 teaches away from using a basic amide substitution at the 4' pyrrole ring. The patentee submitted that in Paragraph 14(d) and also Dr. Cui's first affidavit Para 16, suggest that SU6668 failed because of it being metabolized due to the electron releasing alkyl group attached to the pyrrole ring. So in effect the electron density in the pyrrole ring has increased.

(D28) The patentee submitted that teaching of D3 is as follows:

(a) The substitution on the indolinone core structure decreases the inhibitory effect of the compound. Therefore D3 teaches not to substitute the indolinone structure.

(b) Use an (alk)Z group

(c) Use a acidic side substituent such as propanoic acid (alk=ethyl and Z=COOH) on the 4' position of the pyrrole ring. The lead compound of D3, compound 5 in fact has a propanoic acid substituent

(d) Don't use an electron withdrawing choro or bromo substitution as demonstrated as it will decrease the potency and selectivity of against RTK activity.

(e) Do not use fluorine at the 5' position.

(f) D3 also teaches that small structural changes have a dramatic effect on the activity of the compounds.

(D29) The patentee submitted that the prior art clearly preferred SU6668 over. The patentee submitted that they have shown an unexpected potency of SU11248 (claimed compound) with respect of SU5416 and SU6668.

(D30) The patentee submitted that all prior arts taught that acids are preferred in the art as a side chain on the pyrrole ring as a more favorable interaction with the receptor backbone. D3 alone or with combination with D1 or D2 therefore does not render the invention of IN 209251 obvious. There is no teaching or motivation to combine the core structures from D1, D2 with the Z group (CONRR' group) of D3.

(D31)Patentee's submission on Section 8

The patentee submitted the following –

-that no evidence or pleadings exist in relation to the ground of Section 8 under Section 25(2)(g) either in Form 7, written statement or reply evidence;

-Under Section 65B of the Evidence Act, any information that is produced by a computer will deem to be a document without further proof or production of original as evidence provided it is accompanied with an affidavit to this effect.

- a fair and balanced approach ought to be given. As patent has been granted in 91 countries, it should be a good reason that patent is also maintained in India.

- Section 8 is a requirement that culminates on the date of grant of the patent.

- the patentee provided all the information relating to corresponding foreign applications to the Patent Office at regular intervals and the Asst. Controller while dealing with the application was satisfied and did not require any further information in relation to Section 8 and therefore proceeded to grant the patent.

Patentee placed the following case laws and documents in support of their arguments-

-346 F.2d 600 in the application of Klauze Schutze

-Ayyangar report para 350

-Hon'ble IPAB in Tata Chemicals vs. Hindustan Lever Limited and Ors para's 91 and 92

-Delhi High Court decision on Snehlata Gupte & Ors. Vs. Union of India, para 17

-Therasense Inc us. Becton, Dickinson and Company

-Article 42 of PCT

(D32) Response of the patentee to Recommendations of the Opposition Board

The main submissions by the patentee are as follows –

-The Opposition Board did not identify who the person skilled in the art is and the test of obviousness to be applied and how is it to be applied.

-The Opposition Board has not provided any detailed and cogent reasoning as to how they arrived at closest compound structure (lead compound) in D1 and D2

-The Opposition Board has failed to provide as to how are the claimed compounds of IN 209251distinct from compounds disclosed in D1 & D2.

-The Opposition Board has not identified any reason or motivation that would lead a person of ordinary skill in the art to modify the compounds of D1 & D2.

-The Opposition Board has failed to examine the teachings of D1 & D2 and have compared the compounds of Dl & D2 with respect to only claim 7 of IN '251 and not the other claims.

-The Opposition Board adopted a "hindsight analysis" in arriving at the claimed compounds,

-The Opposition Board have not provided any explanation as to how and why from the laundry list would a person skilled in the art select CONRR' from D1 document.

-The Opposition Board has not identified which of the 5 Markush structures provided in D1 is relevant for the obviousness enquiry

-The Opposition Board has also not provided as to how D1 teaches an amide function as there is no disclosure in D1 of an amide substitution at the 4th position of the pyrrole ring.

The Opposition Board despite having the affidavits of Mr. Rao and Mr. Phull completely ignored the admissions made by them that small structural changes have a dramatic effect on biological activity of compounds.

-They further ignored the admission made by Mr. Rao and Mr. Phull that

(a) There must be a close compound in the prior art for an inventive step enquiry;

(b) That a motivation must exist for obviousness to be established;

(c) That there can be a difference in properties in degree with regard to structurally similar compounds.

(d) That chemistry is unpredictable.

-The Opposition Board failed to appreciate that any structural modification of a pharmaceutically active compound is expected to disturb the pharmacological activity profile unless there is an established correlation between structural features and activity.

(Roche v Cipla; Beecham Group PLC, T0643/96)

-The Opposition Board failed to recognize that the teaching in D2 or other prior art documents do not suggest/ motivate an ordinary artisan to carry out the change from alkyl to (diethyl amino) ethyl

-The Opposition Board has failed to provide any reasons as to why alkyl and amides will be considered as being interchangeable.

-The Opposition Board has erred in understanding that D3 is a document which necessarily teaches an alkyl group attached between the pyrrole ring and the polar group

-The Opposition Board did not examine as to why a person skilled in the art would remove the alkyl group in order to arrive at the compound of claim 7 of IN209251, when the document D3 teaches away from the claimed compounds.

-The Opposition Board failed to observe that the teaching of D3 was to have an alkyl group with an acidic substituent on the 4th position.

. The Opposition Board has also not provided any explanation as to why would a person skilled in the aft would combine the teachings of Dl or D2 with that of D3 as D3 is the latest document in the development line which clearly teaches away from directly linking C-amido substituent to the pyrrole ring.

-The Opposition Board has not even considered the affidavits of the Patentee in their recommendations.

(E) CONCLUSION

Considering the above detailed arguments of the learned attorneys, the opposition board's opinion, comments of opponents and applicants on the report of the opposition board and the facts given in the documents including affidavit submitted by both the parties, I shall now discuss the various grounds of opposition as discussed during the hearing.

GROUND OF SECTION 8

(E1) I opine that the objection of the opponent that patentee have not complied with the requirement of Section 8 is not agreeable. I observe that the patentee has fulfilled its duty to furnish all the information's required u/s 8. The details cited by the opponent are from the WIPO website and espacenet which is freely available to the controller and examiner.

Therefore the ground of section 8 is not maintainable.

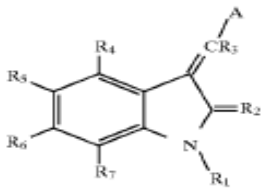
GROUND OF OBVIOUSNESS AND LACK OF INVENTIVE STEP

(E2) I opine that the present claims are not inventive in view of disclosures D1-D3 for the following reasons;

(E3) The claim 1 of the impugned patent read with description of the said patent and comparative statement (Table 2, Table 3 and Table 4) submitted by the opponents in full written statement and arguments submitted by both the parties during fresh hearing reveals that the basic Markush structure of the compounds as claimed in the impugned patent is made obvious by disclosures in documents US5886020 (D1), WO/98/50356 (D2), WO/99/61422 (D3). The documents D1 to D3 submitted by the opponents disclose pyrrole substituted indolinone compounds which overlap with the impugned patent compounds except that of group R6 at position 4th of the pyrrole ring. These documents disclose a broader group of substituents which encompasses the substituent of impugned patent. The R6 group in the impugned patent is C(O)R10, which may be diethyl amide group. This amide group of Sunitinib is allegedly the activity imparting group according to the patentee.

(E4) The disclosure of Dl differs from the present invention in that the claimed compounds of present invention include a (diethylamino) ethyl substituent on the carboxamide nitrogen, whereas the corresponding structures according to Dl possess hydrogen/alkyl/aryl substituent. It is also observed that the substituent C(O)NH(CH2)2N(Et)2 is not disclosed in D1 and the closest substituent on the pyrrole ring at the same position in D1 is CONRR'.

(E5) It is observed that the difference between the compounds of D1 with the compound of present invention is at 4th postion of pyrrole ring. Document D1 discloses pyrrole substituted indolinone compound of formula III at col. 10 page 9



(III)

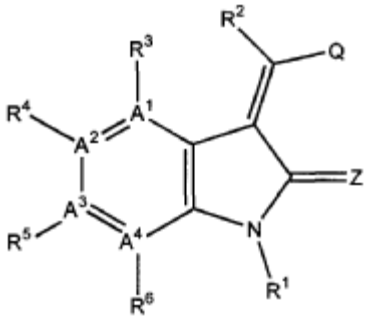
where the substituents when read as R1 = H; R2 = O, R3 = H; R4 = R6 = R7 = H; R5 = Halogen and A = Pyrrole ring and pyrrole ring is substituted at two positions by alkyl group and at one position by –CONRR' wherein R is hydrogen R' is an alkyl group which includes N(CH3)2amino(at column 7, line 12 page 8 of D1).

(E6) Here the difference between the claimed compound sunitinib and compounds of D1 is in two aspects only i.e. the dimethyl group on the terminal amino N atom linked with pyrrole ring and absence of disclosure of the point of the attachment on the pyrrole ring to the doubly bonded carbon connected to the indolinone ring. The difference obviously is of dimethyl and diethyl groups where dimethyl group is in the terminal amino N atom on the amide group of D1 and diethyl group is on the presently claimed compound. Therefore the

patentee replaced only methyl group of D1 with ethyl group to make the present compound.

(E7) Dr. Cui has stated that the diethylamine group is present only in the compound of claim 7 of the instant patent. Therefore, I opine that the compounds of D1 which differ only in the absence of said diethyl amine from Sunitinib, makes D1 a proper disclosure for rendering the markush structure of the instant patent obvious.

(E8) Document D2 discloses the formula

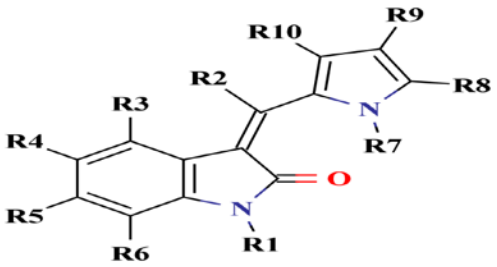


I

where the substituents A1, A2, A3 or A4 may be carbon. R3, R4, R5 and R6 may be hydrogen or halogen, Rl is hydrogen, R2 is hydrogen, Q may be pyrrole ring substituted with R8, R8' and R8" which may be H or alkyl or c-amido and the definition of C-amido group is CONR18R19 wherein R18 may be hydrogen and R19 may be alkyl.

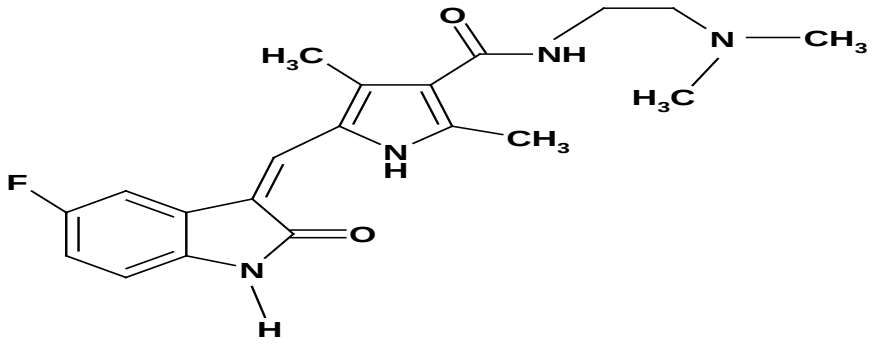
(E9) Teaching of D2 reveals the C-amido substituent present at the 4th position of pyrrole ring. It is clear from the definitions of various substituents, document D2 differs from the impugned patent in that the claimed compounds include a (diethylamino) ethyl substituent on the carboxamide nitrogen whereas the D2 possesses an alkyl substituent. D1 or D2 alone does not motivate, teach or suggest to a person skilled in the art to reach the present invention.

(E10) Document D3 teaches at page 10 the pyrrole substituted 2-indolinone protein kinase inhibitors of the formula I,



wherein the values of substituents when read as R1 = R2 =R3 = R5 = R6 = R7 = Hydrogen; R4 = Halo (F in sunitinib); R8 = R10 = alkyl (methyl in sunitinib); R9 = (Alk1) Z; where Z is selected from the group consisting of –C(=O)NR13R14 wherein R13 and R14 are independently selected from the group consisting of hydrogen, …., lower alkyl substituted with a group selected from the group consisting of amino and –NR11R12, …….., wherein R11 and R12 are independently selected from the group consisting of unsubstituted lower alkyl and, …… (at paragraph bridging pages 21 and 22 of D3).

(E11) D3 generically teaches the presence of intervening alkyl group between polar group Z and pyrrole ring. D3 at page 23 also teaches the various oxindoles and aldehydes in the combinatorial library and each oxindoles can react with each aldehydes. Amongst the various oxindoles and aldehydes in the combinatorial library, D3 specifically teaches the compounds namely 5-fluorooxindole (line 10, page 24), 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylaminoethyl) amide (lines 31, 32 at page 27) where the difference between claimed compound and D3 is only between alkyl group at terminal amino N atom on the amide group i.e. difference of dimethyl (in D3) and diethyl (instant claims). The said compound of D3 is obtained by the reaction of 5-fluorooxindole and 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylaminoethyl) amide and the above said intervening alkyl group between polar group Z and pyrrole ring is removable by the reaction of 5-fluorooxindole and 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylaminoethyl) amide as the process steps and parameters are same as of the impugned patent application and finally obtained compound is different at terminal amino N atom at alkyl group i.e. dimethyl (as shown below) and diethyl.



(E12) Therefore, I observe that the invention as claimed in the impugned patent is obvious to a person skilled in the art in view of disclosures in D1 or D2. Teaching of D1 and D2 could be modified to introduce the polar group Z as taught by D3 to formulate a compound which does not possess the (Alk1) group but retains the protein tyrosine kinase inhibitory activity. Therefore, the invention claimed in the impugned patent under opposition is obvious over D1 in view of D3 and also over D2 in view of D3.

(E13) I observe that the compounds disclosed in D1, D2 and D3 are useful for the treatment of same category of diseases as in the impugned patent.
Dl relates to organic molecules capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. The fact that the compounds disclosed in Dl modulate the activity of kinase, it would readily occur to a skilled medicinal chemist or a person skilled in the art would expect this activity to be retained in the claimed compounds as well.
D2 relates to compounds which modulate the activity of protein kinases and are therefore expected to be useful in the prevention and treatment of protein kinase related cellular disorders such as cancer. The fact that the compounds disclosed in D2 also modulate the activity of kinase, a skilled medicinal chemist or a person skilled in the art would expect this activity to be retained in the claimed compounds as well.
D3 again relates to organic molecules capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation. Accordingly, in view of the structural and functional similarity of the compounds of D1 to D3 and the difference being obviously made by interchangeable substituents it is agreeable that the claimed compounds of the patent under opposition are very much obvious to the skilled person.

(E14) I observe that the structure of compounds of D1 and D2 overlaps with the structure as disclosed in present patent. I also observe that the efficacy data (IC50) given by the patentee is for few selected compounds which are not closest compounds as cited in prior art. The patentee has compared the activities of compounds which are structurally different. The Tables -5 and table-7 submitted by the patentee in reply statement show the comparison of efficacy data (IC50) of claimed compounds having group –C(O)NH(CH2)2N(Et)2 with the D1 or D2 compounds having group –C(O)-OCH2CH3 or group –CH3 and not with the D1 or D2 compounds having group C(O)NRR' that would have reflected the effect of substitution of the alkyl by the diethylamine group.

(E15) I observe that the claimed compounds, as exemplified by SUl1248, have a specific amide substituent (C (O) NR' (CH2) nR", where R" is as defined in the claims) at R6 position, whereas the prior art compounds identified in D1 have an ester (-C(O)OR) in the case of SU5408 and SU5463, or a methyl group in the case of SU5455. Each of these compounds selected from D1 was tested in two assays: a cellular PDGFR assay in 3T3 cells and a cellular VEGFR2 assay in PAE-VEGFR2 cells, and the results are shown in Table -5 submitted by patentee in reply statement.

(E16) I observe that the patentee failed to show the specific improvements in claimed compound as compared with structurally closest compound of D3 document where

terminal group is dimethyl. I agree with the arguments of opponent that "it is known jurisprudence if one alternative (D3 compounds with dimethyl on the terminal amino N atom) is obvious in the group covered by Markus and other (i. e. claimed compounds of the invention) are rendered obvious". The selection of the compound covered by the Markus that too the next member of the alkyl group is obvious to try by a person skilled in the art. In this case skilled person in the art need not to do any undue experimentation and by simple modification in the process of manufacturing of compounds of D1 and D3, the compound of the instant patent could have been prepared. This obviousness may have been inventive if this new member showed unexpected changes in characteristics or properties as compared to its closest prior art member compounds of D1 to D3 as discussed above. However no such description has been given by the Patentee.

(E17) I rely on the decision of Technical Board of Appeal EPO T181 /82, OJ EPO 9/1984, page 401 point 5 last paragraph "where comparative tests are envisaged in order to support an inventive step, these must be carried out between the compounds of the present application having the maximum structural similarity with the compounds of the closest prior art, such that the effect is shown to have its origins in the distinguishing feature of the invention.
In this regard the arguments of opponent is agreeable that " the ideal comparison would have been with compound of D1 where at the position of R6 of the compound of the patent under opposition the substitution is CONRR' Vs the compound of the patent under opposition where R6 is C(O)NR'$(CH_2)_n$R''. That would have reflected the essence and the effect of the substitution of the alkyl by the amine (diethylamine) to be specific".

(E18) According to Dr Cui affidavit (filed on October 2008), the selection of substituents is merely a part of an ongoing optimization process. I observe that the said affidavit fails to show any activity or specific improvement when C(O)NH(CH2)2N(Et)2 group on R6 position is directly attached to the pyrrole ring or through an intervening alkyl group. I observe that the patentee has failed to show as to how the substitution of C(O)NH(CH2)2 N (Et)2 group on the carboxamide nitrogen (Dl or D2) or linking the same directly to the pyrrole ring (D3) gave an improved product and what specific improvements were derived by the use of the claimed compounds.
It has been held in a case "In re Baxter Travenol Labs., 952 F.2d 388, 392 (Fed, Cir. 1991" that when improved results are used as evidence of non-obviousness, the results must be shown to be unexpected compared with the closest prior art.

(E19) The patentee had submitted that construction of indolinone with various substituents and construction of pyrroles with various substituents is not obvious to a person skilled in the art. I observe that the process for preparation of the compound and the conditions required are same in the instant patent with D3. Therefore, it will be obvious to a person skilled in the art to choose from the list of various substituents disclosed in D1 to D3.

(E20) I observe that D1 and D2 describe structurally and functionally related compounds. The description of the instant patent application does not make any reference to D1 to D3 and also does not indicate any draw backs in the disclosure of these documents. Further it is observed that D1 to D3 teaches the structure activity relationship of the compounds with

pyrrole substituted indolinone backbone (Dr Cui affidavit). These teachings would sufficiently motivate a skilled artisan that any structural modification of the compounds of D1 to D3 shall not disturb the pharmacological activity. Therefore, a person skilled in the art doing work in this field will obviously look into the documents D1 to D3 to find out further compounds.

(E21) As for choice of substituents it is observed that D1, D2 and D3 are from patentee and are part of development of Sunitinib. Therefore, a skilled artisan would have sufficient motivation to go forward in the same path traced by D1, D2 and D3 and try to arrive at further or alternative compound suitable for similar purpose by following the teachings of the said documents.

(E22) I observe that when as the instant claims are clearly obvious to a skilled artisan, so, the commercial success of the instant product (Sunitinib) as submitted by the patentee cannot be considered as an evidence of a patentable invention.

I rely on Patent Law by P. Narayanan (4th edition) at page 418 section 16-93 which states that "If an invention is obvious from a technical or practical point of view, it will be invalid even though it was commercially successful and the step taken was not an obvious commercial step to take."

(E23) I observe that the instant claims 2 to 6 are directed to further limitations of the substituents as claimed in claim 1 and do not add any inventive feature to the said claim. Accordingly Dl or D2 in combination with D3 provides sufficient motivation to arrive at the said limitations hence claims 2 to 6 are also obvious.

(E24) I observe that the instant claims 7 to 9 are directed to the specific compounds that are encompassed by the Markush structure of claim 1. As discussed above, it is evident that the specific substituents provided in the claims are motivated from the teachings of Dl or D2 in combination with D3. I observe that there is no invention provided in the selection of the salts and accordingly the same also is obvious vis-a-vis D1 or D2 in combination with D3.

(E25) I observe that the instant claim 10 is directed to composition of the active ingredient as claimed in previous claims. Since the compound is already shown to be obvious and no data is provided in the selection of the salt, claim 9 is also obvious in view of teachings of Dl or D2 in combination with D3.

Therefore I conclude that the claims of impugned patent are obvious and lacking inventive step in the light of disclosures of D1 to D3.

(E26) In light of the above findings, I opine that the recommendations of the opposition board are correct.

FINAL CONCLUSION

In view of all the documents submitted by the opponent and the patentee on records, above mentioned detailed discussion on the arguments of the opponent and patentee, the facts given in the documents including affidavits submitted by both the parties and the recommendations of the opposition board, I conclude that the invention as claimed in the patent does not involve an inventive step and is obvious to the person skilled in the art, hence not patentable u/s 2(1)(j) of Patent act, 1970.

I hereby maintain the revocation of Patent No. 209251 granted on the Patent Application No. IN/PCT/2002/00785/DEL

Date –

(**Dr NILANJANA MUKHERJEE**)
Assistant Controller of Patents and Designs
Patent Office, Delhi