The Patents (Amendment) Act, 2005
And
The Patent (Amendment) Rules, 2006

In the matter of Patent No.209251 (Application No.IN/PCT/2002/00785/DEL)

and

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

Sugen, Inc. USA and Pharmacia and Upjohn Co., USA.....the Patentee.

Cipla Ltd., Mumbai (India).....the Opponent

HEARING HELD ON 21/02/2012

Present –

Sh D. C. Gabriel, Sh Sanjeev K Tiwari, Smt Valini Panta, Sh Amrish Tiwari Of M/s K & S Partners, Gurgaon.....Attorneys for the Patentee

Mr S. Majumdar, Dr Sanchita Ganguly and Ms Mythili Venkatesh of M/s S. Majumdar and Co. Kolkata.....Attorneys for the Opponent

Sh Fadi Haddadin of Sugen, Inc. USA and Pharmacia and Upjohn Co., USA.

Dr Sunil Gautam, Examiner of Patents and Designs

DECISION

The application No. (IN/PCT/2002/00785/DEL) was filed on 09-08-2002 for the Grant of the Patent by the aforesaid applicant. The said application was examined according to the provisions in force of the Act and was recommended for Grant of the Patent on 23-08-2007 and was finally allotted the Patent No. 209251 (hereinafter reffered as patent). The said Patent was published in the Patent Office Journal U/S 43 (2) on 05-10-2007. The Opponents filed an opposition U/S 25(2) on 01-09-2008 for the revocation of the said Patent. Chronological order of the

documents filed relating to the opposition by the opponents and the patentee is mentioned below:

Table-1

S.No.	Name of the Document	Date of filing
1.	Notice of Opposition under section 25(2) of the patent Act, 1970 and Rule 55A and 57 of the Patent Rules by S. Majumdar & Co. On behalf of CIPLA LTD, Mumbai.	01-09-2008
2.	A letter informing patentee's agent U/S 25(3-a)of the Patent Act about the notice of opposition u/s 25(2)	12-01-2009
3.	Reply filed by patentee U/R 58	31-10-2008
4.	Reply evidence filed by opponent U/R 59	06-01-2009

The opponent and patentee have filed all the necessary documents relating to this opposition within the prescribed time limit.

Under the provisions of rule 56, an opposition board consisting of Dr. Sunita Rani, Ms. Reena, Lal and Dr. Archana Gupta, Examiners of Patents & Designs as members were constituted. The board has submitted its recommendation within the stipulated time. Upon completion of the proceedings of the post grant opposition a hearing was held on 21/02/2012.

2. LOCUS STANDI

The opponent's comments

The patent under opposition relates to an alleged invention in the field of medicinal Chemistry. The opponent is currently engaged in the research and development as well as in the manufacture of medicinal products and has interest in opposing the patent. The opponent is therefore a person interested and therefore has locus standi to initiate the present proceedings

The patentee's comments

1. It is denied that the Opponent has any locus standi or interest in opposing the Patent in question (No. 209251).

I observed that arguments or evidences have been submitted by the opponent that whether they are involved in the same kind of the business or not. The opponent (Cipla Ltd.) is very much engaged in the research and development as well as in the manufacture of medicinal products at present. Hence, the locus standi of the opponent is established and therefore the opponents have the right to proceed with the opposition to the patent no. 209251.

3. Now,I shall analyse the arguments of the opponents and the patentee vide their written Statement of opposition/evidence/oral arguments and reply statement/ evidence/oral arguments at the hearing on the various grounds.

In the notice of opposition, following grounds have been relied upon by opponent u/s 25(2)

The opponent's comments

3.1 The impugned patent is opposed on the following grounds:

a. that the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of that claim;

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

c. that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act;

d. the patentee has failed to disclose to the Controller the information. required by Section 8 or has furnished the information which in any material particular was false to his knowledge.

4. A BRIEF ANALYSIS OF PATENTEE'S SPECIFICATION NO. IN 209251

4.1 The impugned patent under opposition issued from a national phase application in India being Indian Application No. IN/PCT/2002/00785/DEL arising out of the PCT Application No. PCT/US01/04813 dated February 15, 2001 which was published under PCT Publication No. WO 01/60814 A3. The application was published in the Official Journal dated January 19, 2007 while the grant notification was published in the Official Journal dated August 31, 2007 and October 5, 2007. The impugned patent under opposition claims an earliest priority of US provisional application number 60/182,710 dated February 15, 2000.

4.2 The alleged invention claimed in the impugned patent under opposition relates to certain 3-pyrrole substituted 2-indolinone compounds which modulate the activity of protein kinases. The compounds of the alleged invention are stated to be useful in treating disorders related to abnormal protein kinase activity.

4.3 The alleged invention also relates to pharmaceutical composition comprising the 3-pyrrole substituted 2-indolinone compounds. The specification of the impugned patent also teaches method of treating diseases mediated by abnormal protein kinase activity. The diseases indicated include by not limited to cancer, diabetes, hepatic cirrhosis, cardio vascular diseases like athero sclerosis, angiogenesis, immunological diseases such as autoimmune diseases and renal diseases. The immune specification also refers to method of modulating catalytic activity of protein kinase. The use of the compound as mentioned above in preparation of medicament is also taught. Further an intermediate compound is also disclosed though not claimed. The specification of the alleged invention states that the compounds of the invention provide a better therapeutic approach to the treatment of many kinds of solid tumors including but not limited to carcinomas, sarcomas including Kaposi's sarcoma, erythroblastonia, glioblastoma, meningioma, astrcytoma, melanoma and myoblastoma.

4.4 Claim 1 recites a compound namely **3-pyrrole substituted 2-indolinone** compound of formula 1 providing its structure,

4.5 Claim 2 is dependent on claim 1 providing limitation as to the substituents provided in the description of the compound in claim 1.

4.6 Claims 3 and 4 provide further limitation of claim 2 with regards to R^3 R^{11} and R^{12} and limitation of

4.7 Claim 5 provide limitation as to R^{13} and R^{14} while claim 6 provides specific limitation for R^1, R8 and R^9. Thus, claim 2 to 6 provide further limitation in terms of various substituents of the compound as claimed in claim 1. Accordingly none of these claims provide additional features which may add on features that would make claim 1 novel and inventive.

4.8 Claims 7 and 9 specifically claim compounds provided by formula or its pharmaceutical acceptable salt and are dependent on claim 1. Thus claims 7 and 9 recite a specific compound within the purview of claim 1.

4.9 Claim 8 recites specific salt of compound which too recites within the purview of claim 1.

4.10 Claim 10 provides a pharmaceutical composition comprising a compound of claim 1 to 9 and a carrier. This claim relating to the composition does not add any novel or inventive feature to claim 1.

4.11 Claim 11 is an omnibus claim.

5. LACK OF INVENTIVE STEP / OBVIOUSNESS

OPPONENTS ARGUMENTS (Obviousness)

5.1 The opponent relies on the following document to bring out its case of lack of inventive step and obviousness

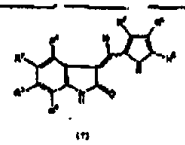
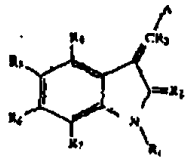
- US 5 886 020, which was published March 23, 1999, hereinafter Dl, and annexed hereto as Exhibit I
- WO/98/50356, published on November 12, 1998, hereinafter D2 and annexed hereto as Exhibit II
- WO/99/61422, published on December 2, 1999, hereinafter D3 and annexed hereto as Exhibit III

5.2 The opponent states that Dl, which was published March 23, 1999 i.e. before the claimed priority date of the impugned patent under opposition, is admissible prior art vis-a-vis the subject matter claimed therein. Dl relates to organic molecules capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation.

5.3 D1 teaches that such compounds are useful for the treatment of diseases related to unregulated TKS transduction including cell proliferative diseases such as cancer. Accordingly, it is stated that modulate the activity of kinase, it would readily occur to a skilled medicinal chemist the subject matter of Dl is directed to the treatment of the same diseases as the subject matter of the impugned patent under opposition. Accordingly, Dl is relevant prior art. The fact that the compounds disclosed in Dl or a person skilled in the art would expect this activity to be retained in the claimed compounds as well.

5.4 The compounds broadly claimed in claim 1 the impugned patent under opposition are compared with the compounds disclosed in Dl in the following table-2:

Table 2-

S No.	Parameter	Claimed compound	D1	Comments
1	Structure of the compound		 **Col 10, line 47:** R3 is hydrogen.	Similar, both the compounds have same backbone structure.
2	R1	R1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy,- (CO) R15,-NR13R14	**Claim 1:** R4 is selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO2NRR', SO.sub.3 R, SR, NO.sub.2, NRR',	Overlapping. The prior art discloses a broader group of substituents which encompasses the substituents claimed in the impugned

		(CH2) rR16 and-C (O) NR8R9 ;	OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH.sub.2).sub.n CO.sub.2 R, and CONRR'	patent under opposition.
3	R2	Preferably halogen, espccially fluorine.	Col. 10, line 50: R5 may bc halogen.	Overlapping.
4	R3 and R4	Preferably hydrogen	Col 10, line 49: Hydrogen	Overlapping.
5	———	Pyrrole ring.	Col 10, line 55: A is a five membered heteroaryl ring selected from ....., pyrrole, ...	Overlapping.
6	———	Pyrrole substituents	Col 10, line 63: The disclosed pyrrole may be optionally substituted with one or more positions with alkyl, ...	Overlapping
7	———	Carboxaminde pyrrole substituent. -C(O)NH(CH_2)$_2$ N (Et)$_2$.	Col 10, line 67: The pyrrole substituent may be – C(O)NR R'. R may be hydrogen.	Overlapping. D1 defines R' as hydrogen, alkyl or aryl.

5.5 It is therefore clear from the above comparative table that the only difference between the compounds claimed in the impugned patent under opposition and the disclosure of Dl is that whereas the claimed compounds include a (diethylamino) ethyl substituent on the carboxamide nitrogen, the corresponding structures according to Dl possesses an alkyl substituent. The above table makes it clear that barring this modification, the compounds claimed in the impugned patent under opposition are substantially same as the compounds disclosed in Dl.

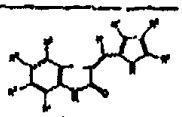
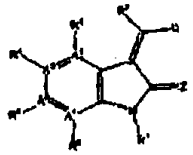
5.6 The opponent states that the compounds of the closest prior art Dl possess an amide substituent at position 4 of the pyrrole ring whereas the definition of R' provided on Col 10, last sentence of Dl makes it abundantly clear that Dl also teaches an amide function at 4 position of the pyrrole ring. Accordingly claim 1 is obvious in view of Dl.

5.7 It is stilted above that Dl teaches compounds that are useful for the treatment of diseases related to unregulated TKS transduction including cell proliferative diseases such as cancer. It would therefore have been clearly obvious to a person skilled in the art that similar compounds wherein the alkyl substituent on the carboxamide nitrogen is replaced diethylamino) ethyl (v. alkyl) would also expectedly possess similar activity, It is therefore stated that the compounds claimed in the claims of the impugned patent under opposition are obvious over Dl alone.

5.8 The opponent states that D2, which was published November 12, 1998 i.e. before the claimed priority date of the impugned patent under opposition, is admissible prior art vis-a-vis the subject matter claimed therein. D2 relates to compounds which modulate the activity of protein kinases and arc 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, 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.

5.9 The compounds claimed broadly in claim 1 in the impugned patent under opposition are compared with the compounds disclosed in D2 in the following table-3:

Table-3

S No.	Parameter	Claimed compound	D2	Comments
1	Structure of the compound		 **Page 9:** A1, A2, A3 or A4 may be carbon. R3, R4, R5 and R6 may be hydrogen (page 9, line 18) or halogen (page 9, line 24). R1 is hydrogen (page 9, line 9). R2 is hydrogen (page 9, line 14). Q may be pyrrole ring substituted with R8, R8' and	Similar, both the compounds have same backbone structure.

			R8'' (Q2, page 10 and Q4, page 11).	
2	Pyrrole substituent	-C(O) – NH – CH_2-CH_2 – N $(Et)_2$.	**Page 11, line 5**: R8, R8' or R8'' may be selected from hydrogen (line 7) or alkyl (line 7) or C-amido (line 12). **Page 25, line 17**: C-amido means – $C(=O)NR^{18}R^{19}$. **Paragraph bridging pages 9 and 10**: R^{18} may be hydrogen (page 9, line 30) while R^{19} may be alkyl (page 9, line 30).	Overlapping. The prior art discloses a broader group of substituents which encompasses the substituents claimed in the impugned patent under opposition.

5.10 It is therefore clear from the above comparative table met the only difference between the compounds claimed in the impugned patent under opposition and the disclosure of D2 is that whereas the claimed compounds include a (dielhylamino) ethyl substituent on the carboxamide nitrogen, the corresponding structures according to D2 possesses an alkyl substituent. The above table makes it clear that barring this modification, the compounds claimed in the impugned patent under opposition are substantially same as the compounds disclosed in D2.

5.11 The opponent states that the compounds of the closest prior art D1 possess an amide substituent at position 4 of the pyrrole ring whereas the definition of C-amido provided on page 11, line 12 of D2 makes it abundantly clear that D2 also teaches an amide function at 4 position of the pyrrole ring. Thus the compounds as claimed in claim 1 are clearly motivated from the teachings of Dl. It is stated that the reason of inventive merit require for the modification as mentioned above. Accordingly claim 1 stands obvious in view of teachings of Dl.

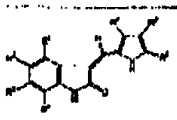
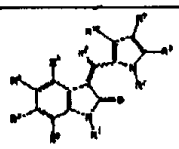
5.12 It is further stated above that D2 teaches compounds that are useful for the treatment of diseases related to unregulated TKS transduction including cell proliferative diseases such as cancer. It would therefore have been clearly obvious to a person skilled in the art that similar compounds wherein the alkyl substituent on the carboxamide nitrogen is replaced by diethylamino) ethyl (v. alkyl) would also expectedly possess similar activity. It is therefore stated that the compounds claimed in the impugned patent under opposition are obvious over D2 alone.

5.13 The opponent states that D3, which was published December 2, 1999 i.e. before the claimed priority date of the impugned patent under opposition, is admissible prior art vis-a-vis the subject matter claimed therein. D3 again relates to organic molecules capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation.

5.14 D3 teaches that such compounds are useful for the treatment of diseases related to unregulated TKS transduction including cell proliferative diseases such as cancer. Accordingly, it is stated that the subject matter of D3 is directed to the treatment of the same diseases as the subject matter of the impugned patent under opposition. The fact that the compounds disclosed in D3 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.

5.15 The compounds broadly claimed in claim 1 of the impugned patent under opposition are compared with the compounds disclosed in D3 in the following table-4:

Table-4

S No.	Parameter	Claimed compound	D3	Comments
1	Structure of the compound		 **Page 10, line 11**: R1 includes hydrogen. **Page 10, line 15:** R2 includes hydrogen. **Page 11, line 10:** R7 includes hydrogen.	Similar, both the compounds have same backbone structure.
2	R1	R1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy,- (CO) R15,-NR13R14 (CH2) rR16 and-C (O) NR8R9 ;	**Page 10, line 17 onwards:** R3, R4,R5 and R6 are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido,	Overlapping.

			trihalomethanesulfonamido, carbonyl, C-carboxy,O-carboxy, C-amido, N-amido, cyano, nitro, halo, 0-carbamyl, N-carbamyl,O-thiocarbamyl, Nthiocarbamyl, aminoand-NR1lR12.	
3	R2	Preferably halogen, especially fluorine.	**Page 10, line 17 onwards:** R4 includes halogen.	Overlapping.
4	R3 and R4	Preferably hydrogen	**Page 10, line 17 onwards:** R5 and R6 include hydrogen.	Overlapping.
5	———	Pyrrole ring.	The structural formula of the disclosed compounds teaches a pyrrole ring.	Overlapping.
6	———	Pyrrole substituents	**Col 11, line 15**: R8 and R10 include an alkyl group as a possible substituent.	Overlapping
7	———	Carboxaminde pyrrole substituent. $-C(O)NH(CH_2)_2N(Et)_2$.	**Col 11, line 15:** R9 may be (alk1) – Z, wherein Z is a polar group and "alk1" is an alkyl, alkenyl or alkynyl group. **Paragraph bridging pages 21 and 22:** Z is selected from the group	The exact 4-pyrrole substituent which is not taught by either of D1 and/or D2 is taught in the most preferred

			consisting of – C(=O) N $R_{13}R_{14}$ wherein R_{13} and R_{14} are independently selected from the group consisting of hydrogen, ….., lower alkyl substituted with a group selected from the group consisting of amino and $-NR_{11}R_{12}$.	embodiment of D3.

5.16 It is therefore clear from the above comparative table that the only difference between the compounds broadly claimed in claim 1 of the impugned patent under opposition and the disclosure of D3 is that whereas the polar group of D3 is attached to the pyrrole ring via an alkyl ("alkl") group, the claimed compounds do not have the intervening alkyl group while the polar group "Z" remains the same. The above table makes it clear that barring this modification, the compounds claimed in the impugned patent under opposition are substantially same as the compounds disclosed in D3.

5.17 It is stated above that all of Dl and/or D2 and D3 teaches compounds that are useful for the treatment of diseases related to unregulated TKS transduction including cell proliferative diseases such as cancer. It would therefore have been clearly obvious to a person skilled in the art that the compounds disclosed in Dl or D2 could be modified to include the polar group "Z" that is taught by D3 each the impugned patent as claimed in claim 1. Accordingly, it is stated that the claimed invention would have been obvious over D1 or D2 in combination with D3.

5.18 It is further stated that modifying the compounds of 'Dl and/or D2 with the polar "Z." groups (which are most preferred according to D3) taught in D3 would lead a person skilled in the art directly to the compounds claimed in the impugned patent under opposition. Accordingly, it is stated that the alleged invention claimed in the impugned patent under opposition is obvious over Dl in view of D3 or alternately, over D2 in view of D3.

5.19 As mentioned above claims 2 to 6 provide further limitations of the substituents as provided in claim 1 and do not add any inventive feature to the said claim. Accordingly Dl or D2 in combination with D3 provides ample motivation to formulate the compound limitations as in claims 2 to 6 and hence claims 2 to 6 are obvious,

5.20 The specific compounds as claimed in claims 7 and 8 reside within the purview of claim 1 and the specific substituents as evident from the formula provided in the claims are motivated from the teachings of Dl or D2 in combination with D3. It is stated 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 and Dl or D2 in combination with D3.

5.21 Since the compound is already shown to be obvious and no data is provided in the selection of the salt, claim 8 is also obvious in view of teachings of Dl or D2 and Dl or D2 in combination with D3.

5.22 Claim 10 only provides for a composition comprising a compound which is already shown to be lacking inventive step. Accordingly no invention can be claimed in the composition and no data has been provided in the specification to show selection of the compound. Thus claim 10 also obvious in view of teachings of Dl or D2 and Dl or D2 in combination with D3.

Opponent's Arguments continued (Lack of inventive step)

5.23 It is seen that the compounds claimed in the impugned patent under opposition are only different from those disclosed in D1 and/or D2 in possessing a defined "Z" group i.e. by the presence of a -C (O)NH(CH2)2 N $(Et)_2$ group on the carboxamide nitrogen. It is well settled that in the case where comparative tests are envisaged in order to support an inventive step, these must be carried out between the compounds of the claimed invention having 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 claimed invention.

5.24 The opponent states that if Dl or D2 is the chosen "closest prior art", it was an obligation placed upon, the patentee to compare the claimed compounds with the compounds of the prior art that did not include an -C(O)NH(CH_2)2 N (Et)2 group on the carboxamide nitrogen. The opponent further states that D3 equally well applies as the "closest prior art" (and provides exactly that "feature" of the claimed compound which is not specifically disclosed in Dl or D2 being the specific polar "Z" group) and places an obligation upon the patentee to compare the activities of the compounds when -C(O)NH(CI-l2)2 N $(Et)_2$ group is bonded directly to the pyrrole ring (as in the claimed compounds) versus the activities of the compounds when -

C(O)NH(CH2)2 N (Et)2 group on the carboxamide nitrogen is bonded to the pyrrole ring via an alkyl ("alkl") group. However, none of these comparative tests have been furnished by the patentee, which could rebut the prima facie case of obviousness of the claimed compounds.

5.25 The opponent relies on Astra Zeneca v. Natco Pharma in 841/DEL/96 dated April 19, 1996, annexed as Exhibit A wherein it was held that:

"The closest prior art is defined as a prior art document having maximum, structural features in common with the subject-matter of the claimed invention i.e. which requires a minimum of structural modifications in traversing from the prior art to the claimed invention. Thus, the "closest prior art" is determined using a "structural approach" as opposed to a "functional approach", wherein the closest prior art is determined to be the document disclosing most relevant "functional features" in common with the claimed invention.

To be relevant, such comparative tests must meet certain criteria. These include the choice of a compound disclosed in the application and of a comparative substance taken from the state of the art; at the same time, the pair being compared should possess maximum structural similarity.

It was held that only by a comparison with such a prior art could an inference be drawn that at least substantive technical feature of the claimed invention is responsible for the origin of the unexpected or surprising advantage over the prior art.

In Berwind Pharmaceutical Services Inc. v. Ideal Cures Pvt. Ltd, (IN/ PCT/2002/00020/DEL dated January 4, 2002 annexed as Exhibit B, the claimed pharmaceutical coating composition claim Polyvinyl Alcohol in an amount of from 25-55% whereas the prior art, disclosing the same ingredients, taught the use of PVA in an amount of at least greater than 65%. Importantly, the comparative test data furnished by the applicant failed to compare the properties of the composition having greater than 65% PVA but compared the properties of the compositions having PVA levels in the claimed range with other compositions having PVA levels in the same claimed range. It was found that:

In the absence of any comparative test data against the closest prior art disclosing greater than 65% PVA, the evidence of record failed to substantiate that the claimed levels of PVA, being the only distinguishing feature of the claimed invention, was indeed the origin of the advantages claimed by the

applicant. Accordingly, the requirements of inventive step over the "closest prior art" could not be said to have been credibly met by the technical features recited in the claimed invention.

5.26 Accordingly, the opponent states that the alleged invention claimed in the impugned patent under opposition also lacks an inventive step over (a) Dl alone; (b) D2 alone; (c) Dl in view of D3; and (d) D2 in view of D3. The impugned patent is liable to be revoked on this ground alone.

5.27 The opponent states that since an object of the invention was to provide further anti-cancer pharmaceuticals, it was an obligation placed upon the patentee to demonstrate that the claimed compounds have an improved activity over the compounds of the prior art. It is stated that the patentee has failed to discharge this onus placed upon him to demonstrate superior activity over the compounds of the prior art. It is stated that no such data is furnished in the specification of the impugned patent comparing the claimed compound vis-a-vis the compounds of the closest prior art, particularly that of Dl to D3 referred to hereinabove and furthermore the patentee has failed to furnish any evidence in support of its claim regarding the alleged improvement in properties of the claimed compound. 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 compound.

5.28 Therefore, it is stated that the patentee has miserably failed to demonstrate any improved activity of the claimed compound over the compounds of the prior art, which is the sole basis for inventive step asserted by the patentee. The only logical conclusion that can be arrived at from the above comparison of the compounds of the impugned patent vis-a-vis the compounds of the prior art is that the claimed compound has not been shown to involve an inventive step.

5.29 The opponent states that the primary issue during the assessment of obviousness and lack of inventive step of a claimed chemical species is whether there exists a teaching of structural similarity of the claimed compound with the prior art compounds. The opponent states that the paragraphs above clearly establish that there exists a closest structural similarity between the compound claimed in the impugned patent and the prior art compounds. It is stated that

this, in itself, constitutes a sufficient motivation for the person skilled in the art to look for compounds within the prior art to identify compounds having an improved activity. The opponent states that this is further bolstered by the patentee's own admission that the compounds of the cited prior art and those of the impugned patent both are protein kinase inhibitors.

5.30 The opponent states that the next enquiry in an assessment of inventive step of a claimed chemical compound is whether there are teachings of similar properties or uses in the prior art. The opponent states that this question must also be answered in "Yes" because both the compounds of the prior art and that claimed according to the opposed patent find use as effective anti-cancer agent, which property is believed to arise from its receptor- tyrosine kinase inhibitory properties.

5.31 The opponent states that the next enquiry in the assessment of inventive step of a claimed compound is whether the state of the art to which the patent belongs predictable such that similar properties could be expected of compounds having similar structures. The opponent states that it is only rational to presume that both the prior art compounds and those claimed in the impugned patent, particularly that claimed in claims 8 or 9 of the impugned patent would have the same properties being tyrosine kinase inhibitory properties because they have the same structure. The improved properties asserted by the patentee are a difference of the properties only in degree but not in kind, and moreover these said improved properties have only been alleged but not convincingly substantiated by evidence. The opponent states the mere statement offered by the patentee is inconclusive regarding the presence of an inventive step for the reasons discussed above. Therefore, this enquiry must lead to the conclusion that the invention claimed in the impugned patent is obvious and does not involve an inventive step. The opponent states that it was incumbent on the patentee to show that the compounds that it claims as its invention demonstrated properties which were wholly unexpected and surprising having regard to the properties of similar compounds in order to justify their claim of a patentable invention having been made.

5.32 The opponent states that under the current standards of tests to determine the patentability of a chemical compound, obviousness of a new chemical compound proceeds through two stages. First, is there a prior art compound sufficiently close in structure to the claimed compound to suggest that the claimed structure would have the same properties? If the answer is negative, then the inquiry is completed: There is no obviousness for such a compound. But, as is the case in

the present alleged invention claimed by the patentee, there is a high degree of predictability of properties of a compound keyed to structure, such that the disclosure of a prior art compound suggests that the claimed compound can and should be synthesized to achieve like results. The opponent states that in the present case, the claimed compound is prima facie obvious based upon the concept of "structural obviousness". Where there is a. prima facie obviousness case based upon closeness of structure, then it is incumbent upon the patentee to demonstrate that there are actual differences between the claimed compound and the prior art such that the invention as a whole is non-obvious. It is well settled law that rebuttal of prima facie obviousness may take the form of a comparison of test data showing that the claimed compounds possess unexpectedly improved properties ... that the prior art does not have, that the prior art is so deficient that there is no motivation to make what might otherwise appear to be obvious changes, or any other argument that is pertinent. It is stated that under the present standard of obviousness review, unexpected results represent one of the indicia of non-obviousness. However, a claim for unexpected results require to be supported by data based evidence and that unsupported allegations cannot support a claim of inventive step.

5.33 In view of the above paragraphs, the opponent states that it has been proved beyond doubt that the compounds claimed by the patentee were obvious over the prior art made of record and clearly does not involve an inventive step. The impugned patent is liable to be revoked on this ground alone.

6. The patentee's comments (Obviousness)

6.1 As regards the averments at para 3 that relate to the grounds of opposition, this Patentee's submission herein below may be read and treated as reply and the same are not being repeated for sake of brevity.

6.2 In paras 4.1 to 4.11, the Opponent has sought to reproduce the claims of the subject patent and analyze the same. The Opponent's analysis of the statement of claims in the subject patent is denied and disputed as the same is inaccurate. In this regard the

Patentee relies on the averments made in the patent. No 209251. The compounds claimed in IP 209251 are hereinafter referred to as "claimed compounds".

6.3 The averments made at paras 5.1 to 5.33 are wrong, incorrect, misleading and hereby denied. First, the Opponent has not produced appropriate evidence, as required in law to found a case of obviousness. Hence, it does not lie in the mouth of the Opponent to argue the compounds claimed are obvious. It is the case of the Opponent that the claims of the impugned patent lacks inventive step in view of Exhibits I, II and III, also referred as Documents Dl, D2 and D3 respectively. The Patentee denies that the compounds claimed are obvious at all.

6.4 The averments at para 5.3 to 5.7 are wrong and hereby denied. In these paras, the Opponent has tried to make out a case as to how the claimed compounds are rendered obvious by a reading of Dl alone. First, the Opponent has failed to point out which compounds specifically from the laundry list of the compounds of Dl actually render the specific compounds claimed in the impugned patent obvious. This makes the ground taken by the opponent vague and ambiguous. Further, this itself is enough evidence of the frivolity of the opposition and this ground as such. Further, it is settled law that a single document cannot be read for purposes of assessing inventive step. Even so, it is specifically denied that upon reading of this document the compounds of Dl the claimed compounds would readily occur to a skilled person or that the skilled person would expect the claimed compounds to retain the activity of the compounds of Dl.

6.5 Without prejudice, it is submitted that the compounds disclosed by Dl do not render the claimed compounds obvious for the following amongst other reasons:

a) The basic backbone or core of the compounds as disclosed by Dl is an indolinone and not a pyrrole substituted indolinone compound. Therefore, Dl as such does not envisage pyrrole substituted indolinone compounds.

b) The compounds at column 10 of the document Dl are a family of a five member ring compounds and is different from the compounds having a structure as claimed in claim 1.

In fact the said five membered compound is not even disclosed or claimed in the document D1.

c) D1 at line 45 col. 10 envisages the possibility of substitution of a nitrogen atom on the indolinone nucleus (R1) which compound is not present in the compounds claimed in the impugned patent. As per col. 10 line 46 of D1, R2 is oxygen or sulphur. If R2 is sulphur, then the basic backbone itself ceases to be an indolinone. Thus, D1 does not recognize the advantages of attaching a pyrrole substituent at the third position of the indolinone ring.

d) Assuming for arguments' sake that the compounds disclosed by D1 are indeed pyrrole substituted indolinone compounds, even then, the substitutions at the 4^{th} position of the pyrrole ring and (counting from the nitrogen atom clockwise & corresponding to R6) are different. For instance the claimed compounds have a specific amide substituent (-C(O)NR'(CH2)n R", wherein R" is as defined in claims; whereas the prior art compounds of D1 have an ester (-C(O)OR) as in the case of SU5408 and SU5463 (D1) or methyl group as in the case of SU 5455. Thus D1 does not recognize the advantages of attaching a pyrrole substituent at the 3^{rd} position of the indolinone ring.

e) D1 relates generally to compounds useful in the treatment of cell proliferative disorders, and these compounds are generally said to be useful as tyrosine kinase inhibitors. D1 does not teach the specific substituents claimed by the impugned patent at position R6.

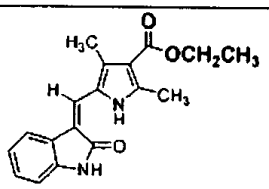
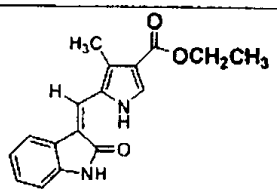
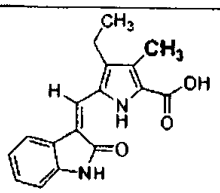
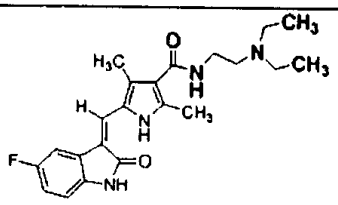
f) The Opponent admits that there is a certain difference between D1 and the claimed compounds, i.e. inclusion of a (diethylamino) ethyl substituent on the carboxamide nitrogen. However, the Opponent has failed to appreciate that the difference between the Markush structures does not lie in the diethylaminoethyl substituent; but in the fundamental nucleus itself. As stated earlier, D1 is drawn to indolinone compounds and not pyrrole substituted indolinone compounds. In fact, there is no carboxamide nitrogen with an alleged diethylaminoethyl substitution in the primary Markush structure claimed in claim 1.

g) D1 does not suggest to any skilled person firstly, to develop a confirmed indolinone nucleus and then add a pyrrole ring specifically substituted at the third position with the specific objective of inhibiting tyrosine and serine kinase. There is no reason given why a skilled person would be motivated to make such a substitution or why such a modification would readily suggest to a skilled person in the absence of a teaching in the art.

h) In fact some of the compounds of DI such as SU5416 (example 5.12) failed in clinical trials and was eventually dropped. In this regard, reference is made to the Press release dated 26.01.2006 which clearly states that SU5416 was dropped. Reference is also made to the chapter, Anti-angiogenesis Agents, Bart. C. Kuenen, in Drugs Affecting Growth of Tumours, H.M. Pinedo and C.H. Smorenburg eds., Birkhauser Vertag/Switzerland (2006), pages 167-183, and in particular the discussion on pages 170-173. Copy of the said Kuenen et al. publication is attached herewith and marked as Annexure A.

i) Without prejudice to whatever has been stated above, some compounds from DI have been tested in two assays and the results are shown in Table -5. The data shows that replacement of the ester or alkyl group at the 4-position of the pyrrole ring with an amide group provides a dramatic increase in both PDGFR and VEGFR activity, resulting in a compound that is a potent inhibitor of both of kinases (serine and tyrosine), an important advantage for an anti-cancer compound.

Table -5: Comparison with DI Compounds

Compound	Structure	PDGFRb IC_{50} (μM)[a]	VEGFR2 IC_{50} (μM)[b]
SU5408 (D1, col. 22, line 30)		> 100	0.578 ± 0.035 (n = 2)
SU5463 (D1, col 26, line 26) (D3, compound 44)		> 100	0.465 ± 0.068 (n = 2)
SU5455 (D1, col. 25, line 66) (D3, compound 48)		> 100	> 10 (n = 2)
SU11248 (present application, Example 80)		0.01	0.008 ± 0.002 (n = 5)

[a]cellular activity in 3T3 cells

[b]cellular activity in PAE-VEGFR2 cells

6.6 A skilled person would from Dl learn of derivatives of compounds but not learn of pyrrole substitution much less the specific compounds of the impugned patent and hence would be unable to arrive at the compounds claimed in the impugned patent.

6.7 Without prejudice to the generality of the foregoing, we submit with regard to the Table-2 at para 5.4 as under in table-6:

Table-6

S. No.	Parameter	Claimed compound	D1	Comments	Comments of Patentee
1	Structure of the compound		Col. 10 lines 47: R3 is hydrogen	Similar, both the compounds have same backbone structure.	D1 discloses only indolinone nucleus and not indolinone with pyrrole substitution; hence, backbones are different
2	R1	R1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxyl, alkoxy, - (CO) R15, -NR13R14 (CH2) rR16 and-C(O) NR8R9;	Claim 1: R4 is selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO2RR', SO.sub.3 R, SR, NO.sub.2,	Overlapping. The prior art discloses a broader group of substituent which encompasses the substituents claimed in the impugned patent under opposition	The comparison is being drawn between substituents within Markush structure. When the basic ring is different, presence of common substituent groups is irrelevant.

			NRR', OH, CN, C(O)R, OC(O)R, (CH.sub.2).sub .n CO.sub.2 R, and CONRR'		
3	R2	Preferably halogen, especially fluorine.	Col. 10 line 50: R5 may be halogen	Overlapping	Halogen is one among the various substituents present and hence R5 may also be aryloxy, alkyl, alkyloxy, aryl, etc.
4	R3 and R4	Preferably hydrogen	Col 10, line 49: Hydrogen	Overlapping	Hydrogen is one among the various substituents specified for R4.
5	--------	Pyrrole ring.	Col. 10, line 55: A is a five membered heteroaryl ring selected from ..... Pyrrole, ...	Overlapping	Pyrrole is one among the various substituents specified for the substituent 'A'.

6	--------	Pyrrole substituents	Col. 10, line 63: The disclosed pyrrole may be optionally substituent with one or more positions with alkyl, ...	Overlapping	Again the substitution in pyrrole is open to various substituents at all available positions.
7	--------	Carboxaminde pyrrole substituent. - $C(O)NH(CH_2)_2N(Et)_2$.	Col. 10, line 67 : The pyrrole substituent may be - C(O)NR R'. R may be hydrogen.	Overlapping D1 defines R' as hydrogen, alkyl or aryl	One amongst various substituents.

6.8 The averments at para 5.8 to 5.12 are denied. It is denied that the compounds claimed are obvious in view of D2 alone. In these paras, the Opponent has tried to make out a case as to how the claimed compounds are rendered obvious by a reading of D2 alone. First, the Opponent has failed to point out which compounds specifically from the laundry list of the compounds of D2 actually render the compounds claimed obvious. This itself is enough evidence of the frivolity of the opposition and this ground as such. Further, it is settled law that a single document cannot be read for purposes of assessing inventive step. It is specifically denied that upon reading the compounds of D2 the claimed compounds of the impugned patent would readily occur to a skilled person or that the skilled person would expect the claimed compounds to retain the activity of the compounds of D2.

6.9 It is also denied that the compounds as claimed by the impugned patent are taught by D2. While D2 relates to certain compounds useful in the treatment of cell proliferative disorders, such a disclosure does not per se make the claimed compounds obvious, contrary to the arguments made by the Opponent. It is specifically denied that upon reading of D2, the claimed compounds would readily occur to a skilled person or that the skilled person would expect the claimed compounds to retain the activity of the compounds of D2. It is further submitted that apart from the fact that the said patent D2 discloses compounds that modulate the activity of the kinase, there is no other thread of similarity between the compounds as claimed to that of D2.

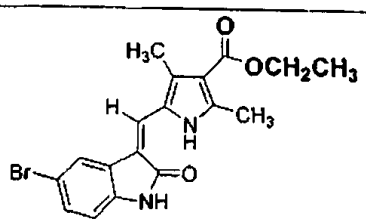
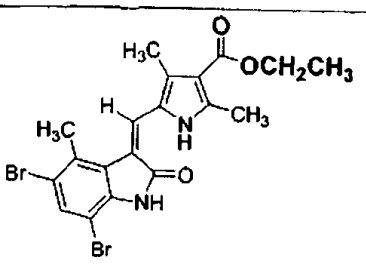
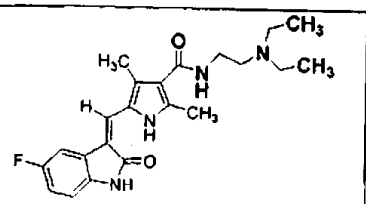
6.10 Assuming but not admitting that such a reading is permissible, it is submitted that the compounds disclosed by D2 do not render the claimed compounds obvious for the following amongst other reasons:

a. The compounds of D2 only contain an indolinone nucleus. There are many substituents on the indolinone nucleus. As per D2 at page 7 line 3, Z, as defined in the basic "Markush" structure may also be sulphur. If such a substitution is made, then there is no question of even arriving at the basic oxindole structure, let alone a pyrrole substituted oxindole. Furthermore, as per the same line of Document D2 as mentioned above, and its next line and as per page 9 lines 3-8, Al, A2, A3 and A4 can also be nitrogen. Further, as per page 9 lines 6-7, if Al, A2, A3 and A4 is nitrogen R3, R4, R5 and R6 does not even exist. Hence, the indolinone structure by itself as suggested by the Opponent is but an empirical structure created by and obvious only to the Opponent, albeit with the benefit of hindsight. The Q can be any substituent as described from pages 10-29. The vast library of substituents is not even limited to 5 membered rings. It can also be 6 membered ring or bicyclic rings. Even if it is a 5 membered ring, it is not restricted to a single nitrogen containing heterocycle. All the disclosures as in the said pages are general and not specific. There is no specific mention of the pyrrole nucleus.

b. D2 neither envisages a specific pyrrole substituent in the oxindole nucleus nor does it disclose the improvement in activity at this specific substituent. Any disclosure in D2 (if any) may be a general disclosure as a part of Markush claims and is not a specific disclosure. It is nothing but a severe case of ex post facto analysis to arrive at the compounds of the impugned patent based on general generic disclosure.

c. Assuming but not admitting that it is possible to arrive at pyrrole substituted oxoindole nucleus of the subject patent, the opponent does not indicate, which compounds specifically, out of the million possible compounds of D2 render the claimed compounds obvious; this makes the ground taken by the opponent vague and ambiguous. To avoid and set to rest any doubts that may arise, the Patentee has compared certain exemplary compounds of D2 with the compounds claimed in the present patent. The results are depicted in table -7 below. It is clear that the inventive compound SU11248 of the impugned patent is a far more potent inhibitor of PDGFR and VEGFR2 than the compounds of D2.

Table 7: Comparison with D2 Compounds

Compound	Structure	PDGFR	VEGFR2
D2, page 30, lines 1-2		15 μM (D2, page 167)	Flk-1R IC50: 4.2 μM (D2, page 167)
10718/H02 (D2, page 44)			Flk Kinase % Inhibition: -1.4% (D2, page 169)
SU11248 (present application, Example 80)		0.01 μM	0.008 ± 0.002 μM (n = 5)

d. It may be noted that the two compounds of D2 as disclosed in Table 2 have the same dimethyl and ethoxycarbonyl pyrrole substituents as SU5408 of Dl, but additionally are substituted on the phenyl portion of the indolinone ring. Hence the chemical nature in terms of aromaticity and electron density are entirely different from the compounds of the impugned patent.

6.11 Without prejudice to the generality of the foregoing, with regard to Table-3 at para 5.9 we submit as under in table-8:

Table 8: See next page

S. No.	Parameter	Claimed compound	D2	Comments	Comments of Patentee
1	Structure of the compound		<u>Page 9:</u> A1, A2, A3 and A4 may be carbon.	Similar, both the compounds have same backbone structure.	Impugned patent is drawn to 3-pyrrole substituted indolinone structure, whereas document D2 discloses only indolinone structure and hence, the backbones are not similar. As per page 9, lines 3-8, A1, A2, A3 and A4 may be either carbon or nitrogen. It is only understood that it is a 9-

					substituents as described in lines 9-14.
			R2 is hydrogen (page 9, line 14).		Again hydrogen is one among the various substituents as described in lines 14-16.
			Q may be pyrrole ring substituted with R8, R8′ and R8″ (Q2, page 10 and Q4, page 11).		At page 10, Q is defined as 3 sub structures 2, 3 and 4, wherein as per description on page 11, lines 5-20, R8, R8′ and R8″ can be various substituents including further sub-structures 5 & 6.

2	Pyrrole substituent	-C(O) - NH - CH_2-CH_2 - N $(Et)_2$.	<u>Page 11, line 5:</u> R8, R8' or R8'' may be selected from hydrogen (line 7) or alkyl (line 7) or C-amido (line 12). <u>Page 25, line 17:</u> C-amido means - C(=O) $NR^{18}R^{19}$. <u>Paragraph bridging pages 9 and 10:</u> R^{18} may be hydrogen (page 9, line	Overlapping. The prior art discloses a broader group of substituents which encompasses the substituents claimed in the impugned patent under opposition.	As per description on page 11, lines 5-20, R8, R8' and R8'' can be various substituents including further sub-structures 5 & 6. Such a disclosure does not exist on this particular page. As per page 9 line 29 and page 10 lines 1-2, R_{18} and R_{19} can be any group amongst the

			30) while R^{19} may be alkyl (page 9, line 30).		various specified groups.

6.12 As per para 5.11, it is denied that D2 specifically discloses the amide substituents at position 4 of the pyrrole ring. The disclosure of the pyrrole ring is not restricted to the fourth position. The substitution may be possible at any position. Neither is the ring limited to a single substituent and the ring may be any heteroaryl ring. Contrary to the averments at para 5.12, there is no diethylaminoethyl substitution on the carboxamide nitrogen in the Markush claim 1 of the impugned patent. Hence, the analysis and conclusion arrived at by the Opponent are misconceived and erroneous.

6.13 The averments at para 5.13 to 5.22, especially the table are denied. The averments at para 5.13 to 5.22 are wrong and hereby denied. In these paras, the Opponent has tried to demonstrate how the claimed compounds are rendered obvious by a reading of D3 alone (although such a reading is not permissible in law). While D3 relates to compounds useful in the treatment of cell proliferative disorders, such a disclosure does not per se make the claimed compounds obvious, contrary to the arguments made by the Opponent. It is specifically denied that upon reading the compounds of D3 the claimed compounds would readily occur to skilled person or that the skilled person would expect the claimed compounds to retain the activity of the compounds of D3. Further, the same document has been referred to in the ISR as "A" category document. ISR defines a category "A" document as "document defining the general state of the art which is not considered to be of particular relevance." The subject

matter of the documents that define the general state of art cannot be considered to render the claims of the impugned patent obvious.

6.14 Assuming but not admitting that Document D3 is prior art, it is submitted that the compounds disclosed by D3 do not render the claimed compounds obvious for the following amongst other reasons:

a. The subject patent is restricted to a 3 pyrrole substituted indolinone nucleus that does not have any substitution in both nitrogens of the indolinone nucleus and the pyrrole nucleus. Also, the R2 of the document D3 is fixed as hydrogen in the compounds claimed by the impugned patent.

b. The Opponent has admitted that there is a difference between the compounds claimed by the patent and D3 "It is therefore clear from the comparative table that the only difference between the compounds broadly claimed in claim 1 of the impugned patent under the opposition and the document D3 is that whereas the polar group of D3 is attached to the pyrrole ring via an "alkyl" (alkl) group, the claimed compounds do not have the intervening alkyl group". Thus, as per the Opponent's own admission the claimed compounds are different from those claimed by the impugned patent.

c. Out of the endless list of substituents as provided in D3 for every substitution position, there is only a chance by picking and choosing from the different substituents in D3 to produce a chemical core structure that resembles the chemical core structure of the compounds as claimed. Even if such an arbitrary selection of a specific compound as suggested by the Opponent, there is literally no guarantee that the compound so chosen hypothetically can be successfully generated in the laboratory and if so generated, would inevitably have the properties sought and desired. d. D3 lists more than 30 possible substituents at the R9 (of D3) position, and of the 64 specific compounds exemplified in D3, every compound has a substituted alkyl group at the R9 position.

An alkyl group at the R9 position in combination with the electron-rich pyrrole ring would result in a compound that is too easily metabolized, with the result that the in vivo half-life of the compound is too short and the potential anticancer effectiveness of the compound is limited. This was not known, of course, to the inventors of D3 or to those skilled in the art at the time, but is known now only because of the inventive contribution of the present impugned patent. Nothing is known about the biological activity, bioavailability, metabolic stability, protein binding, pharmacokinetic properties, and ultimately its anti-cancer effectiveness of the compounds of D3.

6.15 Without prejudice to the above and with regard to Table-4 at para 5.15 we submit as under in table-9:

Table 9:

S. No.	Parameter	Claimed compound	D3	Comments	Comments by Patentee
1	Structure of the compound			Similar, both the compounds have same backbone structure.	Compound of Impugned patent is limited to an indolinone nucleus,

						wherein the nitrogen is not substituted and the pyrrole at the third position of the indolinone nucleus is also not substituted at the nitrogen and there is no chance of any intervening group as disclosed as R2 in D3 and hence, the basic backbone is different.
				Page 10, line 11:		As per page 10 lines 11-

			R1 includes hydrogen. <u>Page 10, line 15:</u> R2 includes hydrogen. <u>Page 11, line 10:</u> R7 includes hydrogen.		14, R1 may also be alkyl, alkenyl or any other substituent. As per page 10 lines 15-16, R2 can also be halo, alkyl, cycloalkyl, aryl, heteroaryl. As per page 11 lines 10-14, R7 can also be alkyl, cycloalkyl, amidino, etc.
2	R1	R1 is selected from the group consisting of	<u>Page 10, line 17 onwards:</u> R3, R4, R5 and R6 are	Overlappling	The comparison is being drawn

		hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxyl, alkoxy, - (CO) R15,-NR13R14 (CH_2) rR16 and-C(O) NR8R9;	independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxyl, alkoxy, aryloxy, mercapto, alkylthio, arylthio, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalomethane sulfonamide, carbonyl, C-carboxy, O-carboxy, C-amido, N-		between substituents within Markush structure, which is not correct.

			amido, cyano, nitro, halo, 0-carbamyl, N-carbamyl, O-thiocarbamyl, Nthiocarbamyl, amino and-NR1lR12.		
3	R2	Preferably halogen, especially fluorine.	Page 10, line 17 onwards: R4 includes halogen.	Overlapping	As per page 10 lines 17 and page 11 line 2, R4 can also be various other substituents as specified.
4	R3 and R4	Preferably hydrogen	Page 10, line 17 onwards: R5 and R6 include hydrogen.	Overlapping	As per page 10 lines 17 and page 11 line 2, R3 and R4 can also be various other substituents as specified.
5	---------	Pyrrole ring.	The structural formula of the	Overlapping	Impugned patent

			disclosed compounds teaches a pyrrole ring.		discloses a pyrrole ring in which N is not substituted with hydrogen.
6	---------	Pyrrole substituents	Col. 11, line 5: R8 and R10 include an alkyl group as a possible substituent.	Overlapping	The comparison is being drawn between substituents within Markush structure, which is not correct. As per page 11, lines 15-23, R8, R9 and R10 can also be cycloalkyl, alkenyl, alkynyl, aryl or any other

					substituents.
7	----------	Carboxaminde pyrrole substituent. – $C(O)NH(CH_2)_2$ $N(Et)_2$	<u>Col.11, line 15:</u> R9 may be (alkyl) – Z, wherein Z is a polar group and "alkyl" is an alkyl, alkenyl or alkynyl group.	The exact 4-pyrrole substituent which is not taught by either of D1 and/or D2 is taught in the most preferred embodiment of D3.	D3 does not teach specifically 4-pyrrole substituent. As per page 11 line 15, R8 and R10 can also be a (alk1) –Z substituent. Hence, the substitution is not limited to R9.
			<u>Paragraph bridging pages 21 and 22:</u> Z is selected from the group consisting of – C(=O) N $R_{13}R_{14}$ wherein R_{13} and R_{14} are independently selected from		As per page 21 line 28 to page 22 line 8, –C(=O) N $R_{13}R_{14}$ is one among various substituents and again numerous substituents

			the group consisting of hydrogen, ..., lower alkyl substituted with a group selected from the group consisting of amino and -NR 11R12.		are defined for R_{13} and R_{14} which includes $NR_{11}R_{12}$.

6.16 The averments of para 5.16 are wrong and hereby denied. As per para 5.16, the various groups as substituents of the pyrrole ring are nothing but various possibilities of a Markush structure. The Opponent again has resorted to ex post facto analysis to demonstrate that the said structures of D3 and impugned patent are similar. All these averments being technically incorrect are denied.

6.17 The averments at paras 5.17 to 5.18 are wrong and hereby denied. As per para 5.17, it is denied that modification of polar group Z or any other groups for that matter is obvious by reading any Markush claim. As per para 5.18, the Opponent has stated that the claims are obvious over Dl in view of D3 or alternately over D2 in view of D3; however, the Opponent has failed to demonstrate how each of the aforesaid combination renders the claims of the impugned patent obvious. Be that as it may, the fact that the Opponent has failed to demonstrate how each of the combinations make the compounds obvious, renders the ground taken by the Opponent vague and ambiguous and ought to be dismissed on this account alone.

6.18 Without prejudice, it is submitted that the basic structures of compounds of Dl and D2 are totally different and arriving at an indolinone nucleus by reading these two documents together is simply not possible for a skilled person. Assuming but not admitting that a skilled person does arrive at the indolinone nucleus, further envisaging a substitution at any specific position is a tall order. Further, the Opponent is suggesting from such a Markush disclosure that it is obvious to arrive at specific substitutions in the pyrrole nucleus at specific positions. Assuming but not admitting that the Opponent is correct, the possibilities of arriving at any compound having the structure as claimed in claim 1 is far remote as too many presumptions and assumptions are required to be made.

6.19 The Opponent admits that D1-D3 per se does not render the compounds obvious and certain "modifications" are required therein. The reasoning as to why a skilled person would consider modifying the polar group 'Z' and how it would be modified has deliberately been left vague and glossed over since there is no such reason. Further, the Opponent miserably fails to explain why a skilled person would consider or be lead to the compounds when starting from Dl or D2 via D3.

6.20 Taken together, based on the above discussions, the comparisons of Document Dl, D2 and D3 show that: (1) the compounds of the present invention are potent inhibitors of both VEGFR2 and PDGFR, whereas the cited prior art compounds of Dl, D2 and D3 do not possess such a property; and (2) the enhanced multi-kinase potency is primarily due to the presence of the amide moiety (-C(0)NR'$(CH2)_n$R", where R" is as defined in the claims) at the 4-position of the pyrrole ring (or R^6, in the present claims). These surprising and beneficial advantages of the compounds of the impugned patent are not taught or suggested in the Dl, D2 or D3 references. Thus the compounds claimed definitely show an inventive step over the Dl, D2 and D3 references.

6.21 The averments at paras 5.19 to 5.22 are wrong and hereby denied. It is denied that claims 2-10 are obvious in view of D1-D3 either alone or in combination. Apart from making vague statements, the Opponent has not shown how a skilled person would be lead to the compounds as claimed in the impugned patent. It is further submitted that first of all, the Indian law does not require a showing of 'data' or 'comparative data' for establishment of inventive step. Hence, all averments made in these paras on this basis are meaningless in law.

PATENTEE'S COMMENTS (LACK OF INVENTIVE STEP):

6.22 The averments at paras 5.23 to 5.33 are wrong, denied and disputed. With regard to paras 5.23 and 5.24, it is submitted that the Opponent has failed to understand the invention and the claims as such. The impugned patent claims contain novel compounds which exhibit tyrosine kinase modulation activity. These are unique compounds which have not been disclosed anywhere in the prior art. The Opponent admits the fact that these compounds are not disclosed by any of the prior art relied upon by them. The particular group -C(O)NH(CH2)2N(Et)2 is not disclosed anywhere in Dl and D2. The group is only one of the several possibilities of a Markush claim. Hence, there is no onus on the Patentee to provide any further data as these compounds cannot be considered as the closest prior art. Opponent states that no comparative tests can be envisaged in law to support an inventive step.

6.23 With respect, the entire premise on which the Opponent has based its arguments is completely erroneous. It is settled law that obviousness cannot be based on possibilities and probabilities; a proper scientific reasoning is required to support the fact that the compounds claimed are indeed an obvious modification. It is

denied that the compounds claimed bear structural similarity to the compounds disclosed in Dl to D3. In fact the process of preparation of compounds of D1-D3 is different from the process for preparation of compounds claimed. Notwithstanding and assuming for argument's sake that such a structural similarity does exist, then mere structural similarity per se does not render the claimed compounds obvious. As per the Opponent structural similarity renders the compounds obvious but this not the case. For example, WO 93/12786 is drawn to indolinone derivatives, but these compounds are used in the treatment of diabetes, a totally different field than protein kinase modulation activity. Thus same/similar structures can and may have totally unrelated biological profiles. When the Opponent has not discharged its burden fully of establishing even a prima facie case of obviousness, the stage of evaluating inventive step on the basis of comparative data does not arise at all. Without prejudice it is submitted that the Indian law is otherwise.

6.24 The averments at para 5.24 are wrong and denied. It is reiterated that Dl-D3 cannot form the closest prior art as the compounds disclosed therein are not even remotely similar to the compounds claimed in the impugned patent. Assuming but not admitting that any of the documents D1-D3 qualify as prior art, even then a prima facie case of obviousness is not established, making the showing of existence of inventive step by submitting comparative data, redundant. It is further submitted that the compounds claimed in the impugned patent, especially compound at claim 7 has passed the stringent tests of the FDA and received approval in the year 2006 (Annexure B), and in India in 2007. We further note that the invention of the impugned patent has had a profound and beneficial effect on the treatment of several deadly forms of cancer. In particular, the compound of Claim 7 (sunitinib, sold under the tradename Sutent) was approved by the FDA in January of 2006, for the treatment of gastrointestinal stromal tumors (GIST; a rare and deadly stomach cancer) and advanced kidney cancer, and marked the first time the FDA has approved a new oncology product for two indications simultaneously

(see the attached FDA press release). Sutent has now been approved for use in more than 80 countries, including India, and has become the standard of care worldwide for the treatment of advanced kidney cancer. Sutent is in late stage clinical trials for the treatment of several additional cancer types, including breast cancer, lung cancer, colorectal cancer, hepatocellular cancer and prostate cancer. Due to its extraordinary effectiveness, this breakthrough drug has achieved annual worldwide sales (2008 projected) of more than $700 million, and is currently helping tens of thousands of patients worldwide, including many patients in India.

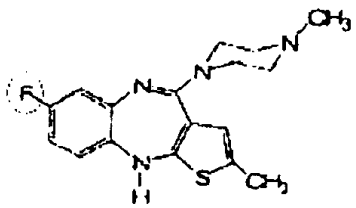
6.25 The averments at paras 5.25 to 5.26 are denied, to the extent of the arguments made by the Opponent in respect of the cases cited in these paras. First, the factual matrix of the AstraZeneca and the Berwind cases are completely different from the factual matrix of the preset case. On that account alone the aforesaid cases stand distinguished and the ratio, if any, in those cases is inapplicable in the context of the present case. Be that as it may, it is denied that the invention as claimed in the impugned patent lacks inventive step over D1-D3 alone or in combination, for the reasons recited in the aforesaid paras.

6.26 The averments at paras 5.27 to 5.29 are wrong and hereby denied. In these paras, the Opponent has primarily emphasized the need for a showing of an improved activity over compounds of the prior art, the showing being a basis for inventive step. It is submitted that the premise on which the Opponent has based its arguments is erroneous in law. It is reiterated that the compounds claimed in the impugned patent are novel and as per the Opponent's own admission have not been disclosed by the prior art. This being the case, the closeness of the claimed compounds to the compounds disclosed in the prior art, is nothing but empirical and imaginary. The establishment of inventive step, on the basis of comparative data or improved activity, does not arise, at least in the factual matrix of the present case. All the averments made to the contrary in this regard by the Opponent may be

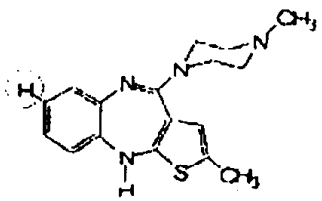
completely disregarded.

6.27 (a) The averments at paras 5.30 to 5.33 are wrong and hereby denied. It is submitted that the Opponent has jumped into "the next stage of enquiry" when the first stage itself remains incompletely proven. It is denied that structural similarities per se lead to a conclusion of obviousness. It is also denied that merely because some compounds of D1-D3 exhibit tyrosine kinase inhibitory properties, all the compounds claimed in the patent are presumed to possess tyrosine kinase inhibitory properties as they allegedly share the same structure, when in reality they do not. It is well known in the field of chemistry that any small modification in any chain or side chain or change of substituent could completely alter the activity of the compound and lead to development of new compounds. Dr. Cui's Affidavit discusses several such examples in the field of indolinone chemistry, but it is a well known phenomenon in medicinal chemistry art. Copy of the said Affidavit publication is attached herewith and marked as Annexure C.

(b) An example is two closely related compounds, olanzapine and flumezapine, both of which belong to same family of thienobenzodiazepines and share the same thienobenzodiazepine base structure. The only difference between flumezapine and olanzapine (as seen in the figure below) is the presence of a fluorine atom in flumezapine where olanzapine has a hydrogen atom. Flumezapine was found to be extremely toxic and caused widespread blood disorders in dogs, whereas olanzapine, marketed under various brand name Zyprexa is a popular antipsychotic drug. This clearly rebuts the notion of the Opponent that structural similarity means similar activity.



Flumezapine



Olanzapine

(c) It is common knowledge that small changes in structure or specific choice of substituents can dramatically alter chemical or therapeutic properties and this principle is as fundamental as arithmetic to those skilled in the art of medicinal chemistry. One need only open any volume of the Journal of Medicinal Chemistry, a premiere academic journal in the field, to see myriad examples of the same. For example, turning to the year 2000, Vol. 43, p. 3335-3343 (Annexure D), one finds the following SAR table-10 on page 3338, which has been edited for size from the original:

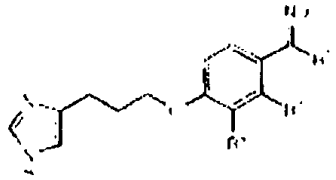


Table-10:

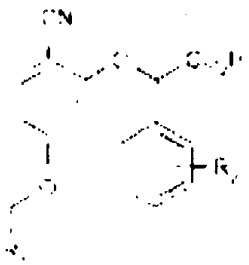
no	R^1	R^2	R^4	K_i (nM)[b] ± SEM	ED_{50} (mg/kg)[c] ± SEM
26	H	OCH_3	H	nd[a]	12 ± 2
27	CH_3	OCH_3	H	371 ± 115	nd[a]
28	CH_3	CH_3	H	1.4 ± 0.6	0.19 ± 0.09
29	CH_3	H	CH_3	1.5 ± 0.3	0.27 ± 0.07
30	CH_3	I	H	0.80 ± 0.08	0.052 ± 0.007

Both Ki and ED50 are measures of compound potency, with smaller values indicating more effective target inhibition. Manipulation of but three substituents, and choosing only among four possible moieties (H, CH3, OCH3

and F), can yield compounds which are highly potent (compounds 28-30) or essentially inactive (compounds 26 and 27).

(d) Similarly, turning to the article on pages 900-910 (Annexure E) of the same volume, one finds this table-11 (edited for size):

Table-11



Compd	R_1	R_2	PDE_4 IC_{50} (nM)
13e	thiophen-3-yl	2-CH_3	16, 20
15a	fur-3-yl	2-CH_3	68
15b	isothiazol-3-yl	2-CH_3	220
15c	thiazol-5-yl	2-CH_3	28, 30
15d	pyrid-2-yl	2-CH_3	> 4000
15e	pyrid-4-yl	2-CH_3	8, 9
15f	pyrid-4-yl	2-Cl	1, 6
15g	pyrid-3-yl	2-CH_3	80
15h	4-F-pyrid-4-yl	2-CH_3	22, 24
15i	pyridazin-4-yl	2-Cl	41, 43
15j	benzoxazol-6-yl	2-Cl	8, 9
15k	benzoxazol-6-yl	2-CH_3	6, 6
15l	benzoxazol-5-yl	2-CH_3	61, 75

Comparing compounds 15e and 15d, for example, merely changing the point of attachment of a pyridyl ring from the 4 to the 2 position changes a potent compound (15e) to an inactive one (15d).

(e) Finally, one need not even change the chemical substituents of a compound in order to dramatically change its properties. For example, the Journal of the Indian Medical Association 2007,105,177-178, describes many examples of chiral compounds, where the two chemical compounds, differing only in their stereochemistry, have very different

properties. Copy of the said JIMD 2007 publication is attached herewith and marked as Annexure F. The article notes:

"Examples of drug candidates in which one enantiomer is 'active', while the other enantiomer is 'inactive' are S-atenolol - beta-blocking property resides in its S-form, laevocetirizine - antihistaminic profile is associated with the R-enantiomer (laevo) while the S-enantiomer (dextro) being essentially inactive; and laevofloxacin - antibacterial activity resides in the S-enantiomer only."

The article provides further examples of compounds where one enantiomer has beneficial properties while the other is antagonistic, or where the two enantiomers have therapeutic utility for completely different uses.

(f) Countless other examples of such dramatic changes are found throughout the literature. In view of the knowledge of a skilled medicinal chemist of the profound sensitivity of compound properties to structural changes, the Opponent's position that one could pick substituents at multiple positions, choosing from perhaps dozens of chemical moieties at each position, and somehow arrive at the compounds of the impugned patent as an "obvious" manipulation of known elements, is simply not credible. In view of the above, the conclusion that structural similarity makes all compounds obvious is a misnomer, erroneous and not tenable in law.

7. RECOMMENDATION OF OPPOSITION BOARD

After perusing the case and the documents filed by both the parties, the opposition board constituted for this case recommended that the patent is liable to be revoked as the invention does not involve an inventive step u/s 2(1) (j), u/s 2(1)(ja) and u/s 2(1)(t) of the Patents Act, 1970.

8. CONCLUSION

8.1 The opponents dropped the grounds related to prior knowledge and sec. 8. They mainly argued on grounds of obviousness/ lack of inventive step in view of citations named as D1 and D3 during the hearing.

8.2 In view of the above detailed discussion, the opposition board's opinion, the arguments of the opponents and patentees and the facts given in the documents including affidavit submitted by both the parties, I shall now discuss the vital grounds of obviousness.

8.3 Opponents relied on prior art documents US5886020 (D1), WO/98/50356 (D2) and WO/99/61422(D3).

8.4 The claim 1 of the impugned patent read with description of patent and comparative statement (Table 2, Table 3 and Table 4) submitted by the opponents in full written statement reveals that the basic Markush structure of the compounds as claimed in the impugned patent lack inventive step in view of disclosures in documents US5886020 (D1), WO/98/50356 (D2), WO/99/61422 (D3). Both documents D1 and D2 submitted by the opponents disclose pyrrole substituted indolinone compounds which overlap with the impugned patents compounds except that of group R6 at position 4th of the pyrrole ring. 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. Moreover, Document D1 discloses an amide substituent at position 4th of the pyrrole ring (R6 group at position 4 in present patent) and also teaches an amide function at 4th position of the pyrrole ring. 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' where R may be hydrogen and R' could be hydrogen, alkyl or aryl. Further it is also observed that the compound of formula III at col. 10 of D1, wherein the values of 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 groups viz. at one position by –CONRR' wherein R' is an alkyl group which includes $N(CH3)_2$(at column 7, line 12 of D1). The compound arrived is different from sunitinib in two aspects only 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.

8.5 During hearing patentee argued that the opponent has withdrawn D2 but opponents denied the allegations and argued that D2 also discloses pyrrole substituted indolinone compounds which is a backbone structure of claimed compound of impugned patent, it is also clear from the table 3 of opponents written statement. Moreover, document D2 also teaches amide function at 4th position of the pyrrole ring (R6 group at position 4 in present patent). In D2 the diethylamine group attached to the amido group present as a substituent on the pyrrole at positions R6 of the compound of impugned patent under opposition. It is clear from the Table 3 of D2, the definition of C-amido group is RCONR18R19 wherein R18 may be hydrogen (page 9, line 8) and R19 may be alkyl (page 9, line 30). 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.

8.6 The document D3 (Table 4) submitted by the opponent teaches the pyrrole substituted 2-indolinone protein kinase inhibitors which is the exact 4-pyrrole substituent and not taught by either of D1 and/or D2. The polar group "Z" of D3 is attached to the pyrrole ring via an "alkyl" (alk) group whereas the claimed compounds do not have the intervening alkyl group. The polar group Z i.e. -C (O) NH (CH2)2N (Et) 2 is not disclosed in D1 and D2, but disclosed in the preferred embodiment of D3 and attached to pyrrole ring via an alkyl group. I observed from the disclosures of D1 or D2 in combination with D3 would motivate a person skilled in the art to develop protein kinase inhibitor compounds as claimed in the impugned patent.

8.7 It is also observed that the preferred embodiment of D3 at page 10 discloses the similar compound of formula I as depicted in the said document, 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 = (Alk_1) Z; where Z is selected from the group consisting of $-C(=O)NR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from the group consisting of hydrogen, ..., lower alkyl substituted with a group selected from the group consisting of amino and $-NR^{11}R^{12}$, ..., wherein R^{11} and R^{12} are independently selected from the group consisting of unsubstituted lower alkyl and, ... (at paragraph bridging pages 21 and 22 of D3).

8.8 Opponent stated that the presence of the (Alk1) group is essential in accordance with D3, however couple of examples of aldehydes mentioned in D3 which do not fall in the aforesaid definition. I observed that the aldehyde is condensed with the oxindole to generate the claimed compounds of impugned patent. The review of the terminal group on

the aldehyde will therefore give a clear indication of (Alk1). The specific examples of aldehydes without (Alk1) are 5-formyl-2,4-dimethyl-1H-pyrrole-3carboxylic acid (line 29, page 27) and 5-formyl-2,4-dimethyl-1Hpyrrole-3-carboxylic acid (2-dimethylaminoethyl) amide (line 31, page 27). Amongst the various oxindoles and aldehydes in the combinatorial library, D3 discloses the compounds 5-fluorooxindole (line 10, page 24), 5-formyl-2,4-dimethyl-1Hpyrrole-3-carboxylic acid (2-dimethylaminoethyl) amide at page 27 lines 31, 32. Opponent also stated that the above compound differs from sunitinib as claimed in claim 7 of the impugned patent only the terminal N atom in as much as the former bears a dimethyl group instead of a diethyl group in the latter; incidentally 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, 4dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylaminoethyl)amide -5-Fluoro-1, 3-dihydro-indol-2-one was condensed with 5-formyl-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid (2- dimethylaminoethyl) amide to give the title compound."

8.9 The affidavit submitted by the Mr. D.R. Rao on behalf of opponents is taken on record and accepted which clearly states "Sunitinib is a novel tyrosine kinase inhibitor and is therapeutically potential in the treatment of renal carcinoma and gastrointestinal stromal tumors (GIST)". It is apparent from this affidavit that the metabolization occurs at the terminal N atom and not at the position of the (Alk1) group. Therefore I observe that the disclosures in D1 or 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.

8.10 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.

8.11 The statement of the opponent is agreeable that, "the compounds disclosed in D1 or D2 only differs from the compounds claimed in the impugned patent under opposition in that the D1 or D2 did not include the -C (O)NH(CH2)2 N $(Et)_2$ group on the carboxamide nitrogen. It is well settled that in the case where comparative tests are envisaged in order to support an inventive step, these must be carried out between the compounds of the claimed invention having 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 claimed invention".

8.12 The structure of compounds of D1 and D2 overlaps with the structure as disclosed in present patent and 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 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.

8.13 It is also observed that the claimed compounds, as exemplified by SU11248, have a specific amide substituent (C (O) NR' (CH2) nR", where R" is as defined in the claims) at this 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.

8.14 The Patentee has also compared certain exemplary compounds of D2 with the compounds claimed in the present patent. The results are depicted in Table -7. It is clear that the claimed compound SU11248 of the patent is a far more potent inhibitor of PDGFR and VEGFR2 than the compounds of D2. It may be noted that the two compounds of D2 as disclosed in Table- 7 have the same dimethyl and ethoxycarbonyl pyrrole substituents as SU5408 of Dl, but additionally are substituted on the phenyl portion of the indolinone ring.

8.15 It is further stated that D3 equally well applies as the "closest prior art" (and provides exactly that "feature" of the claimed compound which is not specifically disclosed in Dl or D2 being the specific polar "Z" group) and places an obligation upon the patentee to compare the activities of the compounds when C(O)NH(CH2)2 N (Et)2 group is bonded directly to the

pyrrole ring (as in the claimed compounds) versus the activities of the compounds when - C(O)NH(CH2)2 N (Et)2 group on the carboxamide nitrogen is bonded to the pyrrole ring via an alkyl ("alkl") group. However, none of these comparative tests have been furnished by the patentee. 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 closet prior art.

8.16 I observed that no such data is furnished by the Patentees in the specification of the patent comparing the claimed compound vis-a-vis the compounds of the closest prior art, particularly that of Dl to D3 referred to hereinabove and furthermore the patentee has failed to furnish any evidence in support of its claim regarding the alleged improvement in properties of the claimed compound. 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.

8.17 It is also observed from the description in complete specification and in the reply statement that the patentee has miserably failed to demonstrate any improved activity of the claimed compound over the compounds of the prior art which is the sole basis for inventive step asserted by the patentee. The only logical conclusion that can be arrived at from the above comparison of the compounds of the patent vis-a-vis the compounds of the prior art is that the claimed compound has not been shown to involve an inventive step.

8.18 As mentioned above; claims 2 to 6 provide further limitations of the substituents as provided in claim 1 and do not add any inventive feature to the said claim. Accordingly Dl or D2 in combination with D3 provides ample motivation to formulate the compound limitations as in claims 2 to 6 and hence claims 2 to 6 are also obvious.

8.19 The specific compounds as claimed in claims 7 and 8 reside within the purview of claim 1 and the specific substituent's as evident from the formula provided in the claims are motivated from the teachings of Dl or D2 in combination with D3. It is stated 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.

8.20 Since the compound is already shown to be obvious and no data is provided in the selection of the salt, claim 8 is also obvious in view of teachings of Dl or D2 in combination with D3.

8.21 Claim 10 only provides for a composition comprising a compound which is already shown to be lacking inventive step. Accordingly no invention can be claimed in the composition and no data has been provided in the specification to show selection of the compound. Thus claim 10 is also obvious in view of teachings of Dl or D2 in combination with D3.

8.22 Therefore in view of the abovementioned discussion I observe that the opponents observations are agreeable and I hold that the invention as claimed in the impugned application is obvious to a person skilled in the art and the documents do not show any technical advancement and unexpected advancement of the properties over the known prior art as discussed above in combination D1, D2 and D3 over the expected properties. Therefore, the invention as claimed in claims 1 to 10 is obvious and does not involve any Inventive step.

9. FINAL CONCLUSION

In view of all the documents submitted by opponent and 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 board, I conclude that in view of documents along with exhibits cited by the opponent, 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 revoke the Patent No. 209251 granted on the Patent Application No. IN/PCT/2002/00785/DEL.

Date – 24/09/2012

Nilanjana

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