INTELLECTUAL PROPERTY APPELLATE BOARD

Guna Complex Annexe-I, 2nd Floor, 443, Anna Salai, Teynampet, Chennai-600 018

ORA/17/2012/PT/KOL
AND
M.P. NOS.4/2013, 9/2013, 10/2013 & 49/2013
IN
ORA/17/2012/PT/KOL

SATURDAY, THIS THE 27TH DAY OF JULY, 2013

Hon'ble Smt. Justice Prabha Sridevan … Chairman
Hon'ble Mr.D.P.S.Parmar …Technical Member(Patents)

Fresenius Kabi Oncology Limited,
An Indian Company of B-310,
Som Datt Chambers-1,
Bhikaji Cama Place,
New Delhi-110066,India …Applicant

(Represented by Shri S.Majumdar, Ms. Sanghita Ganguli and Shri Dominic Alwaris)

Vs.

1. GLAXO GROUP LIMITED,
A Company incorporated in England of Glaxo Welcome House,
Berkeley Avenue, Greenford,
Middlesex, UB6 ONN, England

2. The Controller of Patents,
Patent Office,
Boudhik Sampada Bhawan,
CP-2 Sector V,
Salt Lake City,
Kolkota - 400 037. … Respondents

(Represented by Ms. Archana Shankar, Ms. Vidish Garg and Mr. Devinder Singh Rawat)

ORDER (No.162 of 2013)

Hon'ble Smt. Justice Prabha Sridevan, Chairman

This application is for revocation of Patent No. 221017 titled Bicyclic Heteroaromatic Compounds on the grounds of obviousness, insufficiency of description, non-patentability and non-disclosure under Section 8 of the Patents Act, 1970. Indian Patent No: 221017 was derived from a patent application as a PCT application designating India. It claimed a first priority date from a GB application 9800569.7 dated 12-1-1998. FER was issued on 6-6-2006. Patent was granted on 11-6-2008.

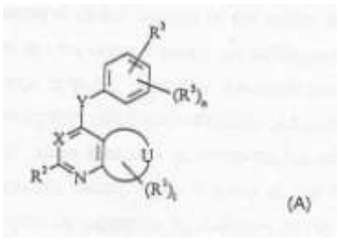
2. But before we begin the discussion relating to the case itself, we would like to comment upon the written submissions that are filed by the counsel. We

usually permit filing of written submissions in addition to oral submissions. The written submissions supplement the notes that we have recorded during the hearing. It would be better if they are brief, and to the point and indicate in a clear and concise manner the points raised and relate it to the relevant pages in the paper book whether they are pleadings or evidences. This will help us when we dictate the order, since it would facilitate easy identification of the relevant particulars and essential materials. Instead, we find that the written submissions contain paragraphs after paragraphs of the extracts from the pleadings or the evidences, and then micro-detailed arguments, which we are expected to read after we have gone through the pleadings, evidence, case laws and our own notes. This cannot be the intention or purpose of filing written submissions. If such detailed submissions are filed then there is no need to hear oral arguments for several days. It may even defeat the object behind the request to file written submissions not to mention the tremendous waste of paper. If parties are insistent on such written submissions, then they may be made ready on the date of hearing, so that counsel can just take us through the pages of the written submissions, thus cutting down the time taken for oral submissions. With this prelude, we begin the order, we might have very well mentioned this at the end but we wanted to drive home the point of the message. We earnestly hope that the message is received well.

APPLICANT'S SUBMISSION:

3. It is stated that Exhibit 1 teaches substituted heteroaromatic compounds, which are protein kinase inhibitors belonging to the same patentee and it therefore relevant prior art vis-à-vis the subject matter of the present impugned patent.

Exhibit 1 teaches a compound of the formula A



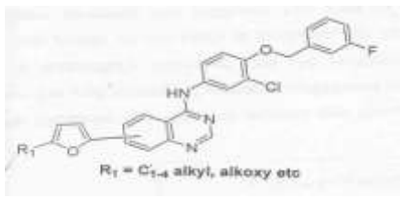
The disclosed compounds of formula A are those wherein

1. X in N OR CH;

2. Wherein  represents a fused 5,6 or 7 membered heterocyclic ring. Exhibit 1 further teaches that:

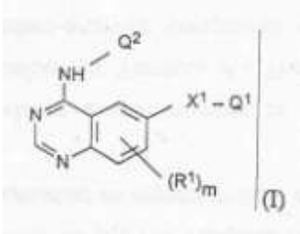
   (i) R_2 group may be hydrogen (page 10);
   (ii) Y is a group NR^a wherein Ra includes hydrogen, therefore Y may be NH (page 8);
   (iii) R5 may be a halogen (page 10); halogen includes chlorine (page 11)
   (iv) "n" may be 1 (Page 10); and
   (v) R_3 may be a group ZR_4, Z may be V(CHs); V may be O; R4 may be an optionally substituted 5,6,7,8,9 or 10-membered carbocyclic or heterocyclic moiety; the carbocyclic groups comprise one or more rings which may be independently saturated, unsaturated or aromatic and contain only carbon and hydrogen(page 10); halo included fluoro (page 11).

4. Regarding the substituent R1, Exhibit 1 teaches on page 12 that "1" may be from) to 3, R1 may preferably be selected as "furan" and may be optionally substituted. Thus, substituting the above groups into the compound of the above paragraph, one arrives at the following structural formula.

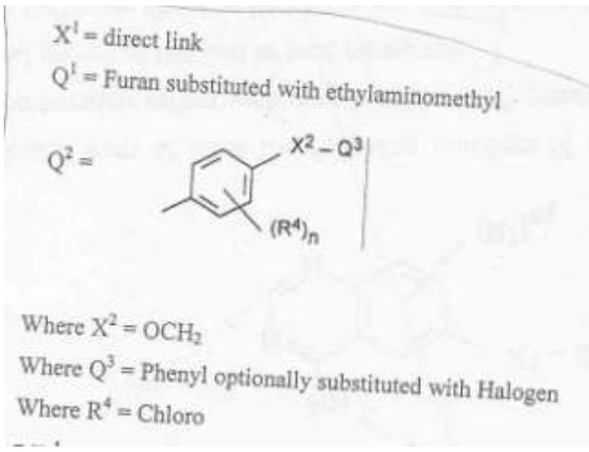


5. It is stated that the only difference between the compounds taught by Exhibit 1 relied upon by the petitioner is that Exhibit 1 does not teach a fused phenyl ring instead of a fused heteroaromatic ring; and does not teach the sulphynyl group on alkyl amine substituent.

6. It is stated that WO 97/30034 (Exhibit 2) relates to quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-proliferative activity such as anti-cancer activity. It discloses Quinazoline derivative of the formula (I).



7. Thus, substituting the following groups into the compound of the above paragraph, one arrives at the following structural formula as shown below, is attained by selecting the following substituents;



8. The petitioner further refers to the Affidavit of the expert Sinha which clearly shows how such choice is obvious to a skilled worker who knows what he is looking for, given the knowledge of documents available. Thus it is stated that choosing the compounds as mentioned above from Exhibit I and 2 and arriving at the impugned patent is wholly obvious and lacks inventive *step* and is nothing more than mere trial and error and experimentation. The petitioner 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.

9. It is amply evident from Sinha Affidavit that quinazoline structure with defined substitutions at defined positions were expected to provide tyrosine kinase inhibition of *EGFR.* From Sinha affidavit the importance of the 4 anilino substitution, the importance of position 6 on the quinazoline ring providing higher potency of tyrosine kinase inhibitor activity, and the furan substituents therein having the amino sulfoxide side chain which is expected to provide higher

bonding effect and better cell permeability is already known. Thus it is expected that quinazoline structure with such substituents would be better suited for tyrosine kinase inhibition of *EGFR* and hence anticancer activity. Thus such substituents are obvious to try as there is a direct motivation of 4 anilino substitutions of quinazolines and also there is motivation of substitutions at 6 position of quinazolines with furan substituted with $CH_2N(H)CH_2CH_2SO_2Me$ for a highly potent tyrosine kinase inhibitor. It is stated that quinazoline ring with 4 anilono substitutions are known. D1 and D2 teach in general compounds which are also substituted quinazolines. The importance of the position 6 and the substitutions therein providing the higher tyrosine kinase inhibitory property is known. Sinha Affidavit clearly shows that from SAR study, a skilled worker looking for further compounds against *EGFR* activity is likely to modify the R group attached to the quinazoline ring at position 6 and it is known that R binds to the protein where ribose and triphosphate rings bind. Hence R must be analogous in character. The R group is located in a pocket corresponding to the ribose-phosphate binding site of ATP and can form electrostatic interactions with the lipophilic amino acids (here Arg 817) located on the catalytic loop. As ribose (sugar) is a 5-membered oxygen containing heterocyclic tetrahydrofuran hence furan is the obvious choice for ribose analogue. D1 teaches the *substituents at position 6 could be many compounds* including furan, pyrrazole, imidazole, piperazine, while ; from D2 teaches 5-membered heteroaryl moiety with upto 3 a heteroatoms is known. Thus a *skilled* worker is motivated to choose the furan at position 6. D2 already provides $CH_2N(H)CH_2Me$. It is further evident from Sinha Affidavit that $CH_2N(Me)CH_2$ COOH which : binds with the Arg 817 is regarded as equivalent to phosphate group is known and that obvious alternative available in the literature is sulfonic acid for carboxylic acid and for similar purpose. It is well known that free acid cannot be used and needs to be derivatized as amide or ester for better cell permeability. Added advantage of amino sulfoxide group is that it enhances the water solubility, an important parameter for cell permeability. Further it is known from Sinha Affidavit that large substituents at C6 of the quinazoline can be tolerated without a major loss

of affinity. Therefore a *skilled* worker would arrive at $CH_2N(H)CH_2CH_2SO_2Me$ with a slight manipulation of chain length and as the target drug is a tyrosine kinase inhibitor some modification in the structure is permissible because of the flexibility available of the catalytic site of the kinases. Hence increase in chain length is unlikely to cause less activity of the target molecule. Thus it is obvious to arrive at the compound of the impugned invention chosen from the compounds of D1 and D2 with amino sulfoxide group on the furan ring at the position 6 of the quinazoline and the 4 amino substituent to achieve protein tyrosine kinase inhibition with reasonable expectation of Success. It stated that the Respondent 1 has failed to demonstrate superior and unexpected activity over the compounds of the prior art. It is stated that the data furnished by the respondent no 1 in the specification of the impugned patent is inconclusive regarding the presence of an inventive step. There is no data to substantiate unexpected result, neither is there any comparative data to show improved effect. Thus the compounds claimed in the impugned patent are nothing but alternate compounds having properties of providing tyrosine kinase inhibition of EGFR as expected from their structures as already pointed out in Sinha Affidavit. Further there is nothing in the process steps which calls for inventive merit as similar components are already shown to be involved leading to formation of the impugned patent by Sinha Affidavit.

The petitioner states that the claimed compounds have been shown above to be obvious and clearly not involving an inventive step. Accordingly, the alleged invention claimed by the patentee fails the definition of an “invention” and “inventive step” provided in Section 2(1)(ja) of the Patents Act, 1970. It is stated that the impugned patent is liable to be revoked on this ground alone.

10. It is stated that the instant claims are drawn to compounds that are useful in treating a disorder in a mammal wherein the disorder is characterized by the aberrant activity of at least one EGF family PTK. The specification of the impugned patent provides a wide list of diverse disorders such as hyperproliferative disorders etc. based on the kinase inhibiting activity. However,

the petitioner states that there is nothing in the disclosure regarding how the provided in vitro data correlates to the treatment of the diverse disorders of the impugned patent.

11. The respondent No.1 has only provided a general method of preparation of an dosage which could be formulated. However there is no mention of actual formulation of dosage and the workability of such dosage in alleviating cancer and treatment of neoplastic growth. There is also no mention of the amount of the drug to excipients to be selected to achieve desired result. Accordingly it is stated that the formulation claims are not clearly defined and based on the results if mentioned in the text.

12. The respondent No.1 has not provided any data as to the comparative effect of the compounds of the impugned patent vis-à-vis the known compounds especially those of Exhibit 1 and 2. It is pertinent to mention that Exhibit 1 is the respondent's own invention. Accordingly respondent No.1 was very much aware of the same and structure of the compound and its activities. However, it failed to show any improvement of efficacy if any over such a compound. In fact, the respondent No.1 has admitted certain prior art in the specification like WO95/19774 and WO98/02434 but even failed to provide any data comparing the impugned patent over the same.

13. The respondent No.1 is required to provide all the information regarding the prosecution of his equivalent applications till the grant of his Indian application to the Controller in writing from time to time and also within the prescribed time, which the patentee has failed to do. Thus the patentee has failed to furnish statement and undertaking under section 8 and has failed to comply with the requirements of the section 8 of the act and the petitioner demands rejection on this ground also.

RESPONDENTS' SUBMISSION:

14. The subject matter of Indian Patent No.221017 is the pharmaceutical compound, Lapatinib. Particularly, Lapatinib is claimed in claim 1 of Indian Patent No. 221017. Lapatinib is a synthetic, orally-active quinazoline compound

having antineoplastic activity. It reversibly blocks phosphorylation of the growth factor receptors EGFR and ErbBs. EGFR and ErbBS have been implicated in the growth of various tumor types. Said compound, as an inhibitor of protein tyrosine kinases(PTKs) of the erbB family, is useful in the treatment of disorders mediated by aberrant activity of such kinases.

15. A pharmaceutical product containing Lapatnib as the active ingredient (the product contains Lapatinib in the form of its ditosylate monohydrate) has been reviewed and found to be safe and effective in the form of its ditosylate monohydrate) has been reviewed and found to be safe and effective in the treatment of such cancer by the Drug Controller General of India(DCGI), the U.S. Food and Drug Administration, and many other corresponding regulatory bodies worldwide. The Patentee/Respondent No.1 markets Lapatinib (in the form of its ditosylate monohydrate) under the proprietary names TYKERB® and TYVERB®. The product is marketed under the trademark TYKERB® in the United States (US) and International markets, including India, and under the trademark TYVERB in the European Union (EU) member states and other countries in Europe.

16. The Petitioner has alleged that the invention as claimed in Indian Patent No.221017 is obvious and lacks inventive step in view of the following documents:

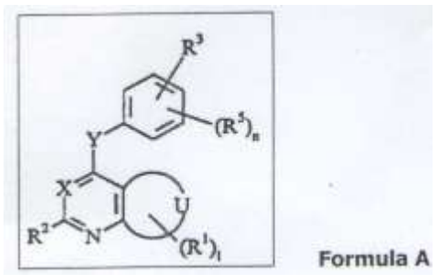
- Exhibit 1: WO97/13771, published on 17th April 1997 from an application filed on 10th October 1996 and claiming priority of 11th October, 1995.
- Exhibit 2: WO97/30034, published on 21st August 1997 from an application filed on 10th February, 1997 and claiming priority of 14th February, 1996.

17. The Sinha Affidavit, submitted by the Petitioner also makes reference to the following documents:

- Rewcastle GW et al., J.Med.Chem. 1995, 38, 3482-3487, referred to as Exhibit A.
- Rewcastle GW et al., J.Med.Chem. 1996, 39, 918-928, referred to as Exhibit B.
- Palmer ED et al., J.Med.Chem.1997, 40, 1519-1529, referred to as Exhibit C.

<u>Exhibit 1</u>: WO 97/13771

i) Exhibit A discloses a vast number of compounds by way of a Markush structure represented below as 'Formula A'. The disclosed Markush structure is directed to substituted hetero-aromatic compounds o Formula A or pharmaceutically acceptable salts thereof:

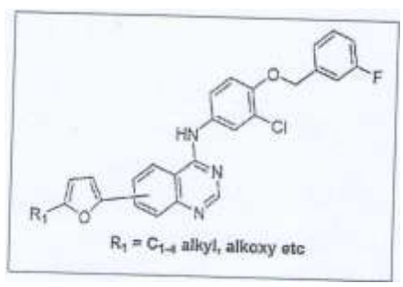


Formula A

Wherein X is N or CH and the ring structure  represented a fused 5-, 6- of 7- membered heterocyclic ring. Further more, a number of possibilities defining each of R^1 R^2 R^3 and R^5 are described.

ii) The definition of the ring illustrated by U in the generic Formula A is in fact broader than that paraphrased by the petitioner in Paragraph 8(q)(ii) since the definition of refers to both the number and nature of the heteroatom(s) and the number and nature of the bonds (double or single). The preferred embodiments at page 12 of Exhibit 1 also reflect a number of alternatives for the ring system U, all of which contain a heteroatom. Of course the correspondent ring system for the compound claimed in the Patent does not contain a heteroatom.

iii) Further, the Petitioner has crafted an imaginary and hypothetical sub-genus of compounds using the Markush structure and choosing a particular substitution pattern:



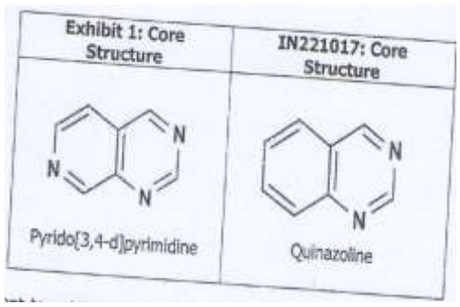
The Petitioner has failed to provide any reason to select particular substituent groups from the vast number of available substituent groups as defined in the Markush structure. It is respectfully submitted that the Petitioner has selected the particular functional groups purely on the

basis of hindsight, i.e. having knowledge of the compound of the present invention the Petitioner has tied to deduce the imaginary and hypothetical compounds illustrated above as well as the compound of the present invention.

18. Therefore, it is clear from the analysis given above that the Petitioner has 'cherry-picked' and selected from the broad definitions in respect of each of the substituents in making the statements in Paragraph 8(a)(ii). The Petitioner has failed to provide any reason for a person of ordinary skill in the art to 'arbitrarily' select such substituents.

19. Without prejudice, the disclosed preferred compounds, especially preferred compounds and Example compounds all have the **pyrido[3,4-d]pyrimidine core structure**. However, the compound claimed in the present invention has a quinazoline core structure.

Exhibit 1 Core Structure



It is pertinent to note that in the pharmaceutical sciences, even a small change in the structure of a molecule may have dramatic and unpredictable effects on the activity of the molecule. More specifically, any change in the structure of a compound can affect the manner in which the compound interacts with the target site of an enzyme and thus alter its biological activity.

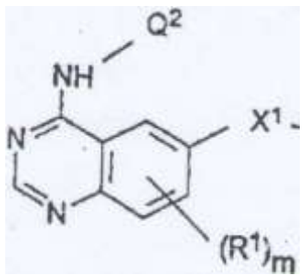
The respondent submitted that:

- U: The Petitioner has not specified which heterocyclic ring would have been chosen from the many possible options. Instead the Petitioner 'jumps' directly to specify a phenyl ring, which of course is not disclosed as an option in Exhibit 1.
- X: The Petitioner has chosen N from the 2 possible options.
- R^2: The Petitioner has chosen hydrogen from 5 classes of disclosed substituents.

- Y: The Petitioner has chosen –NH- from 9 primary classes of disclosed linking groups.
- $R^{5:}$ The Petitioner has chosen halogen from 18 classes of disclosed endgroups, and has chosen chlorine from the multiple halogen options.
- n: The Petitioner has chosen "1" for the n value from the three options, and also chooses the particular position for that single substituent.
- R^3: Where R^3 is defined as ZR^4, the Petitioner has chosen from 3 possible linkers between Z and R^4. Then the Petitioner has chosen to optionally substitute that moiety, and to choose not only one substituent from the myriad of possibilities, but also the precise position of that substituent.
- R^1: The Petitioner has chosen a furan ring from a list of possible R1 substituents that is literally a page long (see page 11), and then chooses to optionally substitute the furan ring. In referring to an alkyl amine substituent on that ring (i.e. such as NHs CHs -) the Petitioner has even gone beyond the disclosed possibilities in terms of the substitution for such a heteroaromatic group for R^1.

<u>Exhibit 2</u>: WO 97/30034

20. According to the respondent the Petitioner has particularly selected some of the possible substituent groups of the Markush structure without any reasoning. The Petitioner has started with the genus of Exhibit 2, as shown in Paragraph 8(a)(vii) as Formula (I)



and has selected from at least the following numbers of substituents (which selected choices in combination reflect well over a billion (109) possibilities) in order to construct the compound.

21. According to the respondent a person of ordinary skill in the art would not combine the teachings of Exhibit 1 and Exhibit 2 in order to arrive at the compound of Formula of the present invention. Ex.2 does not provide any motivation to the person skilled in the art to combine the teachings of Exhibit 1 and Exhibit 2 to reach the compound claimed in the Patent. The compound claimed in the Patent is entirely different from the compounds defined by Formula (I) of Exhibit 2 due to the specific substitution pattern. As such, it is respectfully submitted that, save for the basic 'quinazoline core structure', there is no

structural similarity existing between the compounds of Exhibit 2 and the compound claimed in claim 1 of Indian Patent No.221017. The Petitioner has also completely failed to establish a structural similarity between the compound claimed in claim 1 of Indian Patent No.221017 and the compounds disclosed in Exhibit 1.

22. Without prejudice, even if a person skilled in the art would combine the generic structure or the hypothetical structure deduced by the Petitioner from either of Exhibits 1 and 2, the combination still does not result in the compound of the present invention. The Petitioner has completely failed to provide teaching to link the "**methylsulphonyl-**aminomethyl-amino**"** group with the furan ring.

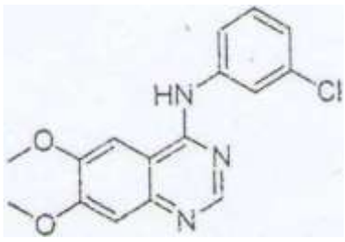
23. According to the respondent that it is not correct to state that there is a close structural similarity between the compound claimed in the Patent and the compounds disclosed in either of Exhibit 1 or Exhibit 2. There was no motivation to choose any such compounds disclosed in either of Exhibit 1 or Exibit 2. There was no motivation to choose any such compounds disclosed in either of Exhibit 1 or Exhibit 2 even as a starting point for finding a dual EGF-R and c-erbB-2 inhibitor. The respondent submitted it is not correct to state that choosing any such compounds disclosed in either of Exhibit 1 or Exhibit 2 and 'arriving at' the compound claimed in the Patent is 'nothing more than mere trial and error and experimentation' given the significant structural differences involved and the specific substitution pattern of the compound claimed in the Patent. Although the Petitioner had indicated that the compound claimed in the Patent and the prior art compounds are all protein tyrosine kinase inhibitors, such a general statement does not show that the compound claimed in the Patent is obvious and lacking in inventive step.

24. According to the respondent the Sinha Affidavit and its analysis of the binding mode for a kinase inhibitor was not correct. The presentation of the binding mode of Lapatinib as suggested by the applicants witness is incorrect based on X-ray crystal structure analysis as discussed in the Heerding Affidavit. In the Heerding Affidavit, it is indicated that Lapatinib (the compound of formula

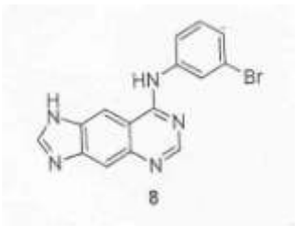
(I) claimed in the Patnet) is shown to bind unexpectedly as a Type II kinase inhibitor as opposed to compounds such as those referenced in Exhibit C which instead bind as a Type I kinase inhibitor. The Heerding Affidavit shows that this binding mode attribute directly contributes to the superior kinase selectivity seen with Lapatinib over other EGFR inhibitors and plays a role in maintaining activity against EGFR with mutations in the kinase domain. According to the respondent this would show that the invention is non obvious.

25. According to the respondent, the invention had clearly established the presence of an inventive step over the identified closest prior arts which disclose compounds which are structurally closer to the compound claimed in the Patent than any disclosure from exhibit 1 and/or Exhibit 2. There is no need to furnish comparative data in respect of a compound which is manifestly remote from the claimed invention.

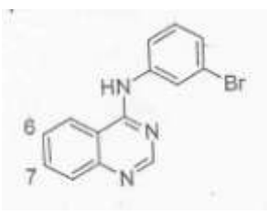
26. According to the respondent, Exhibit A discussed quinazoline analogs as EGFR tyrosine kinase inhibitors. Exhibit A only describes enzyme inhibition of EGF-R and makes no mention of inhibition of c-erbB-2 or of overall kinase selectivity of the compounds discussed therein. The abstract states that their results “show a narrow structure-activity relationship (SAR) for the basis ring system, with quinazoline being the preferred chromophore and benzyl amine and aniline the preferred side chains.” It was therefore submitted the Exhibit A teaches the person skilled in the art nothing about the expected activity of lapatinib, given that the lapatinib compound is clearly outside of the scope of the ‘narrow SAR” represented in this paper. No description of pharmacokinetic data or other drug-like properties are described in Exhibit A. As the person skilled in the art is aware, to achieve potency against an isolated enzyme target is but one aspect to consider within the ambit of small molecule drug discovery. An additional, and often greater, challenge is to balance target potency with all of the other biological and physico-chemical properties required to make a useful medicament. The authors of Exhbit A identify the following compound 3, as the most potent compound in terms of enzyme inhibition of EGF-R:



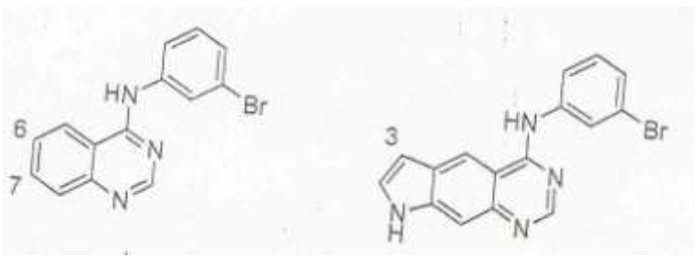
27. According to the respondent Exhibit B evaluates the enzyme inhibition of EGFR by compounds bearing tricyclic heteraromatic cores, including 1H-imidazo[4,5-g] quinazolines. Exhibit B only describes enzyme inhibition of EGF-R and makes no mention of inhibition c-erbB-2 or of overall kinase selectivity of the compounds discussed therein. These compounds were compared to their previously published bicyclic quinazoline EGF-R inhibitors (in Exhibit A). As with Exhibit A, no description of pharmacokinetic data or other drug-like properties are described in Exhibit B. The most potent compound in terms of enzyme inhibition of EGF-R highlighted by the authors is shown below (compound 8).



The salient structure-activity relationship aspects from the previously described bicyclic quinazoline series have been summarized in Exhibit B. In particular, “small electron-donating substituents at the 6- and 7-positions were desirable for high potency.” However, Lapatinib has a substituted furan at the 6-position and a furan group cannot be considered as an electron donating substituent on an aromatic ring and the substituted furan is clearly not small. In fact, the Exhibit B clearly says that increasing the bulk at the 6- and/or-7 position “has been shown to be disadvantageous in the quinazoline series.”

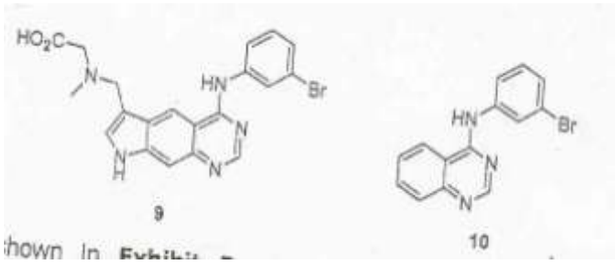


28. According to the respondent the main thrust of Ex. C is the activities of tricyclic heteroaromatic EGF-R tyrosine kinase inhibitors (8h-pyrrolo[3,2-g] quinazolines and 1h-pyrazolo[4,3-g]quinazolines). These compounds are compared to the bicyclic quinazoline series of EGF-R and there is no mention of inhibition of c-erbB-2 or of overall kinase selectivity of the compounds discussed therein. As with Exhibits A and B, no description of pharmacokinetic data or other drug-like properties are described in Exhibit C. It states that the "poor aqueous solubility of these compounds is a major drawback to their further development." According to the respondent the fact that lapatinib has been successfully developed into an effective marketed medicine clearly distinguishes it from the bicyclic quinazolines described in these manuscripts. The importance of small electron-donating substituents at position -6 and position -7 for the potency of the bicyclic quinazoline series is also reiterated in the Introductory paragraph of Exhibit C. The authors then go on to show in the case of the tricyclic 8H-pyrrolo[3,2-g] quinazolines that bulky substituents are in fact tolerated at C-3. This finding sharply contrasts with the previous statement about small electron-donating groups, leading one to believe that the tricyclic 8H-pyrrolo[3,2-g] quinazolines represent a separate chemical series from the bicyclic quinazoline analogs with distinct structure activity relationship requirements.



29. According to the respondent Exhibit C describes a binding mode for two of the analogs. The description fits what is known as a Type I kinase inhibitor (*as discussed in Bikker et al., J.Med.Chem., 2009,52, 1493* enclosed herewith as **Exhibit D**). These inhibitors are only capable of binding to the active for of the

kinase and prefer a specific conformation of a characteristic Asp-Phe-Gly motif such that the Asp and Phe are both oriented towards the ATP binding site (so-called DFG-In).

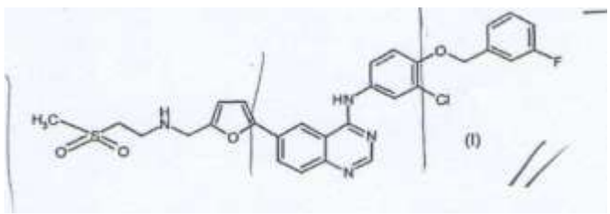


However, as shown in Exhibit D, the substitution pattern around the bicyclic quinazoline core of lapatinib unexpectedly results in a binding mode in EGF-R that is described as a Type II kinase inhibitor. This class of kinase inhibitors is characterized by their ability to bind to the inactive form of the kinase. They are also generally more kinase selective and believed to be less susceptible to drug resistance due to kinase domain mutations. In the case of lapatinib, the binding to EGF-R is described as a DFG-in, alpha C-helix out conformation. This unexpected binding mode contributes to the extremely high kinase selectivity observed for lapatinb when profiled against 287 distinct human protein kinases or approximately 55% of the human protein kinome (as discussed in Karaman et al., *Nature* Biotechnology, 2008, 26, 127, enclosed herewith as **Exhibit E**). Once again, this is an unexpected difference distinguishing lapatinib from the bicyclic and tricyclic EGF-R kinase inhibitors described in Exhibits A,B and C. For all these reasons the respondent defended the patent

30. The Application was filed along with two prior arts Exs 1 and 2 and the affidavit of Dr. Surajit Sinha. The Counter statement was filed along with Exhibit- D Bikker at al J.Med.Chem 2009 52,1493; EX E Karaman et.al Nature Biotechnology 2008 ,26, 127 and Ex F; Yun et. Al Cancer Cell 2007 11(3) 217. and the affidavit of Dr. Heerding. To this a reply statement was filed along with a second affidavit of Dr. Sinha and the Exhibits A to I.

31. The learned Counsel Mr. S. Majumdar for the appellant and Mr. Praveen Anand for the respondent made elaborate submissions and also filed written arguments.

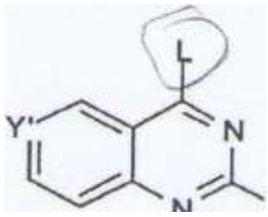
32. We extract some parts of the complete specifications. This was the version that was shown to us. *Later we were informed by the applicant that the PCT application was much longer and the specifications mentioned that"this invention relates to quinoline, quinazoline, pyridopyridine and pyridopyrimidine derivatives which exhibit protein kinase inhibitors". We will deal with this issue later.*

> "The present invention envisages, in particular, the treatment of human malignancies, for example breast, non-small cell lung, ovary, stomach, and pancreatic tumours, especially those driven by EGF-R or erbB,-2 using the compounds of the present invention. For example, compounds which are highly active against the c-erbB-2 protein tyrosine kinase often in preference to the EGF receptor kinase allow treatment of c-erbB-2 driven tumours. However, compounds which are highly active against both c-erbB-2 and EGF-R receptor kinases allow treatment of a broader range of tumour."
>
> "More particularly, the present invention envisages that disorders mediated by protein tyrosine kinase activity may be treated effectively by inhibition of the appropriate protein tyrosine kinase activity in a relatively selective manner, thereby minimising potential side effects.
>
> "Accordingly, the present invention provides the compound N-{3-ChIoro-4-[(3-fluorobenzyl) oxy]phenyl} -6- [5- ({ [2-(methanesulphonyl) ethyl]amino}methyl) -2-furyl]-4-quinazolinamine (hereinafter the compound of formula (I)); or a salt or solvate thereof, particularly pharmaceutically acceptable salts or solvates thereof.
>
> 
>
>
> Solvates of the compound of formula (I) are also included within the scope of the present invention."
>
> "WO 95/19774 discloses heterocyclic tyrosine kinase inhibitors which lack the present ({[2-(methanesulphonyl) ethyl] amino}methyl) -2- furyl substituent. Intermediate document WO 98/02434 discloses compounds of a general formula encompassing the compound of formula (I), but it does not teach the present combination of substituents."
>
> "The compound of formula (I) is of particular interest in the context of c-erbB-2 activity."
>
> "The compound of formula (1) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention."

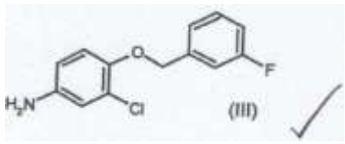
“Salts of the compound of formula (1) may comprise acid addition salts derived from a nitrogen in the compound. The therapeutic activity resides in the moiety derived from the compound of the invention as defined herein and the identity of the other component is of less importance, although for therapeutic and prophylactic purposes It is, preferably, pharmaceutically acceptable to the patient. Examples of pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acid and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and methanesulphonic and arylsulphonic, for example p-toluenesulphonic, acids.”

“According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as defined above which comprises the steps:

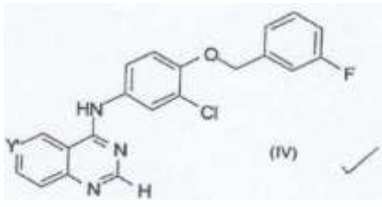
(a) the reaction of a compound of formula (11)



wherein Y' is CL'; and L and L’ are suitable leaving groups, with a compound of formula (III)



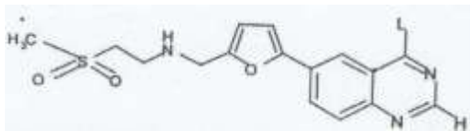
to prepare a compound of formula (IV)



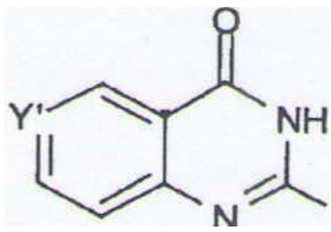
and subsequently (b) reaction with appropriate reagent(s) to substitute the ({[2-(methanesulphonyl)ethyl]amino}methy)-2-furyl group by replacement of the leaving group L’.”

“Alternatively, the Compound of formula (11) as defined above is reacted with the appropriate reagents to substitute the ({[2-methanesulphonyl) ethyl]amino}methyl) -2-furyl group by replacement of the leaving group L’ and then the product thereby obtained (of formula (V) below) is reacted with the compound of formula (III) as defined above.

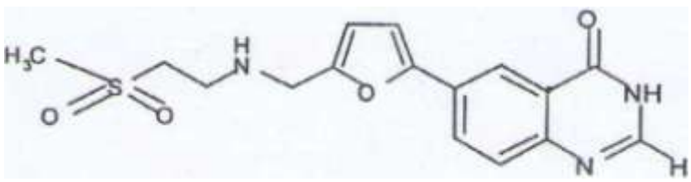
In a variant of this alternative the compound of formula (V)



Wherein L is as defined above, may be prepared by the reaction of a compound of formula (VI).



wherein Y' is as defined above, with appropriate reagents to substitute the ({[2-(methanesulphonyl) ethyl] amino} methyl)-2-furyl group for the leaving group L' to prepare a compound of formula (VII)



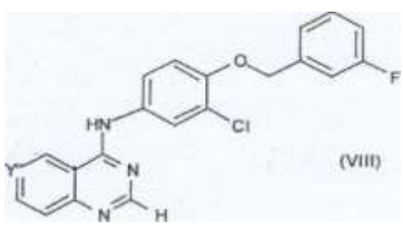
and subsequent reaction to incorporate the leaving group, L. For example, a chloro leaving group can be incorporated by reaction of a corresponding 3, 4- dihydropyrimidone with carbon tetrachloride/triphenylphosphine in an appropriate solvent."

"The ({[2-(methanesulphonyl) ethyl] amino} methyl)-2-furyl group may, therefore, be substituted onto the basic ring system by replacement of a suitable leaving group. This may, for example, be carried out by reaction of the corresponding heteroaryl stannane derivative with the corresponding compound of formula (IV) carrying the leaving group L' in the appropriate position on the ring."

"According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as defined above which comprises the steps:

(a) reacting a compound of formula (IV) as defined above with appropriate reagent

(s) to prepare a compound of formula (Vlll)



wherein Y'' is CT, and T is an appropriately functionalised group; and (b) subsequently converting the group T into the ({[2-(methanesulphonyl)ethyl] amino}methyl)-2-furyl group by means of appropriate reagent(s)."

"In one alternative, the group T would represent a furyl group carrying a formyl group (CHO)."

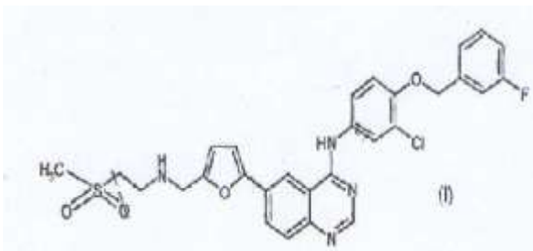
"Where T represents a furyl group carrying a formyl group the compound (of formula (Vlll a)) may be suitably prepared from the corresponding dioxolanyl substituted compound (of formula (Vlll b)), for example by acid hydrolysis. The dioxolanyl substituted compound may be prepared by reaction of a compound of formula (IV) with an appropriate reagent to substitute the relevant leaving group with the substituent carrying the dioxolanyl ring. This reagent could, for example, be an appropriate heteroaryl stannane derivative."

"Therefore a suitable process may comprise reaction of a compound of formula (Vlll a) in which T is a furyl group carrying a formyl substituent (i.e. a -CHO group) with a compound of formula $CH_3SO_2CH_2CH_2NH_2$. The reaction preferably involves a reductive amination by means of an appropriate reducing agent, for example sodium triacetoxyborohydride."

"Alternatively, another suitable process may comprise oxidation of a compound of formula (Vlllc) in which T is a furyl group carrying a substituent of formula $CH_3,SCH_2CH_2NHCH_2$ or $CH_3SOCH_2CH_2NHCH_2$. Suitable methods for the oxidation to the desired compound of formula (I) will be well known to the person skilled in the art but include, for example, reaction with an organic peroxide, such as peracetic acid or metachlorobenzoic acid, or reaction with an inorganic oxidising agent, such as OXONE. The compound of formula (Vlllc) in which T is a furyl group carrying a substituent of formula $CH_3SOCH_2CH_2NHCH_2$ or $CH_3SOCH_2CH_2NHCH_2$. may be prepared by an analogous reaction to that described above, namely reaction of a compound of formula (Vllla) in which T is a furyl group carrying a formy! Substituent (i.e. a -CHO group) with a compound of formula $CH_3SCH_2CH_2NH_2$ or $CH_3SOCH_2CH_2NH_2$ respectively. "

We Claim:

"1. Bicyclic heteroaromatic compounds of formula (I)

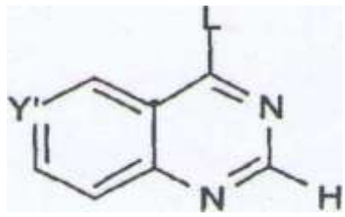


or a salt or solvate thereof.

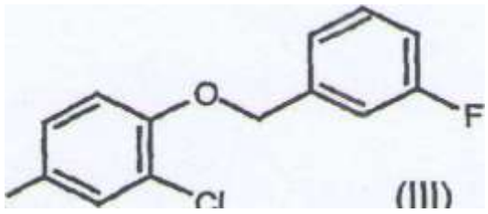
2. A compound as claimed in claim 1 wherein the salt or solvate is pharmaceutically acceptable.

3. A process for the preparation of a compound of formula (I) as claimed in claim 1 which comprises the steps:

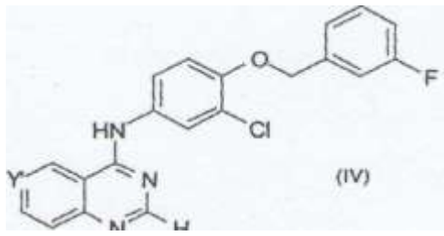
(a) the reaction of a compound of formula (II)



wherein V is CL'; and L and L' are suitable leaving groups, with a compound of formula (III)



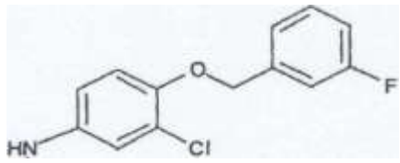
to prepare a compound of formula (IV)

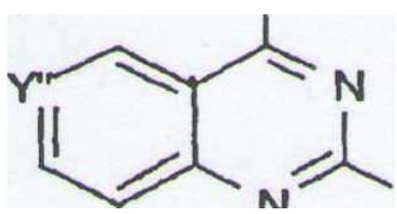


and subsequently (b) reaction with appropriate reagent(s) to substitute the ({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl group by replacement of the leaving group L'.

4. A process for the preparation of a compound of formula (I) as claimed in aim 1 which comprises the steps:

a) reacting a compound of formula (IV) as claimed in claim 3 with appropriate reagent(s) to prepare a compound of formula (VIII)





wherein Y'' is CT; and T is an appropriately functionalised group; and

(b) subsequently converting the group T into the ({[2-(methanesulphonyl) ethyl]amino}methyl)-2-furyl group by means of appropriate reagent(s).

5. A. pharmaceutical formulation comprising a compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

6. A pharmaceutical formulation as claimed in claim 5 in unit dosage form and containing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in an amount of from 70 to 700mg.

7. A pharmaceutical formulation as claimed in claim 5 or claim 6 for the preparation of a medicament for the treatment of a disorder mediated by c-erbB-2 and/or EGF-R protein tyrosine kinase activity.

8. A pharmaceutical formulation as claimed in claim 7 wherein the treatment is of cancer and malignant tumours.

9. A pharmaceutical formulation as claimed in claim 8 wherein the cancer is breast cancer.

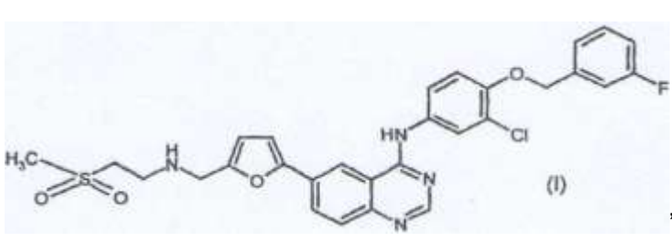
10. A pharmaceutical formulation as claimed in claim 8 wherein the cancer is non-small cell lung cancer.

11. A pharmaceutical formulation as claimed in claim 8 wherein the cancer is bladder cancer or gastric cancer."

BICYCLIC HETEROAROMATIC COMPOUNDS

ABSTRACT

"The present invention relates to a substituted quinazoline compound of formula (I), and salts and solvates thereof which exhibit protein tyrosine kinase inhibition, in particular c-erbB-2 and EGF-R inhibition. Also disclosed are methods for their preparation, pharmaceutical formulations containing them, and their use in medicine, in particular in 'the treatment of cancer and malignant tumours, including breast cancer, non-small cell lung cancer, bladder cancer and gastric cancer."



"

The documents relied on by the Petitioner are

Ex1 WO97/13771 published on 17th April 1997 claiming priority from 11th Oct 1995.

Ex2 WO97/30034 published on 21st Aug 1997 claiming priority from 14th Feb 1996.

Ex A Rewcastle et al; J. Med.Chem 1995 38 3482-3487

Ex B Rewcastle et al ; J.Med.Chem 1996. 39, 918-928

Ex C Palmer et al: J.Med.Chem 1997 40 1519-1529.

Ex D Ward et al; 1994 48 659-666

Ex E WO 1996/15118 23rd May 1996

Ex F WO 1996/09294 28th Mar 1996

EX G Copy of publication PNAS Vol 95 12022-12027 Sept 1998

Ex H Fry D .W. Experimental cell research 284(2003)131-139

Ex I Journal Medical Chemistry Toxicology 1992. 5,211-219.

Ex J Journal Cancer Research 52 4379-4384 15th Aug 1992

33. Miscellaneous Petition No.49/2013 is for amending the address of the respondent. It is allowed. Miscellaneous Petition Nos.4, 9 & 10/2013 relate to reception of additional evidence and the rebuttal evidence. We have allowed the miscellaneous petitions and received the evidence subject to relevances. The evidentiary value of the documents will be dealt with herein below.

S.8 Objection :

34. We will deal at some length how Section 8 should be pleaded and proved, both in this application and in the ORA/22/2012/PT/KOL to revoke the patent granted for Lapatinib ditosylate. The applicant had merely stated that Section 8 requirements were not complied with. The language of the Section was alone reproduced without giving details.

35. In the counter statement at paragraphs 106 to 110 the respondent had pleaded that they had furnished all the documents that were to be filed, according to Section 8 (a) & (b) of the Patents Act, 1970 and in the Annexure to the counter statement they had also given a Tabular Column of the details so furnished in Form 3 of the Patents Rules, 2003.

36. In reply to the counter statement at paragraph 37, the applicant had stated as follows:

> "With reference to paragraphs 106 to 110 of the counter statement it is stated that the contents therein are incorrect and wholly denied."

Nothing more had been stated in the reply to the counter statement. There are no pleadings to show why and how the averments made in the counter statement regarding compliance with Section 8 are incorrect. Therefore it is on the basis of these pleadings that the matter came up for hearing.

37. In M.P.4 of 2013, the applicant filed additional documents as Exhibits EA1 to EA13. The affidavit sworn by one Ramanathan Sankaran does not say how

and why these 13 documents are relevant. Exhibit-EA1 is the copy of the statement and undertaking under Section 8 of the Act dated 12.7.2000. This is followed by the letter dated 9.4.2001 including the Annexure to Form 3. The first examination report dated 6.6.2006 called for details of foreign filing particulars to be furnished with necessary petition, if any, and details regarding search and examination report in respect of some invention filed in any one of the major Patent Offices such as, USPTO, EPO and JPO. In response to this on 17.2.2006 the Patentee's counsel had enclosed the corresponding EP. Patent Nos.1047694 and 1460072 in compliance with Section 8 (2) of the Act and the updated Annexure to Form 3 was also filed. Exhibit EA-3, is the WO1999035146. The various documents relate to the counterparts of the impugned patent granted by the EPO and Exhibit EA5, EA6, EA7, EA8 and Exhibit EA.9 relate to Patents granted by the US-PTO. Exhibit EA13 relates to priority documents of the UK Patent Office and Exhibits EA10, EA11 and Exhibit EA12 are patents granted by E.P.O., in E.P.No.1454907, E.P.No.1047694 and E.P.No.1460072. The respondent had given the latter two documents.

38. S.8 of the Act is not intended to be a bonanza for all those who want an inconvenient patent removed. In The Ayyangar Committee Report it was said, "*It would be of advantage therefore if the applicant is required to state whether he has made any application for a patent for the same or substantially the same invention as in India in any foreign country or countries, the objections, if any, raised by the Patent offices of such countries on the ground of novelty or unpatentability or otherwise and the amendments directed to be made or actually made to the specification or claims in the foreign country or countries.*"

39. In the Hindustan Lever case the FER required the "Foreign filing particulars". The respondent gave wrong particulars about the GB application, and suppressed the IPER relating to EP 1106578 which was not pursued and the IPER had rejected the claims 1 to 3 on the grounds of both novelty and inventive step. We held that the ground under S.64 (1) (m) was made out.

40. In Therasense the disclosure obligations were discussed, and the majority ruled that the materiality required to establish inequitable conduct is a but-for materiality. That is. in assessing the materiality of a withheld reference, the Court must determine whether the PTO would have allowed the claim if it had been aware of the undisclosed reference. In making the patentability determination, the Court should apply the preponderance of the evidence standard and give claims their broadest reasonable construction.

41. In India TV Independent News Service Pvt Ltd. vs Yashraj Films Pvt Ltd, the Delhi High Court considered the de minimis doctrine and the factors to be considered in applying them namely size and type of harm, cost of adjudication, purpose of violated legal obligation, effect on legal rights of third parties and intent of wrong doer. In that case the use of the song was held not to cause any harm to the copyright owner. Here the de minimis doctrine is invoked by the patent owner.

> *If the obligation under S.8 has been violated then the harm caused is the continuance of a patent which deserves to be removed. It appears to us then that the harm is not of a minimal nature. The public is affected by the exclusive monopoly to a patent that law makes revocable.*

42. The law relating to Interpretation of Statutes was referred to and it was submitted that while construing penal sections and two constructions are possible then the lenient one should be adopted. This provision is not a penal provision. A penal provision is one which enacts an offence or imposes a penalty. This is not a penal provision. Failure to comply with S.8 is not an offence. It is a duty cast on the patentee which results in adverse consequences if flouted. Dishonour of cheque (AIR 2012 SC 2795 Aneeta Hada vs Godfather travels and Tours was cited) fastens a criminal liability. S.8 does not. So the cases arising out of the former will not apply. The State of Tamilnadu vs M.K. Kandaswami (AIR 1975 SC1871) related to a tax statute. Evasion of tax has its penal consequences. But in this judgment there is a paragraph which is worth extracting. "*It may be remembered that Section 7A is at once a charging as well as a remedial provision. Its main object is to plug leakage and prevent evasion of tax. In interpreting such a provision, a construction which would defeat its*

purpose and in effect, obliterate it from the statute book, should be eschewed. If more than one construction is possible, that which preserves its workability and efficacy is to be preferred to the one which render it otiose or sterile"

43. The Ayyangar Report makes it clear that the purpose for introducing this provision was to ensure that it would be an advantage for our Patent Office to know the objections raised by the patent offices outside India regarding the patentablity of the invention and the amendment if any made or to be made. It also says that it would be of great use for the proper examination to know if the invention was anticipated. In the Hindustan Lever case we had held that it was in order to secure disclosure of the relevant information regarding the foreign applications that the Ayyangar Report recommended that failure to disclose would be a ground for challenge.

44. In Chemtura Corporation vs Union of India the Delhi High Court said, "*It is not possible to accept the submission, made by referring to the Halsbury's Laws of England that since the omission to furnish particulars is not serious enough to affect the grant of the patent; it did not impinge on its validity. Section 64 (1) (j) and (m) indicate to the contrary. Further under Section 43 (1) (b) a patent can be granted only when the application has been found not to be contrary to any provision of the Act. It cannot be said that the omission to comply with the requirement of Section 8 (2) was not serious enough to affect the decision of the Controller to grant the patent to the Plaintiff. The information, if provided, would have enlightened the Controller of the objections raised by the US patent office and the extent to which the Plaintiff had to limit its claims to the torus shape of the compression spring, which was a key feature of the subject device.*"

45. The object of this provision is to ensure disclosure. We will adopt that construction which is to advance the object. This section has been introduced to make sure that the person who is given an exclusive monopoly is candid and fair in his conduct and discloses all the official actions regarding patent filing outside India in respect of the same or substantially the same inventions. So we cannot adopt a construction which relieves the patentee of this duty.

46. In the Sugen vs Cipla case we said, "*The respondent had also filed OA 6/2013 against the finding on S.8 violation. Now that the matter is to be heard de novo right from the stage of the Constitution of the Opposition Board, this issue will also be decided by the Controller. The IPAB has in its decisions clearly held that it is the duty of the Patentee to furnish the particulars under S.8. We are surprised that the Controller should have held to the contrary and observed that such information is available on the internet. This is not the law. This duty under Sect 8 cannot be breached and if violated results in revocation. It deserves to be accorded due respect. What should be furnished by the Patentee shall be furnished by the Patentee. So the Controller shall bear this in mind while considering the ground under S.8 and examine whether the Appellant has fully complied with the S.8 Requirements.*"

47. We must remember that we are not the law makers. For good reasons S.8 is there in the Act. The Controllers cannot ignore it and condone the breach. The patentee cannot tell the Examiners, "*We are filing applications nineteen to the dozen, compliance is very difficult, and in any case there is the Super Kamadhenu the Internet which will give you what you want."* We cannot wish S.8 a relieved farewell. Tough for Inventors, but they must comply with the requirements of S.8. When George Mallory was asked "Why do you want to climb Mount Everest?" he is supposed to have replied, "Because it is there*."* **To the question "*Why should we comply with S.8?*" The Answer is "*Because it is there*."**

48. Having said that, we must also insist that the IPO shall have a consistent stand with regard to S.8. It cannot be East West Who is best. We request the Controller General to educate and instruct the officers regarding the requirements of law. We must remember what the Supreme Court said in the Novartis case, **"29. In order to understand what the law really is, it is essential to know the "*why*" and "*how*" of the law. Why the law is what it is and how it came to its present form? The adage is more true in case of the law of patents in India than perhaps any other law."** The "why' of S.8 is clear from the Ayyangar report. The office must remember it. **The FER requires the**

patentee to give the details mentioned therein in any one of the major Patent offices such as USPTO, EPO or JPO as per S.8 (2) of the Patents Act. What is meant by "such as"? This request is vague and gives room for manipulation. If out of the three offices mentioned in this request, the details relating to the application in one office is adverse to the Patentee and as regards the proceedings in another it is in favour, the patentee would be justified in giving only the favourable and not the adverse report. But that would defeat the object of the provisions. The intent of the provision is to make known to the officer in India the objections raised to the same/substantially the same application outside India.

49. **Now that S.8 compliance is insisted upon, the applicant seeking revocation may think that it is enough if he just types the password "*S.8 not complied with*" and the IPAB will do the rest. The IPAB will do no such thing**. He will have to say that these are the foreign office actions that were not filed with the office. The applicant cannot plead that he is not privy to those applications. These documents are now being downloaded by the reams and placed before us at the time of the hearing, and the affidavit says it is available to all and sundry. So the applicant must embark on this exercise at the time of filing of the application and plead how S.8 was violated and why that particular foreign filing ought to have been filed. He must plead how it is the "*same or substantially the same invention.*" That will be fair to the defender who will know what he has to traverse in his counter statement. Producing a list of foreign applications allegedly covered by S.8. (1) on the eve of the hearing is not fair. At the same time if a document is filed belatedly we will not shut it out on that ground alone, if it shows a S.8 violation. For after all the IPAB is a guardian of Public Interest. We will however have to think of imposing some costs for filing evidence with delay. **This litigation is adversarial in nature with an unmistakeable public interest component, and hence unique. The adversary cannot take advantage of the public interest component and abandon his duty as a litigant to plead and prove his case.** We would also urge the counsel to examine each document and

consider if it is necessary to be filed. Not every document which is downloaded is worthy of being “uploaded” in to the litigation.

50. When we look at the Ayyangar Committee Report it indicates that the object behind introducing S.8 is that the applicant should disclose all foreign applications so that the examiner here may know if it contains obviousness objections or any amendments and so on. The application outside India must be for the same invention or for substantially the same invention. The Ayyangar Committee Report also speaks of anticipation coming to light if the disclosure is made. So the Ayyangar Committee Report is clearly talking of the same invention or almost the same invention. The subject matter of the invention must be the same or almost the same. If there is a divisional, then according to the Indian law there is a plurality of inventions, which means there are more than one invention. The applicant may argue that the divisional application is not”the same or substantially the same invention”. There are no guidelines for the office to construe these words. In view of what is stated in the Ayyangar Committee Report, we are of the opinion if in any of the foreign offices the patentee had made a division or was required to make a division, in respect of the same or substantially the same invention or had amended or was required to amend in respect of the same invention or substantially the same invention, such information regarding division or amendment would also be information required to be furnished under Section 8. It is therefore necessary that the person seeking revocation demonstrates that the foreign application the details of which were not furnished, was for the same or the substantially the same application. It is true that the IPAB is not bound by the rules of the CPC, and it is enough if the procedure is guided by the principles of natural justice. If the opponent does not know what the case against him is, then there is a clear violation of natural justice which implies procedural fairness. The strict technical requirements may not be insisted upon e.g. witnesses do not appear before us. But an issue will still have to be pleaded and proved.

51. In this case in the Revocation application, the applicant has merely stated that S.8 has not been complied with and foreign filing particulars have not been

given. Nothing more is stated. In the petition filed for receiving additional documents, the affidavit filed by the applicant merely lists the documents were downloaded. We do not think that is sufficient. We understand that the S.8 ground is being raised regularly only after the Delhi High Court's Chemtura judgment and the IPAB orders mentioned above. The Examiners have not given this provision the attention that it deserves. But these proceedings have to be conducted correctly, consistently and fairly. Patentees must comply with S.8 (1) provision however inconvenient it is.

52. In the present case we are rejecting the S.8 objection only because the applicant has not made out the grounds of attack by stating the facts. A bald statement will not suffice by merely reproducing the language of the section. The facts have to be pleaded and the applicant must state how the particular undisclosed application was for the same or substantially the same invention. It is also not enough to just file the documents along with an affidavit. The least that the deponent shall state is how it is the same or substantially the same. In this case the respondent had stated in the counter statement that the two documents filed were in compliance of the provision. In the reply the applicant had merely denied it, without saying why it was not in full compliance. That is not enough. We have indicated the principles behind a S.8 objection, how it should be raised, defended and decided. For the above reasons, we hold that violation of Section 8 has not been proved by the applicant and this ground is rejected.

Section 3(d) :

53. As regards Section 3 (d) objection, the case of the applicant is that the Claimed compound is a derivative of prior art compounds, and that there is no data in the alleged specification to show that the claimed compound differs significantly having regard to the efficacy of the known compound of prior art especially those Exhibit-1 and Exhibit-2. It was submitted that the respondent had admitted the prior arts in Exhibit 1 and Exhibit 2, but has failed to provide comparative data nor had they shown any enhancement in efficacy and the therapeutic effect. The respondent submitted that this is a new chemical entity

and the applicant will have to show and prove that Section 3 (d) bars the grant and that it is the mere discovery of a new form of a known substance. The applicant has contented himself with saying that the prior arts in Exhibit-1 and Exhibit-2 is known compound and the invention is a mere discovery of a known form.

54. The respondent submitted that there are no pleadings in this regard and that the claimed compound is a New Chemical Entity. According to the respondent the Annexure –A to the FER comparative data on selectivity and kinase inhibitory values during the patent prosecution was provided, and the patent specification provides a long range of values in Table 1&2 in relation to the kinase inhibitory values of Lapatinib. .According to the respondent the claimed compound is not a derivative of a known substance,

55. In the Novartis case decided by the Supreme Court, it was held that the Section 3 (d) sets up a secondary tier of qualifying standards for chemical substance/Pharmaceutical in order to leave the door open for true and genuine invention. The Supreme Court held that Section 3 (d) places the invention threshold further higher. The Explanation to Section 3 (d) says that for the purpose of this clause “salts esters, ethers…….. And other derivatives of known substance shall be considered to be the same substance.” In the earlier Novartis case decided by the Madras High Court, it was held “ Therefore when the Explanation to the amended section says that any derivatives must differ significantly in properties with regard to efficacy, it only means that the derivatives should contain such properties which are significantly different with regard to efficacy to the substance from which the derivative is made. Therefore in sum and substance what the amended section with the Explanation prescribes is the test to decide whether the discovery is an invention or not is that the Patent applicant should show the discovery has resulted in the enhancement of the known efficacy of that substance and if the discovery is nothing other than the derivative of a known substance, then, it must be shown that the properties in the derivatives differ significantly with regard to efficacy”

56. It is true that it is the patentee who must prove the enhanced therapeutic efficacy of his invention. But in a revocation the applicant must plead and prove that it is hit by S.3(d) and that it has the same therapeutic efficacy as the known substance. Then the respondent will counter it either by proving that it is not a derivative of a known substance or by proving that though it is only a new form of a known substance he has shown that it has enhanced therapeutic efficacy. In the present case, there are no such pleadings. It is not enough to plead that because Ex1 and 2 are admitted prior arts, this is only a new form of those compounds. That is vague. It is only when the pleadings show how the invention is one kind of a derivative of known substance the patentee will have to explain how the grant of patent is justified because of the enhancement of therapeutic efficacy. In this case the pleadings are not adequate. We hold that the S.3(d) ground has not been proved.

Obviousness

57. The Applicant has produced two affidavits by Dr. Sinha, hereafter referred as Sinha 1 and Sinha 2. The respondent has produced two affidavits byt Dr. Heerding

58. According to the applicant, the process of all preparations of the invention shows that it is built upon the compounds known in the prior art by substitution from various options. This process of substitution involves standard methodology known to the person skilled in the art and it does not involve any inventive faculty. Only one Example has been shown in the complete specification of Lapatinib and its use. The petitioner relied upon the prior arts, Exhibits A to F and Exhibits 1 and 2 to make out the case of the obviousness.

59. According to the applicant Exhibit-A clearly shows that the Primary Pharmocophore is the Quinazoline Pharmocophore and that -3 position on an Aniline 6 and 7 position on the Quinazoline is important. Then referring to Exhibit B, it was submitted that Exhibit- B teaches a fused tricyclic analogue as EGFR inhibitors. According to the applicant from this Exhibit-B, it would be seen that the -6 and -7 positions can accommodate some change without affecting the

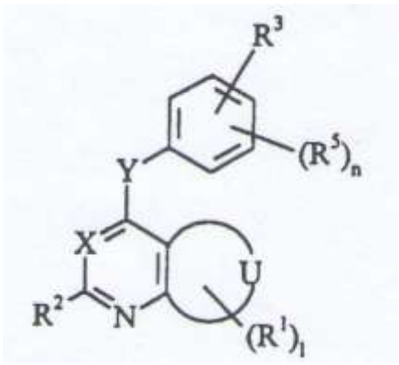
inhibitory activities much. It was submitted that out of 6 anti-cancer drugs Erlotinib, Varlitnib Gefitinib, Dasatinib have the same primary pharmacophore as Lapatinib. It was further submitted that out of these ERlotinib and Gefitinib are prior art and both these have polar bulky groups at 6 and 7 positions which enables solubility and other druggable properties. For the alteration of said structure, bulky groups could be used in positions 6 and 7 but not in position 3'. Then Ex C clearly shows that position -6 and -7 have a role in solubility. The third ring can be fused with bicyclic quinazoline system without loss of binding affinity. According to the applicant, Ex. C shows that pyridopyrimidine show similar Structure Activity Relationship to quinazoline, so those teachings may be extrapolated to Quinazoline, since both quinazoline and pyridopyrimidine have similar activities. The applicant relied upon the expert affidavits of Dr. Surjith Sinha. The most effective substitution of the 3- substituted Pyroloquinazoline ring series included Alkylamino quinazoline series of compounds of 4 to 9 of the said documents. Therefore according to the expert, based on the Structure Activity Relationship (SAR) study, the skilled worker looking for further compounds against EGFR activity is likely to modify R-Group attached to the Quinazoline ring at position 6. From the SAR study, it will be known that this must be analogous in character. It was submitted that the primary Pharmocophore was known from Exhibit-A and Exhibit-C. EXs A, B, & C teach the importance of 4- Anilinoquinazoline. The applicant also referred to the slides shown by the respondents in connection with ORA/22/2011/PT/KOL relating this Anti Cancer molecular structures of which the five have the same primary Pharmocophore as that of Lapatinib and all have activities against EGFR out of which Erlotinib and Gefitinib are prior art. But they have polar drug group and for alteration of the said structure, the bulk groups would be used in position 6- and 7- as cited in Exhibit-E. The skilled worker would look for Compounds with substitution in these positions keeping in mind the importance of Furan**.**

60. Mr. Sinha's affidavit shows that the most effective substitution of the 3-substituted Pyrolominoline Ring series included Alkylamine series of compounds 4 to 9 of Exhibit-C. The extract in Exhibit-C also teaches the structure activity

relationship. The applicant also referred to WO.99/35146 which discloses various compounds, which may cover the Markush structure of Formula-I. According to the applicant, compound-2 is Quinazoline, and the specification mentions 2 to 6 are more preferred. Therefore the skilled person will be motivated by the teachings of Exhibit-1 read with other Exhibits. Exhibit-D teaches mechanism of inhibition of CAQ to arrive at the invention structure and it teaches that CAQ is a lead in the search for Cancer therapy and therefore it was clear CAQ is exploited as a lead compound from which further search for agents to treat Cancer would be definitely encouraged. The person skilled in the art, who is looking for another Tyrosine kinase inhibitor in the process, would look into Exhibit-A which teaches the Primary Pharmocophore. Then he would move on to Exhibit-C which provides the binding to occur with the main scaffold and that bulky substituents allowable at 6^{th} or 7^{th} position. And if one added the teaching of Exhibit-D showing CAQ as a lead compound , and one took the teaching of the prior arts in combination it would disclose the Quinazoline ring with 4-Aniline substitutions and further substitutions of 6^{th} position with 5-membered Heteroatom. He submitted that if all the documents are taken together, it is clear that the invention is obvious. It was also pointed out that in Exhibit-F Table-I example 120 shows the same scaffold and this disclosure is sufficient to reach the structure of Lapatinib. There is only one example in the specifications and there is no whisper of binding pattern and Type-I and Type-II Kinase activity in the specification or the crystal structure of Lapatinib. Without any support in the specifications, the respondents have attempted to establish the Patentability of the invention on the basis of latter date documents. The learned counsel for the applicant submitted that the teaching was all there in the prior arts and the person skilled in the art would find the invention obvious.

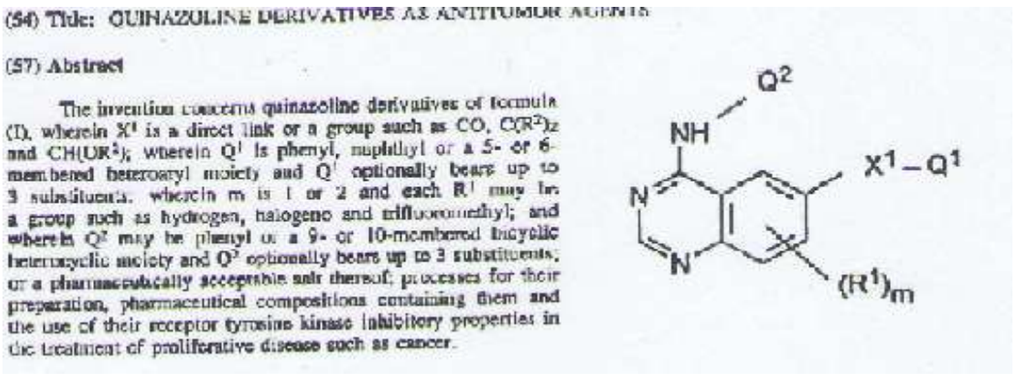
61. Sinha 1 deals with two prior arts Ex1 (WO 97/13771) and Ex2 (WO97/30034) According to the expert this compound is a derivative of quinozaline, with the basic quinozaline structure having substituents at specific sites.

62. Ex1 is Bicyclic HeteroAromatic Compound as Protein Tyrosine Kinase Inhibitors. This is the respondent's own patent. This prior art provides a compound



Ex 2 is Quinazoline Derivatives as Anti Tumour Agents.

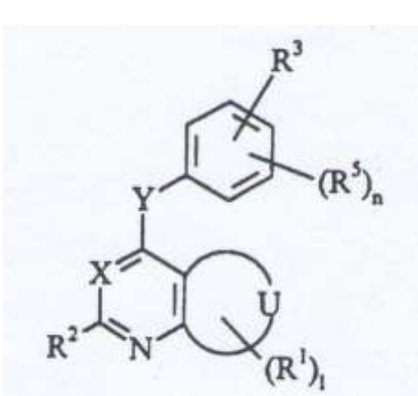
The abstract is as follows:


(54) Title: QUINAZOLINE DERIVATIVES AS ANTITUMOR AGENTS

(57) Abstract

The invention concerns quinazoline derivatives of formula (I), wherein X^1 is a direct link or a group such as CO, $C(R^2)_2$ and $CH(OR^2)$; wherein Q^1 is phenyl, naphthyl or a 5- or 6-membered heteroaryl moiety and Q^1 optionally bears up to 3 substituents, wherein m is 1 or 2 and each R^1 may be a group such as hydrogen, halogeno and trifluoromethyl; and wherein Q^2 may be phenyl or a 9- or 10-membered bicyclic heterocyclic moiety and Q^2 optionally bears up to 3 substituents; or a pharmaceutically acceptable salt thereof; processes for their preparation, pharmaceutical compositions containing them and the use of their receptor tyrosine kinase inhibitory properties in the treatment of proliferative disease such as cancer.

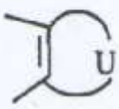
Exhibit 1 discloses many compounds represented by a Markush structure which is shown as Formula A.



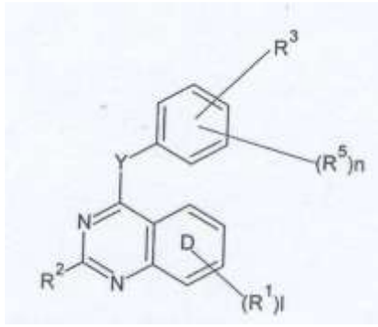
or a pharmaceutically acceptable salt thereof,

wherein X is N or CH;

wherein



The U represents a fused 5, 6 or 7-membered heterocyclic ring containing 1 to 5 heteroatoms which may be the same or different and which are selected from N,O or $S(O)_m$. Therefore all the alternatives for the ring system U contain a hetero atom. The corresponding ring system in the Invention does not contain a hetero atom. The applicant has taken this Markush structure and claims that by substituting the above preferred groups into the compound of Formula A the petitioner arrives at**.**



But this is different from the structure in The Invention, since the core of Ex 1 is pyrido [3,4-d]pyrimidine while the core structure of quinozaline. Now how do we work towards that?

The petitioner claims

That R_2 group *may* be hydrogen

Y is a group NR^a wherein Ra includes hydrogen, therefore Y *may* be hyrdrogen

R5 *may* be a halogen; halogen includes chlorine

"n" *may* be1

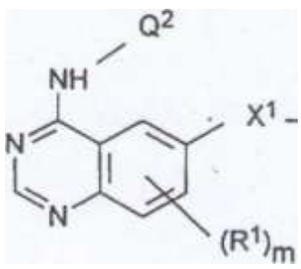
R3 *may* be a group ZR_4 Z *may* be $V(CH_2)$; V may be O ; R4 *may* be an optionally substituted 5,6,7,8,9 or 10 membered carbocyclic or heterocyclic moiety; the carbocyclic groups comprise one or more rings which *may* be

independently saturated, unsaturated or aromatic and contain only carbon and hydrogen; halo includes fluoro.

62. If all the above substitutions are incorporated then a structure may be arrived at which is the structure of the invention excluding the methane sulphonyl 6 substitution. Then the applicant says that since Ex 1 says at page 12 that R1 may preferably be selected as furan and if furan is substituted then one would arrive at the structural formula which would be identical to the Invention except for the further substitution on the 5-position of the furan. The applicant admits that the Exhibit 1 does not teach a fused phenyl ring nor the sulphonyl group on the alkyl amine substituent.

So we go to

Exhibit 2 – WO 97/30034.



wherein X' is a direct link or a group of the formula CO, $C(R^2)_2$ $CH(OR^2)$, $C(R^2)_2$ - $C(R^2)_2$ $C(R^2)$, C=C, CH(CN), O, S, SO, SO 0, S, SO_2, $N(R^2)$, $CON(R^2)$, $SO_2N(R^2)$, $N(R^2)CO$, $N(R^2)SO2$, $OC(R^2)$, $SC(R^2)2$, $N(R^2)C(R^2)2$, $C(R^2)2O$,$C(R^2)2S$ or $C(R^2)2N(R^2)$, and each R2 is independently hydrogen or (1-4C)alkyl;

wherein Q' is phenyl, naphthyl or a 5- or 6-membered heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic moiety is a single ring or is fused to a benzo ring, and Q' optionally bears up to 3 substituents selected from halogeno, hydroxy, ammo, trifluoromethoxy, trifluoromethyl, cyano, nitro, carboxy, carbamoyl, (l-4C) alkoxycarbonyl, (l-4C)alkyl, (l-4C)alkoxy, (2-4C)alkenyloxy, (2-4C) alkynyloxy, (l-3C)aikylenedioxy, (l-4C)alkylamino, di-[(l-4C)alkyl]amino, pyrrolidin-1-yl, piperidino, 1-yl, piperidino, morpholino, piperazin-1-yl, 4-(l-4C)alkylpiperazin-l-yl, (2-4C)alkanoylamino, N-(1-4C)alkyicarbamoyl, N,N-di-[(l-

4C)alkyl]carbamoyl, ammo-(l-4C)alkyl, (l-4C)alkylamino-(l-4C)alkyl, di-[(1-4C)alkyl]amino-(l-4C)alkyl, pyrrolidin-1-yl-(1-4C)alkyl, piperidino-(1-4C)aIkyl, morpholino-(1-4C)alkyl, piperazin-1-yl-(l-4C)alkyl, 4-(1-4C)alkylpiperazin-1-yl-(1-4C)alkyl, halogeno-(2-4C)alkoxy, hydroxy-(2-4C)alkoxy, (l-4C)alkoxy-(2-4C)alkoxy, amino-(2-4C)alkoxy, (l-4C)alkylamino-(2-4C)alkoxy,di-[(l-4C)alky!]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-l-yl-(2-4C)alkoxy, (l-4C)alkylthio-(2-4C)alkoxy, (l-4C)alkyIsulphinyl-(2-4C)alkoxy, (l-4C)alkylsulphonyl-(2-4C)alkoxy, halogeno-(2-4C)alkylamino,hydroxy-(2-4C)alkylamino,(1-4C)alkoxy-(2-4C)alkylammo, amino-(2-4C)alkylamino, (l-4C)aikylamino-(2-4C)alkylamino,di-[(1.4C)alkyl]amino-(2-4C)alkylamino, pyrrolidin-1-yl-(2-4C)alkylammo, piperidino-(2-4C) alkylamino,

64. Here in this structure each of the groups contains a wide selection of substituents. How do we move with this prior art?

According to the applicant,

X^1 is a direct link or a group of the formula consisting of twenty odd possible linking groups,

Q^1 is phenyl, napthyl or a 5- or 6-membered hetero-aryl moiety (3 options) Containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur (3 options) which moiety is a single ring or is fused to a benzo ring (2 options) and Q^1 optionally bears up to 3 substituents selected from 30 odd ring groups and the point of attachment is also matter of selection

Q^2 is a group of the Formula II

Wherein X^2 is a group of the formula CO , $C(R^3)_2$.....$OC(R^3)_2$.....(20 options) wherein R^3 is independently hydrogen or (1-4C)alkyl.

Q^3 is again a matter of choice. Phenyl or napthyl or a 5- or 6- membered heteroaryl moiety containing up to 3 hetreoatoms selected again from 3options oxygen , nitrogen and sulphur which heteroaryl moiety is a single ring or is fused to said phenyl or napthyl group or heteroaryl moiety which bears up to 3 substituents selected from halogeno.....(1-4C)alkylamino.....(17options). Here n is 1,2or 3 and each R^4 is independently hydrogen, halogeno.....(12 options)

65. The applicant's expert has stated that with these prior arts it is possible to "arrive at" the Invention, and that it was only a matter of experiment by the Person Skilled in the Art. The Learned counsel submitted that the presence of a large number of choices may mean more labour but there is no imagination nor

an inventive step. It is purely a matter of trial and error and experiments such as Ms. P. Sita is capable of and that she will find it obvious to have a substitution on the furan ring and that the phenyl has to substituted with halogen and that is by chlorine. According to the applicant the importance of the 4 anilino substitution, the importance of the position 6 on the quinozaline ring was known (vide Sinha affidavit.) the furan substituents having the amino sulfoxide chain was also known. The former was known to have better tyrosine kinase inhibitor activity and the latter better bonding and cell permeability, therefore what could be more obvious than to choose these since there is motivation? A skilled worker looking for compounds against EGFR activity is *likely* to modify the R group attached to the quinazoline ring at position 6. Now since it is known that R binds to the protein where ribose and phosphates bind, R must be analogous in character. Since R *must* be analogous in character, and since R is located in a pocket which corresponds to the ribose phosphate binding site of adenosine triphosphate, and since ribose is also a five-membered ring like furan, furan becomes the obvious choice. Further the person skilled in the art would know that the side chain of the quinazoline would require a 5 membered structure similar to ribose which has tetrahydrofuran, she would know the furan fits the bill. Since it is known from Exhibit D1 many compounds can be accommodated at position 6, Ms. P. Sita will nail the furan at position 6. Therefore with a slight manipulation of the chain length and with some modification and in view of the flexibility available at the catalytical site of kinases the skilled worker will arrive at this compound. In Sinha II affidavit, the expert had considered Heerding affidavit, and three Ex D, E and F all of which are post patent. In this affidavit, it is stated that Laptanib is a dual inhibitor of both c-erbB-2 and EGFR receptor kinases.

66. According to him WO1996015118 Exhibit E shows that the 4-position of aniline ring can accommodate further different types of substitution having very good IT_{50} values and substitutions are aromatic in nature. According to him, compound 4 and 5 where the substitution is at the 6-position is likely to increase the solubility of the compounds. But at the 6-positon substitution to some extent, some structural change can be accommodated. According to him, Exhibit F

teaches that the compounds which are very good inhibitory activity in which he has given in Table 1, which contain compounds which are dual inhibitors and it was pointed out by the learned counsel for the applicant that 120 structure is close to the Invention Compound. According to the expert, example 120 demonstrates higher inhibition against both EGFR and c-erbB-2 enzymes than the other compounds. According to this expert, this document shows that benzyloxy moiety is responsible for interacting with certain structural components of erbB2 and Lapatinib has such benzyloxy group. According to him that example 120 in figure 3 of Exhibit-F, when compared with the Lapatinib structure would show that there is a common scaffold and in example 120 there is 3-OMe in the aniline ring which position is occupied by Cl in the case of Lapatinib, The study on SAR has disclosed in Exhibit-A shows that presence of Cl is more potent inhibitor. With this common scaffold by incorporation of Cl at 3' position in the aniline ring "as surmised from Exhibits A and E", one reaches the structure B.

67. According to this expert from this disclosure, there is an impetus to combine the prior arts Exhibits 1 and 2, to arrive at Lapatinib. The expert has called this substitution as a trivial modification which does not contribute to the inventive feature of the patent under revocation and no added effect is demonstrated by the presence of such fluorine. According to him, Exhibit-C, the model predicts that large substituents at C-6 and C-7 of the quinazoline can be tolerated without the major loss of affinity. According to him Fig.5 of Exhibit-C would show that there are similarities in the binding of the EGFR and that the difference in furan, a five membered cyclic ring like Ribose of ATP and since electrostatic interactions with Arg817 takes place with phosphate groups of ATP. The similar receptor binding activity would have been obvious and an absolute overlap is not necessary. Since both furan and ribose are five membered cyclic ring for a skilled worker selection of furan ring connection at 6-position is easy.

68. According to him, from Exhibit-C with slight variation and help of molecular docking such minor change can be achieved very easily to get methylsulfonylethylaminomethyl in the furan ring as substitution and hence provides for selection after substitution. According to him once the main

pharmacophore is known to be a dual inhibitor, the substituents do not contribute to the inventiveness of the patent. According to him, Exhibit-A to C have been mentioned in Sinha-I to show the general knowledge in the field of quinazoline derivatives and with these background teachings chosen the specific substitutents from Exhibits 1 and 2 is not wild or beyond the purview of skilled worker. So in view of Ex 1 and 2 in the back ground of the other exhibits, the invention is obvious.

69. The respondent countered the obviousness argument. Mr.Praveen Anand submitted that Lapatinib is a new chemical entity it has chemical structure that can be split into three parts for convenience.

> A) The Quinazoline Pharmocophore
>
> B) At the 4-position , (A) is substituted with a 3' chloro-aniline and the phenyl ring of the aniline is substituted by a 3-fluoro-benzyloxy group at the 4'position
>
> C) At the 6-position (A) is substituted with a 2-furyl ring system having a further substitution on the 5-position of the furan with methyl-sulfonyl-ehtyl-amino-methyl.

70. The combination of distinct structural characteristics has not been taught by any prior document. The prior documents have provided a number of choices and except by hindsight, this Lapatanib Compound could not have been arrived at nor predicted. According to the respondent, the specific substitution on the Aniline ring system gives specific advantages. According to him, Dr. Dirk Heerding's affidavit shows that each different element contributes to optimal cellular activity. The complete specification discloses Biological data Lapatinib and it has been tested for Protein kinase inhibitor activities in substrate phosphorylation assays and cell proliferation assays. According to the respondent, the applicant's own pleadings and affidavit speaks of the Complexity of Oncology, the Selectivity of Protein Tyrosine Kinase Mechanism ,described the importance of position of Atoms and substituents on Pharmocophore. He referred to the observations of the Delhi High Court in **ROCHE Vs. CIPLA** which observed that,

> "(W)hy there would be an arbitrary adoption of example 51 and why the said plaintiff would apply and react the ethynyl only be replacing the methyl at the third position, when the as per the plaintiff's version which is not disputed by the defendant EP '226 teaches to keep the methyl component stable and not variable. ..If the chemical compounds are held to be obvious on the basis of mere perusal and appearance of the structures and assuming that the slight change here and there is inconsequential without a positive evidence medically and clinically as to how the said reaction is immaterial, then several novel compounds can be declared obvious by such exercise and the same shall affect the research process adversely. The innovation or invention in the sense of chemical compound is not merely to innovate a new set of the compound *per se* but also making improvements in the existing state of the art by taking the aid of the experimentation by way of the reactants. This is the reason why, the Court cannot simply be satisfied by mere reliance of similar structure in the previous art and thereafter assuming that sight substitutions are inconsequential."

71. He submitted that once the choice of compound as a lead compound is made the petitioner shall not be allowed to keep changing their position to some how arrive at the Lapatinib Molecule. It was submitted that the applicant had attempted to arrive at Lapatinib, by using the invention as a blue print and work from what is found in the prior art. The applicant has not given any explanation why a person skilled in the art would replace COOH with amide. No reasoning is provided for the choice of a methyl group on the suphonamide terminal, for the choice of furan as a substituent, for linking the 2-position of the furan ring at the 6-position of the quinazoline ring, for use of a methylene (CH_2) linker, for choosing chlorine when the current direction was towards bromine at the 3' position of the aniline ring, for including a fluorine substitution at the 3' position of benzyloxy or for dropping the methoxy group at the 7- position when the prior art taught that substitution at the 7- position on the quinazoline improved the potency. Each of the above choice must be made and it is not a matter of random pulling out. The applicant has created hypothetical compound only to bring in the Furan ring-1. The applicant completely ignored the various changes that may be required to arrive at Lapatinib even after Exhibits A to C with Exhibits 1 and 2. It was submitted that expert Dr.Sinha surprisingly calls the modifications at the 6-position as trivial modification. Once the invention is known, it is easy to make substitution of one group for another group or one halogen for another halogen or different bridge linker. The Counsel for the respondent submitted that

the case of obviousness has been built purely by hindsight and by “cherry picking” and it deserved to be rejected’

72. The learned Counsel for the respondent dealt with the Sinha affidavit and Exhibits 1 and 2 and Exhibits A,B and C According to the respondent, the applicant has built upon the Markush structure by making specific choices without giving the reasons. This is purely a hindsight deduction. It was submitted that when there are wide options at each point, the compound cannot be arrived at without the template of the Invention itself. It was submitted that the specific substituted aniline group was not in any way disclosed nor was the optionally subsitituted furan ring. It was submitted that the possible aromatic rings do include (C_{1-4} alkyl) amino and di-(C_{1-4}alkyl) amino being substituted on to the ring system being attached at the nitrogen atom, but this would not equate to a –CH_2 NH_2 group. The suggested substitution is not a minor difference as compared to the corresponding substitution in Ex 1. Ex1 does not exemplify and quinazoline compound and the reference only exemplifies two substituted furanyl compounds but many more options. As regards Ex 2 it was submitted that while it relates to substituted quinozaline compounds of Formula (I), the applicant has selected some of the possible substituent groups of the Markush structure without any reasoning. There are a long list of possible substituents in each list, some of which are not fully listed and on the basis of this it is difficult to see how it is ‘disclosed’ . Even accepting the hypothetical structure proposed by the applicant there is no teaching to link the methylsulphonyl-aminomethyl-amino group with the furan ring. There is no motivation to choose form any of the compounds disclosed in Ex. or 2 even as a starting point for finding a dual EGFR and c-erbB-2 inhibitor. The respondent referred to the Heerding affidavit where it is stated that Lapatinib is shown to bind unexpectedly as a Type II kinase inhibitor as opposed to those described in Ex C which bind as A type I kinase inhibitor. It was submitted that it is wrong to state that furan is an obvious choice for tetrahydrofuran since the two are different properties and the former is an aromatic ring and the latter is an aliphatic ring. The co-relation made between the substitution to the ATP and furan is flawed since the two are structurally different.

The bicyclic quinazoline in Exhibit A is not the same as the tricyclic pyrroquinazoline in Ex B .as admitted in the Sinha affidavit and the small electron donating substituents are preferred on the former while larger bulky groups are tolerated on the latter. The expert Heerding is also of the opinion that the compound cannot be “arrived at” as indicated by the applicant. According to him there is nothing in the teachings of the prior art to make the structural changes to the known compounds to “arrive at’ the Invention. He has stated that Lapatinib is not any kind of derivative still less a simple derivative of any compound disclosed either specifically or generically in Ex 1.Ex A teaches the person skilled in the art that there is a narrow structure activity relationships for the basic ring system with quinazoline being the preferred compound and benzyl amine and aniline the preferred side chains, and not about the activity of lapatinib.

73. In the **Roche v CIPLA** case which dealt with another quinazoline compound called Erlotinib and its patentability the Delhi High Court held that, *“It cannot be assumed on a priori basis that the mere factor that there are some similarities in the structure of ranges, the replacement of the third position with ehynyl may follow and thus the said patent is obvious based on trial and error method.” And Therefore even if it is shown that the starting point of the invention is EP ‘226 and there are changes made in the chemical structures cited as example compounds in the said patent by reacting the same with ethynyl later on in relation to selected range, I do not find such selection can be arbitrary rather it can be inferred that there may be some further experimentations done in future on the Gefitinib compounds which narrowed down the examples cited by the ..ultimately resulted in the claim No.1 of the patent. All this rather indicates towards purposeful selection rather than arbitrary one.*” It is the case of the respondent this applies to the present case.

74. According to the respondent Ex B evaluates the enzyme inhibition of EGFR by compounds bearing tricyclic heteroaromatic cores, and not of c-erbB-2 or of overall kinase selectivity of the compounds. ”However Lapatinib has a substituted furan at the 6th position and a furan group cannot be considered as an electron donating substituent on an aromatic ring and the substituted furan is

clearly not small. In fact the authors .....go on to say that increasing the bulk at the 6- and/or 7-position ‘has been shown to be disadvantageous in the quinazoline series”

75. Regarding Ex C Heerding says that it only describes enzyme inhibition of EGFR and makes no mention of c-erbB 2 or overall kinase inhibiting activity and while discussing the bicyclic quinazolines it says the poor aqueous solubility of these compounds is major drawback for further development. He therefore concludes that the success of lapatinib would clearly distinguish it from these compounds mentioned in Ex.C. He has also explained why furan cannot mimic ATP. .

76. The respondent has filed the affidavit of Mr. Kaizad Hazari to prove the secondary considerations. He has spoken of the great commercial success of Lapatinib which is the active ingredient in the marketed product TYKERB® and TYVERB®

77. The respondent has also filed a second affidavit of Dr. A. Heerding to meet Sinha II. With regard to figure 2 in Sinha II, Heerding says that instead of looking at enzyme activity, one should consider the structurally distinct compound which are compound specific activity data disclosed in Exhibit-E contain a ‘benzyloxy group’ substitution at the 4-position in the anilio ring. He has stated the persons skilled in the art would know that to achieve potency against an isolated enzyme target is but one aspect to consider within the ambit of small molecule drug discovery. According to him, there is nothing in disclosure of Exhibit-F which would motivate a person skilled in the art to arrive at the specific group substitution claimed in the Patent without the benefit of hindsight knowledge. According to him, the Exhibit-F does not teach a furan ring substituted at the 6-position of the quinazoline ring and being further substituted at the 5-position by a methylsulphonylethylaminomethyl group. As regards, the example 120 which according to the applicants expert is a compound that a person skilled in the art would use as a starting point for the further development. This expert says that Exhibit 120 contains a methoxy group at the 3—position of

the aniline ring, which is an electron donating group is contradictory to the teaching which alleged to be taught from Exhibits A, B, C and D to include an electron withdrawing group at the 3'-position of the aniline ring.

78. According to this expert the alleged "common scaffold A" would result only after a choice of a number of different groups and substitutions which can result only that hindsight knowledge. The teachings of Exhibit-F is apparently teaches to include an electron withdrawing group and in contrast Exhibit-F which apparently teaches inclusion of an electron-donating group. According to him, It is not correct to call the substitution at the 6-position and the 5-position is trivial modification. He has referred to Annexure–G, **M.D. Gaul et al.**, which is a post patent document and which says specific substitution pattern on the quinazoline ring system has been shown to provide optimal cellular efficacy. He has also referred to Annexure – H Cockerill and Lackey, Current Topics I medicinal Chemistry 2002, 2, 1001-1010) which is again a post patent document and which is a review article of small molecule inhibitors and which specifically refers to compound 4557W which is the same as example 120 of Exhibit-F has solubility and pharmacokinetic properties. According to him, Sinha II makes gross simplifications in discussing the binding side and the use of molecular model.
He has referred to his earlier affidavit which states that lapatinib has unexpectedly been shows to have quite exceptional kinase selectivity. This expert also speaks of the difference between Lapatinib and IRESSA and that Lapatinib protrudes past the surface defined by IRESSA and there is a major shift in the C -helix with lapatinib which is the reason for its remarkable kinase selectivity.

79. The respondents cited **Janssen Pharmaceutica N.V., and Janssen Pharmaceutica Products, L.P., Vs. Mylan Pharmaceuticals., Inc., - 456 F. Supp. 2d 644** – to show the importance of secondary consideration like the commercial success, failure of others and copying.

80. **Ortho-McNeil Pharmaceutical, Inc., Vs. Mylan Laboratories, Inc.** – to show that the pathway to the invention may follow the logical steps but at the

time of invention “the inventor’s insights, willingness to confront and overcome obstacles and yes, even serendipity cannot be discounted.

81. **Otsuka Pharmaceutical Co., Ltd., vs. Sandoz, Inc., Sun Pharmaceutical Industries, Ltd., Synthon BV, Synthon Holdings BV, Synthon Laboratories, Inc., and Synthon pharmaceuticals, Inc., -** the court held that “absent reason or modification based on prior art evidence mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection.

82. **Takeda Chemical Industries, Ltd. And Takeda Pharmaceuticals North America, Inc., vs. Alphapharm Pty., Ltd and Genpharm, Inc.,** - the court held that to prove unpatentability, it must be shown that the prior art taught the specific molecular modifications necessary to achieve the claimed invention.

83. **Yamanouchi Pharmaceutical Co., Ltd., vs. Danbury Pharmacal, Inc.,** - the court held that “*virtually all inventions are combinations of old elements*.” Therefore, an examiner or accused infringer may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner or accused infringer to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention.

84. In **Merck Sharp and Dohme Corporation & Anr. Vs. Glenmark Pharmaceuticals Ltd.,** The Delhi High Court **held**

> “26. The plaintiff in a suit restraining infringement of patent ought to have known the defence which the defendant has put forth and ought to have met the same in the plaint, as has been done in the arguments in rejoinder by arguing on ‘basic’ and ‘improvement’ patents. There is not an iota of pleading on the said aspect. The plaintiff, to show that the defendants product, in spite of combining Phosphate with patented SITAGLIPTIN, medically remained equivalent to SITAGLIPTIN, was expected to plead in detail on the aspects of efficacy of SITAGLIPTIN, reason for itself combining the same with Phosphate and the role of Phosphate being inconsequential in the disease which SITAGLIPTIN cures. It was for the plaintiffs to have made a case of Sitagliptin Phosphate being merely a new form of SITAGLIPTIN which does not result in the enhancement of the efficacy of SITAGLIPTIN or being a mere combination

of other derivatives of SITAGLIPTIN. I am unable to find any pleading of the plaintiffs to the said effect. Rather, the plaint proceeds on the premise that Sitagliptin Phosphate is the same as SITAGLIPTIN but which is not found to be the case of the plaintiffs in its own application for grant of Sitagliptin Phosphate and which was abandoned."

The counsel for the appellant also referred the relevant paragraphs of the Supreme Court judgment.

85. **F. Hoffman-La Roche Ltd. vs. Cipla Limited –** The Delhi High court held

"45.....Biswanath Prasad Radhey Shyam vs Hindustan Metal Industries cited as AIR 1982.SC 1444 .....is a landmark judgment....is still holding the field .....

46.....in the case of **Biswanath Prasad Radhey Shyam (cited supra)**.....it was observed thus:-

'24.....

25.....

26. Another test of whether a document is a publication which would negative existence of novelty or an "inventive step" is suggested, as under:

"Had the document been placed in the hands of a competent craftsman (or engineer as distinguished from a mere artisan), endowed with the common general knowledge at the 'priority date', who was faced with the problem solved by the patentee but without knowledge of the patented invention, would he have said, "this gives me what I want?" (Encyclopaedia Britannica; ibid). To put it in another form: "Was it for practical purposes obvious to a skilled worker, in the field concerned, in the state of knowledge existing at the date of the patent to be found in the literature then available to him, that he would or should make the invention the subject of the claim concerned ?" Halsbury, 3rd Edn, Vol. 29, p. 42 referred to by Vimadalal J. of Bombay High Court in Farbwrke Hoechst & B. Corporation v. Unichem Laboratories." (Emphasis Supplied)

47. From the bare reading of the afore quoted observations of Supreme Court, it is manifest that the Hon'ble Supreme Court has laid down the test for the purposes of ascertaining as to what constitutes an inventive step which to be seen from the standpoint of technological advancement as well as obviousness to a person who is skilled in the art. It is to be emphasized that what is required to be seen is that the invention should not be obvious to the person skilled in art. These are exactly the wordings of New Patents Act, 2005 u/s Section 2(ja) as seen above. Therefore, the same cannot be read to mean that there has to exist other qualities in the said person like unimaginary nature of the person or any other land of person having distinct qualities."

The respondent submitted that the obviousness theory of the applicant is based only on hindsight knowledge.

86. We will now consider the issue of obviousness. We have already explained how the applicant had built his case of the teachings from Exs 1 & 2. There are other documents which were referred to by the applicant's experts.

Ex A concludes that the SAR in the 4-(phenylamino) quinazoline class of EGFR tyrosine kinase inhibitors indicate a requirement for small lipophilic electron withdrawing groups at the 3-position on the aniline and for electron-donating groups at the 6 and 7 positions of the quinazoline and a possible more specific requirement for high electron density in the vicinity of the 8-position of the quinazoline ring. It says that 4-(phenylamino) quinazoline is the primary pharmacophore for this class of EGFR inhibitors. In the two series explored in this it was found that the benzylamino compounds were less effective than the corresponding (3-bromophenyl) amino derivatives.

Ex B shows that it explores the effects of incorporating the electron donating amino substituents into a fused 5- or 6- membered ring which is part of the aromatic system. It deals with the synthesis. It mentions whether protected amino functions without increasing steric bulk would increase the potency; this is because this has been shown to be disadvantageous in the quinazoline series. It also says that the results obtained were consistent with SAR studies previously developed for the 4-[(3-bromophenyl)amino]quinazolines which suggested that small electron donating substituents at the 6- and 7- positions were desirable for high potency as exemplified by the 6,7-dimethoxy derivative7.

Ex C. refers to Ex A and B and says that the poor aqueous solubitlty of the compounds 2a and 3a is a major drawback to their further development. The known quinazolines were converted to thiones, then methylated to form thioethers, these were alkylated and the resulting products were reacted with 3-bromoaniline to give the desired aniline derivatives. This was found to be a significantly superior to the previously reported route to these compounds via the 4-chloroquinazolines which give lower yields due to poorer solubility. This exhibit discusses a possible binding model for these inhibitors on the EGFR enzyme. It noted that both previous SAR for the general class of 4-(phenylamino)quinazolines and molecular modelling studies suggested significant bulk tolerance at the 6 and 7 position. It studies N-substituted pyrazolo and pyrrolo compound listed in Table 2 to probe the extent of bulk tolerance and found that the 3-substituted pyrrolo series was over all the most effective. But it also records that "no clear trend was present.". Only one binding mode was found that satisfied all the SAR data" and which had no major unfavourable steric interactions. The results showed that N-1 and C-3 substituted pyrroloquinazolines in particular retain high potency against the enzyme. It identified a possible binding mode for this class of tricyclic inhibitors, where the *pyrrolo* or *pyrazolo* ring occupies the entrance of the ATP binding pocket of the of the enzyme with the nitrogen located at the bottom of the cleft and the C-3 position pointing towards a pocket corresponding to the ribose binding site of ATP. A similar approach had been reportedly made to the dianilinopthalimide EGFR inhibitor CGP 52411 , but it was different from the one which was published for a series of related 4-(phenylamino)pyrrolopyrimidines and that the extensive SAR data presented in Ex C excluded that binding mode.

Ex D is prior to ex A and this speaks of 4-(3-chloroanilino)quinazoline as a novel and potent lead in the search for tyrosine kinase inhibitor. It was found to act as an ATP analogue but there were differences too. **This is part of the bibliography of the above three Exhibits and yet the subsequent prior arts had chosen bromine.**

87. In **In re Winslow**, 365 F.2d 1017 (C.C.P.A. 1966) Rich J said, "*In performing the obviousness analysis,"* courts should "*picture the inventor as working in his shop with the prior art references . . . hanging on the walls around him."* This is a very evocative scene and does help us in figuring out what the hypothetical person: the Person Skilled In The Art will do.

88. In Exhibit 1 the skilled person who has to decide if X is N or H, and whether R2 should be hydrogen and if why R5 was to be a halogen which of the halogen should be chosen and then to identify 'n' and as regards R_3 and R_4 you have a variety of choices from which selection has to be made and for the substituent to R_1 Furan may be preferably be substituted. Neither the expert nor the pleadings indicate why the persons skilled in the art would make those specific choices from out of myriad choices in front of the persons skilled in the art. Even if the background of Exhibit 1 is admitted to be similar to that of the impugned patent, only 3 out of the 49 examples include a furan ring. So why would Ms. P. Sita choose furan? Unless she picks out randomly from the multiple choices, she is unlikely to arrive at the claimed compound on the teachings of Ex1, because the permutations and combinations are numerous. The hypothetical compound that the applicant arrives at on the basis of the Ex 1 is the Invention Compound minus the substitution on the Furan ring at the 5 position with methyl sulphonyl-ethyl-amino-methyl.

89. Even assuming that a correct choice is made by the persons skilled in the art at every point in the Markush structure shown in Exhibit1, Ms. P. Sita will have to go through the same process successfully with Exhibit 2. Here the teaching toward having a furan ring is quite remote, since only 5 of the 39 compounds have a furan ring. Not only should the person skilled in the art make the correct choice of the substituent, she must also choose the correct position. In this prior art the compounds which have furan ring substitution at the 6^{th} position of the quinazoline are 4-(3-chloro-4-fluoroanilino)-6-(3-furyl)quinazoline and 4-(3-chloro-4-fluoroanilino)-6-(furan-2-carboximado)quinazoline. It is clear that the furan substitution at the 6^{th} position in the claimed compound with the

further 5th position substitution cannot be arrived at from this Ex 2 as the applicant's expert seems to indicate.

90. According to the applicant Exhibit A, B and C clearly teach the importance 4-Anilino Quinazoline and their analogues in terms of inhibition of PTK activity against EGFR and the importance of 6,7 and 4 for bulk . Here again, the applicant does not state why the specific substitution should be made on the Exhibit-2 structure. The Core structure of Exhibit-1 and Exhibit-2 differ, but the applicant very conveniently states that since Quinazoline and Pyrroloquinazolines have both been referred as more preferred, they are alternative compounds and either of them can be used. There is no explanation why the substituent at the 6-position was chosen except to state that the persons skilled in the art who looks at Exhibit-A, which teaches the Primary Pharmacopore would look at Exhibit-C which provides the binding teaches bulky substituents are allowable at -6 and -7 position and would go to Exhibit-D which shows the CAQ as the lead compound for the inhibition of EGFR activity. **We doubt if such hip-hopping over prior arts would be possible unless the Hopscotch-outline of the Invention was before Ms. P. Sita. Too many randomly made right choices cannot be called a matter of obviousness.**

91. The applicant does not tell us why the persons skilled in the art would select those examples in Exhibit-1 containing a Furan ring as the starting point at every stage. There were several options available in the generic structure shown in Exhibit-1 and only by a purposive choice, the invention compound can be arrived at. Similar is the case with Exhibit-2. To show obviousness, it must be explained why the persons skilled in the art would choose from Exhibit-2 a furan ring substitution on the quinazoline ring out of the 39 examples. Many of the substituents on the quinazoline ring include only Methyl Sulphonyl, Nitro, Amino, Amino Methyl, Morphilino Ethyl etc., The applicant does not say why out of the separate individual possibilities these specific substitutions were made at the 4-position on the quinazoline , and the substitution at the 4'position of the phenyl ring of the aniline and also the 2-furyl ring substitution at the 6th position with the further substitution on the 5th position of the furan.. The obviousness

disqualification would arise only if the invention appears obvious from the teachings of the prior art. The choices that the applicant has made for R^1, X^1 , $Q^{1,}$ substituents and Q^2 could have been made only if the person skilled in the art had the invention itself before her, otherwise each choice had to be made from multiplicity of choices for which they should be a logical explanation as to why these choices were made or these choices were apparent/obvious. We have seen that after Ex D there was a teaching away from Chlorine and towards bromine in Ex A to C. In fact Ex C says that the previous route through chloroquinazoline gave less yield due to poorer solubility. It said that for bulk tolerance 3 substituted pyrrolo series was the most effective. The Table 1 in Ex F does not help the applicant .Example 25 has no substitution at the 6^- position of the quinazoline, Example 26 has substitutions at 6-and 7- and in Example 120 which is said to be the diving board to reach the claimed compound the substitution is at 6- and 7- on the quinazoline and there is no furan nor is there the sulphonyl substitution.

92. Try as we might we do not find that even considering all of the evidence a reasonable fact finder would have been motivated to produce Lapatinib applying **Pfizer v Apotex 2006-1261** . The applicant cited **Dystar Textil Farben Gmbh v. C.Patrick and co** and submitted that the motivation may be “found in any number of sources including common general knowledge” and that one must consider “ varying levels of imagination and ingenuity in the relevant field , particularly with respect to problem solving abilities.” We have held in an earlier case that the Person Skilled in the art is not ordinary , not a dullard or a moron and “knows how to proceed in the normal course of research with what he knows of the state of art.” (**Sankalp Rehabilitation Trust v. Hoffman la Roche).** But the process explained by the expert and argued by Mr.S.Majumdar does not appear to be in the normal course of research. Even granting that this Person Skilled in the Art will have some imagination and some creativity as we had held in **Sankalp**, we had also said that “(This person) reads the prior arts as a whole and allows himself to be taught by what is contained therein. He is neither picking out ‘the teaching towards’ passages like the challenger, nor is he seeking out the

'teaching away' passages like the defender." In this case there are too many choices and too many "may's and too many surmises. No doubt in **T 0133/01** the European Board of Appeals had held that a skilled person will not require any inventive skill to pick out at random from the structural variant in the prior art the substitution of the basic structure with an OH- and a benzylaminomethyl group," In that case the prior art taught that all the compounds covered by it show dopamine D_2 receptor agonist activity and therefore the "choice of an OH- group at the 8 position and of a benzylaminomethyl group at the 2- position of the indol ring system was within the ambit of the generic disclosure of the prior art." There is no such clear teaching in the prior arts in this case and in any event the applicant wants to pick and choose from multiple options not just from one prior art but more than one exhibits. We are unable to find anything but hindsight knowledge and the case is built by working with the invention in front of her. **We do not find the invention obvious**.

93. The next ground raised by the learned Counsel for the applicant is that the applicant should be asked to disclaim the tosylate salt (Patent No: 221171) which is the impugned invention in ORA/22/2011/PT/KOL. His objection is that under our law double patenting is not allowed and that this patent cannot cover a compound which was invented at a later date. He also relied on the observations of the Supreme Court in the Novartis case. "The submissions on behalf of the appellant can be summed up by saying that the boundary laid out by the claim for coverage is permissible to be much wider than the disclosure/enablement/teaching in a patent. 139. The dichotomy that is sought to be drawn between coverage or claim on the one hand and disclosure or enablement or teaching in a patent on the other hand, seems to strike at the very root of the rationale of the law of patent. Under the scheme of patent, a monopoly is granted to a private individual in exchange of the invention being made public so that, at the end of the patent term, the invention may belong to the people at large who may be benefited by it. To say that the coverage in a patent might go much beyond the disclosure thus seem to negate the fundamental rule underlying the grant of patents.." He also referred to the Dr. Eswaran's evidence

in ORA/22/2012/PT/KOL where with reference to this Invention (Patent No: 221017) which was the prior art. Dr. S.V. Eswaran the expert had said that the prior arts do not teach the invention 221171. According to this expert, significant scientific exploration and experimentation have resulted in the discovery that this ditosylate salt (221171) has better sorption profile and better stability. He had said that an objective reading of D1 (221017) shows that "there is no disclosure of ditosylate salts of 4-quinizoline amine. And there is no teaching or direction to prepare the salts in D-1." According to him D1 (221017) relates principally to the free base forms (although salts in general and dihydrochloride salts in particular are disclosed" and this invention (221171) claims the novel ditosylate salts. And D1 (221017) will not teach Ms P. Sita, Person Skilled In The Art to prepare the salt (221171). He says that one of the key considerations "Is whether a skilled person would have been able to predict *a priori* the precise properties of a particular salt, solvate or a crystalline form." The respondent had obtained patents for Lapatinib free base (221017) and Lapatinib tosylate (221171). Both have been challenged by the applicant. For the reason that the respondent had maintained that ditosylate (221171) was not taught by this Invention in the revocation applicaton relating to ditosylate, we do not think we can make the respondent disclaim tosylate from these claims relating to the free base (221017). In the other Revocation Application the applicant had conceded that the invention (221171) was novel; but had contended that the tosylate salt was obvious and was hit by S.3(d). We have accepted these grounds of attack and revoked the patent. Here we are concerned with this Invention and these claims. If we find the invention non-obvious and does not suffer from any non-patentability grounds, the patent will stand as claimed. It is true that the Form 27 is identical in both these cases. But they have to be since both contain the same active ingredient. This is admitted by the respondent. We have held here that the applicant has not proved his case on S.8 and S.3(d) and that the invention is non-obvious. We do not see on what grounds we can ask the respondent to disclaim the tosylate salt (221171). The 3(d) ground would mean that the applicant proceeds on the footing that it is New, but there is no enhanced

therapeutic efficacy. The respondent's expert had given his opinion that not only did this invention (referred to as D1) not teach the tosylate salt, but the tosylate salt also displayed additional properties. We were not persuaded by this. The respondent has taken a stand in this and the other Revocation application, so has the Applicant. In the Novartis case the Supreme Court held in the context of disclosure and enablement quoting from Terrel on Patents" It is, of course, a fundamental principle that the construction of a claim is the same whether validity or infringement is to be considered; no patentee is entitled to the luxury of an "elastic claim which has a narrow meaning in the former case but a wide meaning in the latter. Under English procedure, infringement and validity are normally litigated at the same time and therefore the court is astute to avoid such a result." We do not have this luxury here which ensures consistency, but we are sure that the parties will not be allowed to resile from their respective stands when the issue of infringement is decided. We have found that the claims made by the Respondent are not hit by obviousness and we leave it there. There will not be double patenting as we have revoked 171. Further this ground is raised only in the argument, it is not pleaded.

94. We have already commented that there is a difference between the PCT application (Nat. Phase) as filed and the patent specification that is before us. Several passages including examples have been deleted. We did not know under what provision or by what procedure this was done .So we asked the Office of the Controller at Kolkata to give us the details. We find that a Form13 was filed on the 23.12.2005 seeking leave to amend the complete specification and the reason given is "by way of correction and explanation" The Note accompanying form 13 speaks of substantial modification of claims and limitation of definition of formula1, $R^{2,}$ R^4 etc. It does not explain why examples were deleted. The Controller had accepted this Form and the Patent specification that was published has undergone a change. **Such sweeping and large scale deletions and changes when allowed must be cautiously done and not casually.** We again and again have to repeat the importance of the officers examining and granting the patent.

95. Pending the hearing of this revocation application, we thought, we would appoint an independent expert as court witness to get his opinion on the patent. We requested both the counsel to suggest the name of an expert agreed to by both the parties. We have found, when expert evidence is filed by one side the opposite party attacks not only the evidence but also the expert. Witnesses are requested by courts to assist them and it is required that they are treated with respect. In a patent matter, in particular the expert who gives evidence comes with the considerable reputation in his field and deserves to be treated with respect. But in adversary litigation sometimes this is lost sight of.

96. The members of the Bar must remember this and shall not attack the expert. We thought that we would avoid this situation, if we appointed a court witness. The applicant suggested the names of scientist in India but the respondent had names of scientists from abroad. We really feel that with increasing patent litigation the evidence such court expert will become a necessity. When the complete specifications must be sufficient to "enable a person in India possessing average skill and average knowledge" the insistence of the respondent that only scientists from outside India can explain the patent, probably argues this ground against themselves. Members of the bar must assist the IPAB as officers of court in this regard atleast, instead of spokesperson of the client. If witnesses have to come from outside India, the payment in foreign exchange in fees will involve a problem. The evidence of these expert witnesses will enhance the quality of the orders. We found that we had reached an impasse in view of what was filed before us by the parties. So we deferred the appointment of expert on 01.04.2003 with the hope that the parties would come to an agreement on the expert. We, infact mentioned in our order dated 01.04.2003 that if they are able to agree on an expert they could approach us. It is obvious that it was a fond and an unrealistic hope, since the parties did not come to us with a consensus. We believe that India has enough number of scientists with the expertise credentials and credibility who could have explained to us the complete specifications, the scope of the prior art to decide the matter. We have decided the matter without the evidence of the court expert.

96. In view of the above, the ORA/17/2012/PT/KOL is dismissed with costs of Rs.50,000/-. The miscellaneous petitions are ordered as above.

(D.P.S. Parmar)
Technical Member (Patents)

(Justice Prabha Sridevan)
Chairman

SRK

REPORTABLE : YES / NO