THE PATENTS ACT, 1970
(As amended by Patent Act 2005)
&
The Patent Rules 2003
(As amended by Patent Rules, 2006)

IN THE MATTER of Patent application No. 537/Del/1996 made by PFIZER PRODUCTS INC., of Eastern Point Road, Groton, Connecticut 06340, USA; a US corporation and OSI PHARMACEUTICALS, INC., 41, Pinelawn Road, Melville, NY-11747, USA, a US corporation.

…….Applicants

And

IN THE MATTER of the representation by way of an opposition thereto by NATCO PHARMA LIMITED, Natco House, Road No.2, Banjara Hills, Hyderabad-33, India, an Indian company.

…….Opponent

And

IN THE MATTER of opposition u/s section25(1) of Indian Patents Act, 1970 and Rule 55 of the Patent Rules.

Hearing held on 27.06.2007

Present :
Opponent side
Mr. S. Majumdar of M/s. S. Majumdar & Co., Kolkata……..Opponent's Attorney
Mr. Adinarayan of M/s. Natco Pharma, Hyderabad…Representative from Natco Pharma
Dr.BhuJanga Rao of M/s. Natco Pharma, Hyderabad..Representative from Natco Pharma
Applicant side

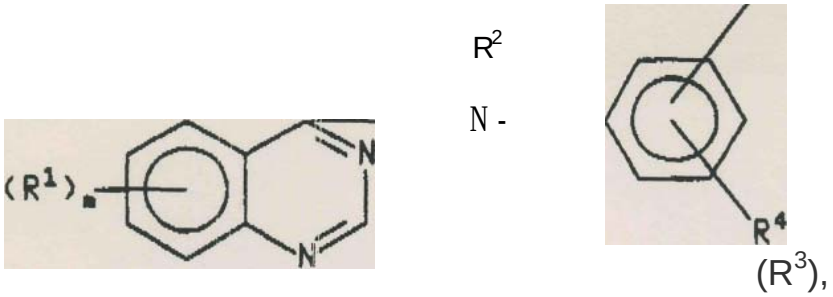
Mr. D.J. Solomon of M/s. DePenning & DePenning, Chennai- Applicant's Attorney

DECISION

An application with complete specification was filed by PFIZER INC., USA on 13.03.96 with priority of US dated 30.03.95 for grant of Patent on invention "QUINAZOLINE DERIVATIVES COMPOUNDS AND COMPOSITION THEREOF". Later the PFIZER INC., USA assigned its rights to PFIZR PRODUCTS INC., USA and OSI PHARMACEUTICALS, INC., USA and the same was taken on records in Patent office on 08.11.05. 2. The application was filed with total of 27 claims as recited below

CLAIMS

1. A compound of the formula



(R^3),

and pharmaceutically acceptable salts and prodrugs thereof, wherein

m is 1, 2, or 3;

each R^1 is Independently selected from hydrogen, halo, hydroxy, amino, hydroxyamino, carboxy, $(C_1\text{-}C_4)$alkoxycarbonyl, nirtro, guanldlno, ureido, carbamoyl, cyano, trifluoromethyl, $(R^6)_2$N-carbonyl, and phenyl-W-alkyl wherein W is selected from a single bond, 0, S and NH;

or each R^1 it Independently selected from cyano$(C_1\text{-}C_4)$-alkyl and R^9 wherein R^8 is selected from the group consisting of R^5, $R^5$0, $(R^5)_2$N, R^7C(=O), R^5ONH, A and R^5Y; wherein R^5 is $(C_1\text{-}C_4)$alkyl; R^8 is hydrogen or R^8 wherein the R^5s are the same or different; R^7 is R^5, R^5O or $(R^8)_2$N; A is selected from piperldino-, morphollno, pyrrolldino and 4-R^6-plperozin-l-yl, lmldazol-1-yl, 4-pyridon-1-yl, carboxy-$(C_1\text{-}C_4)$-alkyl, phenoxy, phenyl, phenylsulfanyl, $(C_2\text{-}C_4)$-alkenyl, $(R^8)_2$-N-carbonyl-$(C_1\text{-}C_4)$-alkyl; and Y Is selected from S, SO, S0$_2$; the alkyl moieties In (R^6),N are optionally substituted with halo or R^8 wherein R^8 Is defined as above, and the alkyl moieties in R^5 and R^5O are optionallv substituted with halo. R^8O or R^9 wherein R^8 and R^9 are defined as above, and wherein the resulting groups are optionally substituted with halo or R^9 with the proviso that a nitrogen, oxygen or sulfur atom and another heteroatom can not be attached to the same carbon atom, and with the further proviso that no more than three "R^8" units may comprise R^1;

or each R^1 is independently selected from R^5-sulfonylamino, phthallmldo-$(C_1\text{-}C_4)$-alkylsulfonylamino, benzamido, benzenesutfonylamino, 3-phenylureido, 2-oxopyrrolidin-1 -yl, 2,5-dioxopyrrolidln-l-yl, and R^{10}-$(C_2\text{-}C_4)$-alkanoylamino wherein R^{10} is selected from halo, R^5O, $(C_2\text{-}C_4)$-alkanoyloxy, R^7C(=0), and $(R^8)_2$N; and wherein said benzamido or

R^1 may optionally bear one or two halogens, (C1-C4)alkyl, cyano, methansulfonyl or (C1-C4)-alkoxy substituents;

or any two R^1s taken together with the carbons to which they are attached comprise a 5-8 membered ring comprising at least one or two heteroatoms selected from oxygen, sulfur or nitrogen; and wherein the alkyl groups and alkyl portions of the alkoxy or alkylamino groups may be straight chained or if comprised of at least three carbons may be branched or cyclic;

R^2 is selected from hydrogen and optionally substituted (C_1-C_6)-alkyl;

n is 1 or 2 and each R^3 is independently selected from hydrogen, optionally substituted (C_1-C_6)-alkyl, optionally substituted amino, halo, hydroxy, optionally substituted hydroxy;

R^4 is azido or R^{11}-ethynyl wherein R^{11} is selected from hydrogen, optionally substituted (C_1-C_6)alkyl wherein the substituents are selected from hydrogen, amino, hydroxy, R^5O, R^5NH and $(R^5)_2N$.

2. The compound according to claim 1 wherein R^2 is hydrogen and R^4 is R^{11}-ethynyl wherein R^{11} is selected from hydrogen, optionally substituted (C_1-C_6)-alkyl wherein the substituents are selected from hydrogen, amino, hydroxy, R^5O, R^5NH and $(R^5)_2N$.

3. The compound according to claim 2 wherein m is 1 or 2, each R^1 is independently selected from hydrogen, hydroxy, amino, hydroxyamino, carboxy, nitro, carbamoyl, ureido, R^5 optionally substituted with halo, R^6O, HOC(=O), $(R^6)_2NC(=O)$, A and $(R^6)_2N$;

R^5O optionally substituted with halo, R^6O, (C_2-C_4)-alkanoyloxy, HOC(=O), $(R^6)_2N$, A, phenyl;

R^5NH, $(R^5)_2N$, R^5NH_2, $(R^5)_2NH$, $R^5NHC(=O)$, $(R^5)_2NC(=O)$, R^5S, phenyl-(C_2-C_4)-alkoxy, $R^{12}O$, wherein R^{12} is HK and K is (C_2-C_4)alkyl, optionally substituted with halo, R^6O, (C_2-C_4)-alkanoyloxy, HOC(=O), A and $(R^6)_2N$, R^6OKO, R^6OKNH, CN and phenyl; R^5NH optionally substituted halo, (C_2-C_4)-alkanoyloxy, R^60, $R^7C(=O)$, $(R^6)_2N$, A, R^6OKO, R^6OKNH, C_6H_5Y, CN;

$(R^6)_2NC=O)$, R^5ONH R^5S, (C_1-C_4)-alkylsulfonylamino, phthalimido-(C_1-C_4-)-alkylsulfonylamino,3-phenylureido,2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halo-(C_2-C_4)-alkanoylamino, hydroxy-(C_2-C_4)-alkanoylamino, (C_2-C_4)-alkanoyloxy-(C_2-C_4)-alkanoylamino,(C_1-C_4-)-alkoxy-(C_2-C_4-)-alkanoylamino,carboxy-(C_2-C_4)-alkanoylamino,

(C_1-C_4)-alkoxycarbonyl-(C_2-C_4)-alkanoylamino,carbamoyl-(C_2-C_4)-alkanoylamino,N-(C_1-C_4)-alkylcarbamoyl-(C_2-C_4)-alkanoylamino, N,N-di-[(C_1-C_4)-alkyl]carbamoyl-(C_2-C_4)-alkanoylamino, amino(C_2-C_4)-alkanoytamino, (C_1-C_4)-alkyl-amino-(C_2-C_4)-alkanoylamino, di-(C_1-C_4)-alkyl-amino-(C_2-C_4)-alkanoylamino, and wherein said phenyl or phenoxy or anilino substituent in R^1 may optionally bear one or two halo, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy substituents; or any two R^1s taken together with the carbons to which they are attached comprise a 5-8 membered ring comprising at least one or two heteroatoms selected from oxygen,

sulfur or nitrogen; and wherein the alkyl groups and alkyl portions of the alkoxy or alkylamino groups may be straight chained or if comprised of at least three carbons may be branched or cyclic;

each R^3 is independently selected from hydrogen, methyl, ethyl, amino, halo and hydroxy;

R^4 is R^{11}-ethynyl wherein R^{11} is hydrogen.

4. The compound according to claim 3 wherein each R^1 is independently selected from hydrogen, hydroxy, amino, hydroxyamino, nitro, carbamoyl, ureido, R^5 optionally substituted with halo, R^6O, HOC(=O), $H_2NC(=O)$;

R^5O optionally substituted with halo, R^6O, (C_2-C_4)-alkanoyloxy, HOC(=O), $(R^6)_2N$, A, phenyl;

R^5NH, $(R^5)_2N$, R^5NH_2, $(R^5)_2NH$, $R^5NHC(=O)$, $(R^5)_2NC(=O)$, R^5S, phenyl-(C_2-C_4)-alkoxy and wherein said phenyl substituent in R^1 may optionally bear one or two halo, R^5 or R^5O substituents; or any two R's taken together with the carbons to which they are attached comprise a 5-8 membered ring comprising at least one or two heteroatoms selected from oxygen, sulfur or nitrogen; and wherein the alkyl groups and alkyl portions of the alkoxy or alkylamino groups may be straight chained or if comprised of at least three carbons may be branched or cyclic.

5. The compound according to claim 1 wherein R^2 is hydrogen and R^4 is azido.

6. The compound according to claim 5 wherein m is 1 or 2, each R^1 is independently selected from hydrogen, hydroxy, amino, hydroxyamino, carboxy, nitro, carbamoyl, ureido, R^5 optionally substituted with halo, R^6O, HOC(=O), $(R^6)_2NC(=O)$, A and $(R^6)_2N$;

$R^{12}O$, wherein R^{12} is HK and K is (C_2-C_4)alkyl, optionally substituted with halo, R^6O, (C_2-C_4)-alkanoyloxy, HOC(=O), A and $(R^6)_2N$, R^6OKO, R^6OKNH, CN and phenyl; R^5NH optionally substituted halo, (C_2-C_4)-alkanoyloxy, R^6O, $R^7C(=O)$, $(R^6)_2N$, A, R^6OKO, R^6OKNH, C_6H_5Y, CN;

$(R^6)_2NC=O$), R^5ONH R^5S, (C_1-C_4-alkylsulfonylamino, phthalimido-(C_1-C_4)-alkylsulfonylamino, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, halo-(C_2-C_4)-alkanoylamino,hydroxy-(C_2-C_4)-alkanoylamino,(C_2-C_4)-alkanoyloxy-(C_2-C_4)-alkanoylamino,(C_1-C_4)-alkoxy-(C_2-C_4)-alkanoylamino,carboxy-(C_2-C_4)-alkanoylamino, (C_1-C_4)-alkoxycarboynl-(C_2-C_4)-alkanoylamino,carbamoyl-(C_2-C_4)-alkanoylamino,N-(C_1-C_4)-alkylcarbamoyl-(C_2-C_4)-alkanoylamino, N,N-di-[(C_1-C_4)-alkyl]carbamoyl-(C_2-C_4)-alkanoylamino, amino-(C_2-C_4)-alkanoylamino, (C_1-C_4)-alkyl-amino-(C_2-C_4)-alkanoylamino, di-(C_1-C_4)-alkyl-amino-(C_2-C_4)-alkanoylamino, and wherein said phenyl or phenoxy or anilino substituent in R^1 may optionally bear one or two halo, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy substituents; or any two R^1s taken together with the carbons to which they are attached comprise a 5-8 membered ring comprising at least one or two heteroatoms selected from oxygen, sulfur or nitrogen; and wherein the alkyl groups and alkyl portions of the alkoxy or alkylamino groups may be straight chained or if comprised of at least three carbons may be branched or cyclic; and

each R^3 is independently selected from hydrogen, methyl, ethyl, amino, halo and hydroxy.

7. The compound according to claim 6 wherein each R^1 is independently selected from hydrogen, hydroxy, amino, hydroxyamino, nitro, carbamoyl, ureido, R^5 optionally substituted with halo, R^6O, HOC(=O), $H_2NC(=O)$;

R^5O optionally substituted with halo, R^6O, (C_2-C_4)-alkanoyloxy, HOC(=O), $(R^6)_2N$, A, phenyl;

R^5NH, $(R^5)_2N$, R^5NH_2, $(R^5)_2NH$, $R^5NHC(=O)$, $(R^5)_2NC(=O)$, R^5S, phenyl-(C_2-C_4)-alkoxy and wherein said phenyl substituent in R^1 may optionally bear one or two halo, R^5 or R^5O substituents; or any two R^1s taken together with the carbons to which they are attached comprise a 5-8 membered ring comprising at least one or two heteroatoms selected from oxygen, sulfur or nitrogen; and wherein the alkyl groups and alkyl portions of the alkoxy or alkylamino groups may be straight chained or if comprised of at least three carbons may be branched or cyclic.

8. The compound of claim 7 wherein R^3 is halo and R^1 is hydrogen or R^5O.

9. The compound of claim 8 wherein R^5 is methyl.

10. The compound of claim 1 selected from the group consisting of:
(6,7-(dimethoxyquinazolin-4-yl)-(3-ethynylphenyl)-amine;
(6,7-(dimethoxyquinazolin-4-yl)-[3-(3'-hydroxypropyn-1-yl)phenyl]-amine;
[3-(2'-(aminomethyl)-ethynyl)phenyl]-(6,7-(dimethoxyquinazolin-4-yl)-amine;
[(3-ethynylphenyl)-(6-nitroquinazolin-4-yl)-amine;

(6,7-dimethoxyquinazolin-4-yl)-(4-ethynylphenyl)-amine;
(6,7-dimethoxyquinazolin-4-yl)-(3-ethynyl-2-methylphenyl)-amine;
(6-aminoquinazolin-4-yl)-(3-ethynylphenyl)-amine;
(3-ethynylphenyl)-(6-methanesulfonylaminoquinazolin-4-yl-amine;
(3-ethynylphenyl)-(6,7-methylenedioxyquinazolin-4-yl)-amine;
(6,7-dimethoxyquinazolin-4-yl)-(3-ethynyl-6-methylphenyl)-amine;
(3-ethynylphenyl)-(7-nitroquinazolin-4-yl)-amine;
(3-ethynylphenyl)-[6-(4'-toluenesulfonylamino)quinazolin-4-yl]-amine;
(3-ethynylphenyl)-{6-[2'-phthalimido-eth-1'-yl-sulfonylamino]quinazolin-4-yl}-amine;
(3-ethynylphenyl)-(6-guanidinoquinazolin-4-yl)-amine;
(7-aminoquinazolin-4-yl)-(3-ethynylphenyl)-amine;
(3-ethynylphenyl)-(7-methoxyquinazolin-4-yl)-amine;
(6-carbomethoxyquinazolin-4-yl)-(3-ethynylphenyl)-amine;
(7-carbomethoxyquinazolin-4-yl)-(3-ethynylphenyl)-amine;
[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)amine;
(3-azidophenyl)-(6,7-dimethoxyquinazolin-4-yl)amine;
(3-azido-5-chlorophenyl)-(6,7-dimethoxyquinazolin-4-yl)amine;
(4-azidophenyl)-(6,7-dimethoxyquinazolin-4-yl)amine;
(3-ethynylphenyl)-(6-methansulfonyl-quinazolin-4-yl)-amine;
(6-ethansulfanyl-quinazolin-4-yl)-(3-ethynylphenyl)-amine
(6,7-dimethoxy-quinazolin-4-yl)-(3-ethynyl-4-fluoro-phenyl)-amine;
(6,7-dimethoxy-quinazolin-4-yl)-[3-(propyn-1'-yl-phenyl)]-amine.
[6,7-bis-(2-methoxy-ethoxy)-quinazolin-4-yl]-(5-ethynyl-2-methyl-phenyl)-amine;
[6,7-bis-(2 -methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-4-fluoro-phenyl)-amine;
[6,7-bis-(2-chloro-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine;
[6-(2-chloro-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine;
[6,7-bis-(2-acetoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine;
2-[4-(3-ethynyl-phenylamino)-7-(2-hydroxy-ethoxy)-quinazolin-6-yloxy]-ethanol;
[6-(2-acetoxy-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine;
[7-(2-chloro-ethoxy)-6-(2 -methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine;
[7-(2-acetoxy-ethoxy)-6-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine;
2-[4-(3-ethynyl-phenylamino)-6-(2-hydroxy-ethoxy)-quinazolin-7-yloxy]-ethanol;

2-[4-(3-ethynyl-phenylamino)-7-(2-methoxy-ethcxy)-quinazolin-6-yloxy]-ethanol;
2-[4-(3-ethynyl-phenylamino)-6-(2-methoxy-ethoxy)-quinazolin-7-yloxy]-ethanol;

[6-(2-acetoxy-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine;

(3-ethynyl-phenyl)-{6-(2-methoxy-ethoxy)-7-[2-(4-methyl-piperazin-1-yl)-ethoxy]-quinazolin-4-yl}-amine;

(3-ethynyl-phenyl)-[7-(2 -methoxy-ethoxy)-6-(2 -morpholin-4-yl)-ethoxy)-quinazolin-4-yl]-amine;

(6,7-diethoxyquina2olin-1-yl)-(3-ethynylphenyl)-emine;
(6,7-dibutoxyquinazolin-1-yl)-(3-ethynylphenyl)-amine;
(6,7-diisopropoxyquinazolin-1-yl)-(3-ethynylphenyl)-amine;
(6,7-diethoxyquinazolin-1-yl)-(3-ethynyl-2-methyl-phenyl)-amine;
[6,7-bis-(2-methoxy-ethoxy)-quinazolin-1-yl]-(3-ethynyl-2-methyl-phenyl)-amine;
(3-ethynylphenyl)-[6-(2-hydroxy-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-1-yl]-amine;

[6,7-bis-(2-hydroxy-ethoxy)-quinazolin-1 -yl]-(3-ethynylphenyl)-amine; and
2-[4-(3-ethynyl-phenylamino)-6-(2-methoxy-ethoxy)-quinazolin-7-yloxy]-ethanol.

11. The compound of claim 1 selected from the group consisting of
(6,7-(dipropoxy-quinazolin-4-yl)-(3-ethynyl-phenyl)-amine;
(6,7-(diethoxy-quinazolin-4-yl)-(3-ethynyl-5-fluoro-phenyl)-amine;
(6,7-(diethoxy-quinazolin-4-yl)-(3-ethynyl-4-fluoro-phenyl)-amine;
(6,7-(diethoxy-quinazolin-4-yl)-(5-ethynyl-2-methyl-phenyl)-amine;
(6,7-(diethoxy- quinazolin-4-yl)-(3-ethynyl-4-methyl-phenyl)-amine;
(6-aminomethyl-7-methoxy-quinazolin-4-yl)-(3-ethynyl-phenyl)-amine;
(6-aminomethyl-7-methoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
(6-aminocarbonylmethyl-7-methoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
(6-aminocarbonylethyl-7-methoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
(6-aminocarbonylmethyl-7-ethoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
(6-aminocarbonylethyl-7-ethoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
(6-aminocarbonylmethyl-7-isopropoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
(6-aminocarbonylmethyl-7-propoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
(6-aminocarbonylmethyl-7-methoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
(6-aminocarbonylethyl-7-isopropoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine; and
(6-aminocarbonylethyl-7-propoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine.

12. The compound of claim 1 selected from the group consisting of:

(6,7-diethoxyquinazolin-1-yl)-(3-ethynylphenyl)-amine;

(3-ethynylphenyl)-[6-(2-hydroxy-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-1-yl]-amine;

(3-ethynylphanyl)-[6-(2-hydroxy-ethoxy)-7-(2-methoxy-ethoxy)-qulnazolln-1-yl]-amine;

[6,7-bls-(2-hydrexy-ethoxy)-quinazolin-1.yl]-(3-ethynylphenyl)-amine;

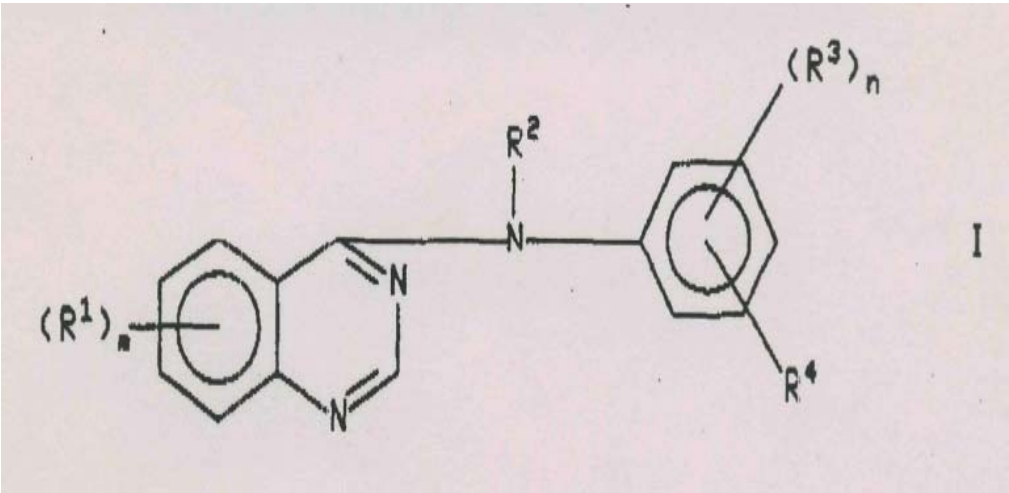
[6,7-bis-(2-methoxy-ethoxy)-qulnazolin-1-yl]-(3-ethynylphenyl)-amine;

(6,7-dimethoxyquinazolin-1-yl)- (3-ethynylphenyl)-amine;

(3-ethynylphenyl)-{6-methanesulfonylamino-qulnazolln-1-yl)-amine;

(6-amino-quinazolin-1-yl)-(3-ethynylphenyl)-amine;

13. A process for preparing a compound of the formula



I

wherein, m is 1, 2, or 3;

each R^1 is independently selected from hydrogen, halo, hydroxy, amino, hydroxyamino, earboxy, $(C_1$-$C_4)$alkoxycarbonyl, nitro, guanldino, ureldo, carbamoyl, cyano, trtfluoromethyl, $(R^8)_2N$ - carbonyl, and phenyl-W-alkyl wherein W is selected from a tingle bond, O, S and NH;

or each R^1 Is Independently selected from cyano-$(C_1$-$C_4)$-alkyl end R^9 wherein R^9 Is selected from the group consisting of R^5, R^5O, $(R^6)_aN$, $R^7C(=O)$, R^5ONH, A and R^5Y; wherein R^5 is $(C_1$-$C_4)$alkyl; R^6 is hydrogen or R^5 wherein the R^5s are the same or different; R^7 is R^6, R^5O or $(R^5)_2N$; A is selected from plperidlno-, merpholino, pyrrolidino and 4-R^6-piperazln-1-yl, lmidazol-1-yl, 4-pyridon-1-yl, carboxy-$(C_1$-$C_4)$-alkyl, phenoxy, phenyl, phenylsulfanyl, $(C_2$-$C_4)$-alkenyl, $\{R^5)_2$-N-carbonyl-$(C_1$-$C_4)$-alkyl; and Y is selected from S, SO, SO_2; the alkyl moleties in $(R^5)_2N$ are optionally substituted with halo or R^9 wherein R^9 is defined as above, and the alkyl moleties in R^5 and R^{50} are optionally substituted with halo R^5O or R^9

wherein R^9 and R^6 are defined as above, and wherein the resulting groups are optionally substituted with halo or R^9 with the proviso that a nitrogen, oxygen or sulfur atom and another heteroatom can not be attached to the same carbon atom, and with the further proviso that no more than three "R^9" units may comprise R^1;

R^1 may optionally bear one or two halogens, (C1-C4)alkyl, cyano, methansutfonyl or (C1-C4)-alkoxy substituents;

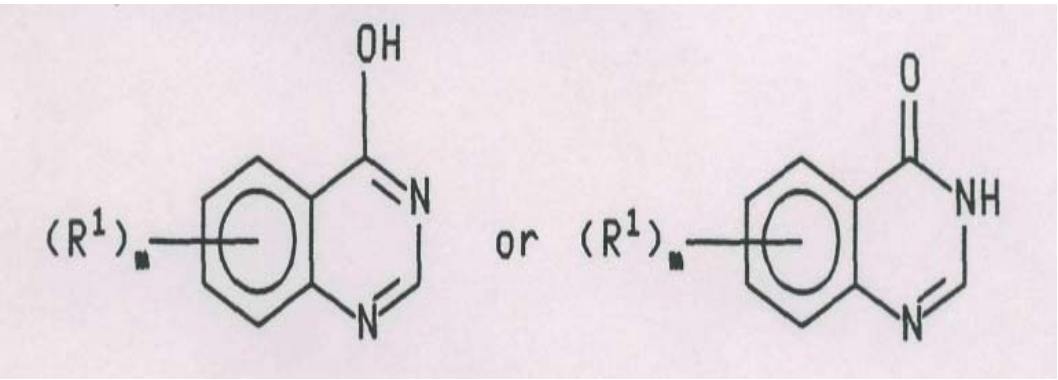
or any two R^1s taken together with the carbons to which they are attached comprise a 5-8 membered ring comprising at least one or two heteroatoms selected from oxygen, sulfur or nitrogen; and wherein the alkyl groups and alkyl portions of the alkoxy or alkylamino groups may be straight chained or if comprised of at least three carbons may be branched or cyclic;

R^2 is selected from hydrogen and optionally substituted (C_1-C_6)-alkyl;

n is 1 or 2 and each R^3 is independently selected from hydrogen, optionally substituted (C_1-C_6)-alkyl, optionally substituted amino, halo, hydroxy, optionally substituted hydroxy;

R^4 is azido or R^{11}-ethynyl wherein R^{11} is selected from hydrogen, optionally substituted (C_1-C_6)alkyl wherein the substituents are selected from hydrogen, amino, hydroxy, R^5O, R^5NH and $(R^5)_2N$. which comprises

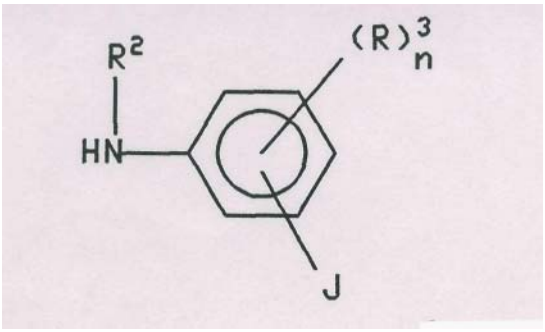
a) Treating a compound of the formula



wherein R^1 and m are as defined above,

with CCI_4 and an optionally substituted triarylphosphine, optionally supported on an inert polymer, of the formula Ar_3P wherein each Ar is an optionally substituted (C_6-C_{10})aryl group and each of the substitutents is independently selected from (C_1-C_6)alkyl; and

b) Treating the product of step a) with a compound of the formula



wherein R^2, R^3 and n are as defined above, and J is Y or R^4, wherein R^4 is as defined above, with the proviso that when J is Y then the product of step b) must further be treated with an alkyne.

14. The process of claim 13 wherein each aryl group is selected from phenyl, naphth-1-yl and naphth-2-yl.

15. The process of claim 14 wherein each aryl group is independently substituted with from zero to the maximum number of (C_1-C_6)alkyl groups.

16. The process of claim 14 wherein each Ar is phenyl.

17. The process of claim 13 wherein said triarylphosphine is supported on an inert polymer.

18. The process of claim 17 wherein said polymer is a divinylbenzene-cross-linked polymer of styrene.

19. A method of treating hyperproliferative diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 1.

20. A method as recited in claim 19 wherein the hyperproliferative disease is cancer.

21. A method as recited in claim 20 wherein the disease is brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, gynecological or thyroid cancer.

22. A method as recited in claim 19 wherein the hyperproliferative disease is noncancerous.

23. The method of claim 22 wherein said disease is a benign hyperplasia of the skin or prostate.

24. A pharmaceutical composition for the treatment of hyperproliferative diseases in a mammal which comprises a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

25. A compound of the formula I as defined in claim 1 substantially as hereinbefore described with reference to the foregoing examples.

26. A process for preparing a compound of the formula substantially as herein described with reference to the foregoing examples.

27. A pharmaceutical composition substantially as hereinbefore described with reference to the foregoing examples.

As is evident from opening description of the complete specification the claimed compounds are useful in the treatment of hyperproliferative diseases, such as cancers in mammals.

The finally corrected title preferred by the Applicant is as under :

"A novel [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-3-ethynylphenyl)amine hydrochloride and a process for preparing the same"

3. A request for examination in prescribed manner was filed in the Patent office on 16th August, 2004.

This application has been published under section 11[A] on 11.03.05 and the minimum statutory time limit to oppose grant of patent as per section 25(1) was over on 11.09.05.

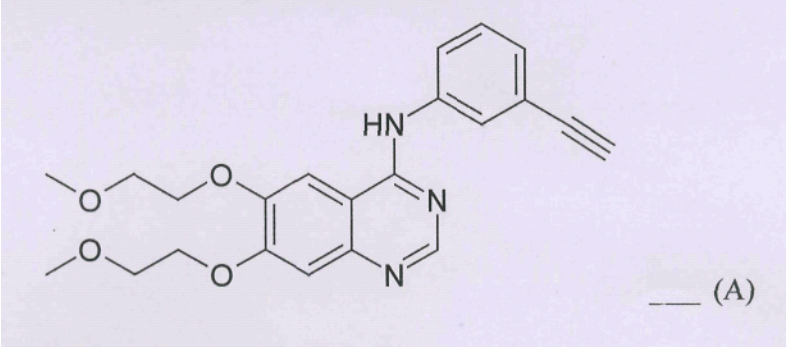
A First Examination Report was issued on 22.02.06 with following objections:

1. Subject matter of claims does not constitute an invention under section 2(l)(j) as it lacks novelty and inventive step in view of citation nos. JP 7138238, JP6073023 & JP 6336481.
2. Claims 19 to 24 falls within the scope of sub clause of section 3(i).
3. Claims 1 to 27 are not clear in respect of the expression as indicated therein.
4. Claims 1 to 27 are not clearly worded.
5. Title is inconsistent with description and claims.
6. Power of Authority should be filed.
7. Pages of the specification should be renumbered.
8. Extraneous matter of the specification should be deleted.
9. Abstract should be filed with a title and concise summary of the invention within 150 words in accordance with rule 13(7)(a) of Patent Rules, 2003.
10. Details regarding applications for patents which may be filed outside India from time to time for the same or substantially the same invention should be furnished within three months from the dates of filing of the said application(s) under clause (b) of sub section (1) of section 8 and rule 12(1) of the Indian Patent Act.
11. Details regarding the search and/or examination report including claims of the applications allowed, as referred to Rule 12(3) of the Patents Rule, 2003, in respect of the same or substantially the same inventions filed in all the major Patent offices, such as USPTO, EPO and JPO etc., along with appropriate translation where applicable, should be submitted within a period of three months from the date of receipt of this communication as provided under section 8(2) of the Indian Patents Act.

Further, to make the statement of claims and whole the documents upto the satisfaction level and for compliance of all the objection of FER several exchange of correspondence and discussions took place.

4. Finally, this case was placed in order for grant of Patent on 23.02.07 and final number of claims restricted to the Applicant are two which are reproduced below:-

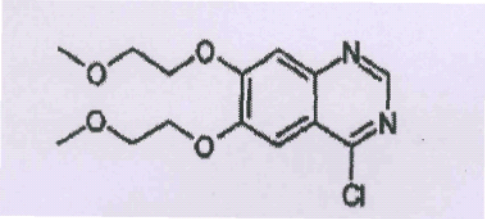
1. A novel [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl) amine hydrochloride compound of the formula A



___ (A)

2. A process for preparing the compound as claimed in claim 1, wherein :

a) the compound



is reacted with the compound

(5). On 10.04.2007 an opposition to the grant of patent under section 25(1) was filed by "M/s.Natco Pharma Ltd., Hyderabad"

The main grounds taken by the opponents are as under:

(A) The compounds of formula I as given in claim 1 are obvious in view of earlier patents Publication No. EP 0566226 A1; EP 06335507 A1; EP 0635498 A1 and EP 0520722 A1.

(B) The process for preparation of the compound of claim 1 is also obvious.

(C) The disclosure of the invention in complete specification is insufficient.

(6) The statement of opposition under section 25(1) was forwarded to the Applicant's attorney M/s. DePenning DePenning, Chennai on 27.04.07 so as to invite their reply to the said opposition within the prescribed time limit.

The Applicants filed the reply statement under rule 55(4) on 05.06.2007. A copy of which was forwarded to the opponents on 11.06.2007 for their perusal.

(7) The Applicants have submitted their rebuttal as under:

(i) Since the Controller has placed the application in order for grant and the opposition was filed afterwards therefore this opposition should have been treated as post grant opposition under section 25(2).

(ii) The Applicants has reduced the number of claims to two only and therefore the opponent's allegations are rendered moot by the amended claims.

(iii) The claims are not obvious over the prior art as cited by the opponents.

(iv) The claims 2 are novel over the cited prior art.

(v) The method claim no. 2 is novel and inventive over the cited prior art.

(vi) The description in the complete specification is sufficient for the person skilled in the art.

(vii) After receiving all the relevant documents the date of hearing was fixed on 27.06.2007. The opponents requested to adjourn the hearing for some next date which was accepted by the Controller and date was rescheduled to 09.07.2007. However, due to strong objection from the Applicants side, the date of hearing originally decided i.e. 27.06.2007 remained unaltered and the opponents also gave consent for the same. Both the parties were heard at length on 27.06.07.

(8) On the date of hearing the opponents filed an interlocutory petition in prescribed manner with the following main prayer :-

(i) The photocopy of complete specification was received by the opponent on or about March 20, 2007.

(ii) The opponent after studying the complete specification and analyzing the contents thereof and after conducting novelty and other investigations prepared and filed a representation by its letter dated April 5, 2007.

(iii) The reply statement of the applicant revealed that the applicant had amended the claims and retained only two claims. It is stated that the amended claims 1 and 2 are not allowable under the provisions of Section 57 read with Section 59 of the Act.

(iv) The claims as amended also suffers from the latches of lack of novelty and inventive step, obviousness, insufficiency of disclosure and not patentable.

(v) Had it known of the amendments opponents would have relied upon more relevant documents that would reinforced the case. The opponent would like to place on record documents entitled BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY, Fifth Edition and "Isoterism and molecular modification in Drug Design, Thornber et al.,. It is stated that the aforesaid document clearly states that cyanide and ethynyl groups are bioisoteric equivalents and therefore interchangeable.

(vi) The Ld. Controller is prayed to kindly consider the petition and be pleased to allow the opponent to file an amended representation.

The applicants opposed the allowance of filing of Interlocutory Petition and the discussions on Interlocutory Petition.

(9) In the interest of the justice, I would like to consider the prayer of the opponents contained in the said petition and shall discuss in next para to dispose off the petition along with the decision on present proceedings under section 25(1).

(10) The prayers made in Interlocutory Petition are being considered hereunder:

On scrutiny of the originally filed claims and finally amended claims it has been observed that both the amended claims are well within the preview of the original claims 1, 10 and 13. Moreover, the revised claims are more restrictive in scope as compared to the originally filed claims. Section 57 and 59 of the Patents Act do not prohibits such amendments. It is also clear from the examination reports issued by this office that such amendments have been carried out by the applicants to comply with the requirements of the law. The opponents are not allowed to file a fresh opposition under section 25(1).

However, the "Burger's Medicinal Chemistry And Drug Discovery" Vth edition Vol.1 © 1995 submitted by opposition may be taken on record to examine the strength of opposition. For this conclusion, I rely on decision:-

49 RPC 565

"In his decision the Controller disregarded the publications on the ground that they were inadmissible at this stage. The opponents appealed to the Law officer-Held, that the Comptroller is bound in the public interest to consider any alleged prior publication which may be brought to his notice after the hearing and before the issue of his decision."

Therefore, Interlocutory Petition filed on 27.06.2007 stands disposed off with the decision:

(i) Amended claims are well allowable under section 57 and 59 and are more restrictive than earlier set of claims (therefore opponents are not allowed to file any fresh pre-grant opposition.

(ii) The citation as submitted by opponents for consideration to evaluate the novelty and inventiveness of the invention claimed and under question is taken on record shall be considered.

(11) Now, I shall consider the grounds of opposition one by one in the light of finally allowed claims of application under question.

(i) ***Novelty*** :- The opponents have withdrawn this ground of opposition during hearing. However, if seen on merit basis, the opponents have relied upon the prior art citation EP 0566226, published on 20.10.93, EP 0520722 published on 30.12.92. No citations have been specified for product claims.

It is observed that none of the document is disclosing the same invention i.e. neither process for preparation of the compound finally claimed nor the product itself.

The document produced along with Interlocutory Petition i.e. “Burger’s Medicinal Chemistry and Drug Discovery” also failed to establish that the compound and process for preparation of that compound is not novel.

For the scrutiny of novelty of the present invention the principal laid down in Hills vs. Evan is relied upon, which is reproduced below:-

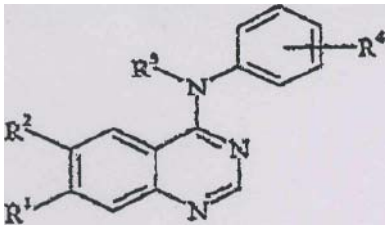
'The test whether the disclosure contained in a prior document is such as to invalidate a subsequent invention was stated by Lord Westbury LC in Hill Vs. Evans in the following terms:
'the antecedent statement must, in order to invalidate the subsequent patent, be such that a person of ordinary knowledge of the subject would at once perceive and understand and be able practically to apply the discovery without the necessity of making further experiments ..... the information ..... given by the prior publication must for the purpose of practical utility be equal to that given by the subsequent patent’.

On the basis of above quoted decision Claim 1 & 2 are novel. I hereby held that the invention claimed in both the claims 1 and 2 is novel.

(ii) ***Inventive step*** : The opponent argues that the compound of the present invention is an obvious derivative derived from 4-Anilinoquinazoline nucleus. All the compounds claimed by the applicant are the compounds actually originating from the 4- Anilinoquinazoline nucleus and such compounds have been covered by earlier patents EP 0566226 A1; EP 0602851 A1, EP 0635507 A1, EP 0635498 A1, EP 0520722 A1 published before the priority date of the present application.

The opponent further argues that combination of simple functional groups like alkoxy, alkyl, alkynyl, halo to already known basic nucleus or compound is obvious to a person of ordinary skill in the art.

The opponents argue that even the finally claimed compound in claim 1 can be derived easily from the Markush structure as shown below :-



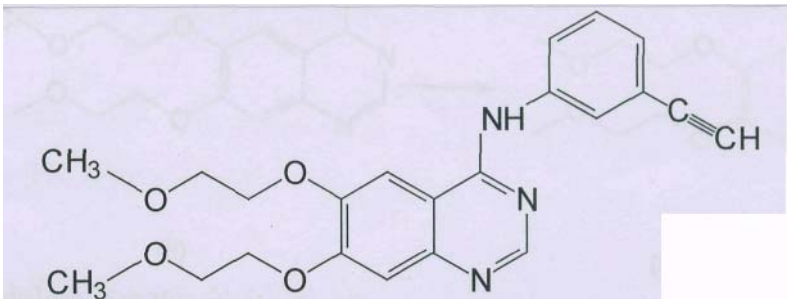
When R_1 = $CH_3OCH_2CH_2$-O (2-methoxy)

R_2 = $CH_3OCH_2CH_2$-O (2-methoxy ethoxy)

R_3 = H

R_4 = 3 Ethynyl (-C $\equiv$ CH)

One can arrive easily to the formula of claimed compound as given below :



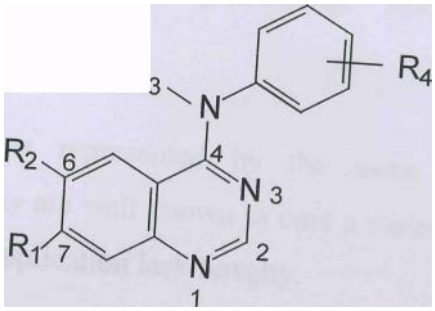
Therefore, claimed compound is obvious to a person skilled in the art.

The opponent has pointed out during hearing that prior art compounds that are structurally similar to the claimed compound render the compound obvious. The opponent referred the statements and description given in the documents 'Burger's Medicinal Chemistry and Drug Discovery' the document has been submitted along with Interlocutory Petition by opponent which stated to indicate that the cyanide and ethynyl groups are bio isosteric equivalents and therefore interchangeable. Therefore the compound as claimed in claim 1 is structurally similar. It is stated and mentioned in the same literature that structural. Similarity is often found in cases of homologus series of compounds, isomers, steroisomers, esters and corresponding free acids, and the like. Bioisosterism, which maybe of particular interest to the medicinal and pharmaceutical researcher, can also give rise to *prima facie* obviousness for both a compound and for methods of using such compounds (58). Bioisosterism recognizes that substitution of an atom or group of atoms having similar size, shape, and electron density generally provides compounds having similar biological activity.

The opponents also referred the Chapter 19 "Analog Design" of the same document. Page-785, where the definition of Bioisosteres has been given, page 786 – where bioisosteric groups and ring equivalent have been mentioned within a particular indication to –N=, -CH=, -P=, -AS= groups. The opponents have also pointed out page 3148 of chemical Review 1996 Vol. 96, No.8, where Grimm's Hyrdride Displacement law has been pinpointed to be operative between N and CH.

The Applicant in their counter states that the compound as finally claimed is not obvious in view of the prior arts cited by the opponents.

The Applicant argues that the opponent has created their own chemical formula (as mentioned below) to establish that the claimed compound is a obvious derivation of said formula which is a actually not found in any of the prior



citation.

Applicant further states that their claimed compound has an “ethynl group” present at methane position of phenyl group at a very specific position namely position 3-i.e. metha position. None of the prior art as indicated by opponents discloses presence of ethynyl group, particularly substituted at metha position of phenyl ring. This group and its position make the present compound inventive over the prior art documents. Therefore in absence of no prior art teaching presence of Alkynl group at Metha position of phenyl moiety a person skilled in the art would not arrive at the invention in an obvious manner.

The Applicant states by the above said substitution to form a new compound for which no body would be able to predict such a potent effects as inhibitor of the EFG receptors for the treatment of NSCLC (non small cell wing cancer). Therefore such a substitution can not be said an obvious modification.

The applicant has further stated that the compound has been proven for Drug’s efficacy on NSCLC and pancreatic cancers and this is a well known fact now a days.

This according to applicant, a person skilled in the art would not evolve the invented compound by simply substituting one functional group with another and could not have predicted the surprising effects of the claimed compound to provide an active molecule for treating NSCLC and Pancreatic Cancer. Therefore claims 1 and 2 are the non-obvious and inventive claims.

Regarding non-obviousness of the process claim the applicant states that A product obtained by a process for preparing the novel compound falls with a single inventive concept and are allowed universally.

In view of all the above arguments, discussion and scrutiny of the prior art citation no. EP 0566226 A1, 0602851 A1, 0635507 A1, 0635498 A, scrutiny of the Abstracts of the Book "Burger's Medicinal Chemistry and Drug Discovery V^{th} edition, and all the circumstances of this case. I am of the conclusion that opponents probably failed to properly evaluate the strength of the invention. Sometimes the modification in the prior art technologies which appear to be minor may bring great revolutions in the world which could never be predicted by the society of intellectuals. A substitution of group alkynl at metha position of phenyl moiety of known basic compound [i.e. (substituted phenyl amino) quinazolines derivative] has brought revolution in the treatment of NSCLC and Pancreatic Cancers and proved its efficacy as compared to the drugs available in the prior art. The Journal of clinical oncology volume 25 No.15, May, 2007, Volume 24, No.24, August, 2006 may be referred to look into all the facts. The compound appears to be much more effective as compared to the compounds for the similar purpose. None of the prior art citations, therefore are able to establish any motivational factors to the person skilled in the art by looking into the prior

art citations and also their appears no possibility of prediction of such a great improvement in the properties of the invented new derivative compounds. The same appears to me for the allegation of opponents about structural similarities of the now derivative compound. Such a structural similarity as deduced by the opponent for a compound having great medicine value may not be accepted to establish the now derivative as obvious.

Therefore it is hereby held that the product as claimed in claim 1 and process as claimed in claim 2 both are inventive and non-obvious.

Moreover, The Patent Office, of various advanced countries has examined this invention for novelty and invention is found to have presence of inventiveness and novelty in the invention. These countries have issued the Patent on this invention. Form-3 filed in Patent Office discloses this fact.

(iii) ***Insufficient disclosure***:

The opponent states that for the compound of EX-20 XRD data has not been given. This amounts to insufficiency of disclosure in view of the fact that polymorphic version of the same Drug substance have been subsequently disclosed in US 6900221 filed on 11.11.99.

Opponent further states that it is also not clear to which polymorphic class the preferred compound viz 6, 7 – Bis (2methoxy ethoxy)-quinanazoline –4yl-(3-ethynyl phenyl) amino hydrochloride III of the current Patent application belongs. It is very pertinent and relevant to have the details of the current form for the product claimed in the current application.

Applicant strongly objected to the above said allegations of the opponents. They stated that EX-20 has given all the required information for a person skilled

in the art to understand the invention. Not providing of XRPD spectra and IR spectra does not prevent any person skilled in the art to perfectly reproduce the invention. Regarding kind of polymorphic form of the compound of EX-20 applicant states that the object of the invention was to provide potent EGFR inhibitor and not to provide polymorphic of the compound of the present invention and this was achieved by providing following compound: (6,7-bis-(2-mehtoxy ethoxy)-quinazoline-4-yl-(3-ethyl-phenyl) amino, hydrochloride which is an active EGFR inhibitor.

All the compounds have been tested including above said compound of (EX-20) for efficacy as EGFR receptor and they all showed promising inhibition value.

Therefore applicants strongly believe that invention has been sufficiently disclosed.

After considering the above said views of the both the parties and considering all the points submitted during the hearing, it appears to me that opponents have not properly supported this ground or in other words they could not establish this ground properly. Whatever presently appears from statements, claims and description of the invention in specification the applicant have described everything about the invention sufficiently so as to be reproducable for a person skilled in the art.

Therefore opponent cannot succeed on this ground.

(iv) ***Section 3(d):***

The opponents during the hearing raised the issue that the present compounds fall under section 3(d) of the Indian Patents Act as the claimed compounds are obvious variants of prior art compounds and do not significantly differ in

therapeutic efficacy over the compounds of prior art: This issue was not taken in the representation. The applicants submit that the providing of efficacy data at filing was not possible. However, the same has been given as and when asked by Controller. The data regarding survival rate increase has been significant as indicated in the Journal The Oncologist, Feb 5th 2007. In view of the fact that the opponents have not substantiated and elaborated this ground of objection. And further once the invention has been found inventive the invention can not be Patentable under section 3(d) of the Patents Act. Therefore, I held that the invention can not be held non-patentable under section 3(d) of the Patents Act, 1970.

(v) ***Pre-grant/Post grant opposition:***

The applicant has agitated the issue of considering this proceeding only under post grant opposition if filed in prescribed manner because of the fact that this application was found in order for grant on 23.2.07 and whatever opposition as pre-grant opposition has been filed due to official delay in granting a letters patent to the applicant quoted various section of Patent Law to justify that the order as "In order for grant" by the Controller is equivalent to grant of patent and thereafter no pre-grant opposition should be allowed and letters patent should be issued.

I am of the conclusion that section 43 clearly put a distinction between "a patent has been found to be "in order for grant of patent" and the "grant of patent". The time gap between these two activities is actually allowed by the law to complete the official formalities.

Section 25(1) clearly defines the time limit for opponents to file a pre-grant opposition upto grant of a patent. In this case the patent could not be granted up to 10.04.07 therefore the opposition has been taken u/s 25(1) instead of section 25(2).

Therefore as discussed above, I hereby decide that:

(1) The present invention is novel and inventive over the prior art cited and including the document filed along with Interlocutory Petition.

(2) The description of the invention is sufficient in accordance with section 10(4).

(3) Interlocutory petition filed on 27.6.07 stand disposed off as discussed in para 8 to 10.

(4) The opposition has been decided as pre-grant opposition U/S 25(1).

(5) The invention cannot be held un-patentable U/S 3 (d) of the Patents Act 1970).

Opponents if still aggrieved may proceed for opposition under section 25(2). The Patent is hereby granted. No order for cost. In view of the Applicant's concern about delay in issue of patent certificate the concerned section is directed to issue Patent Certificate immediately.

Dated: 4th July, 2007

(N.R.MEENA)
ASSISTANT CONTROLLER OF PATENTS AND DESIGNS