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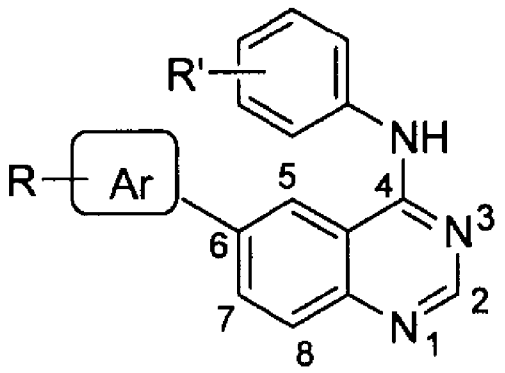

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(57) Abstract: The present invention relates to 6-aryl-4-phenylamino quinazolines of formula I wherein, R and R′ are as herein described. The present invention particularly relates to synthesis and anticancer and phoshpoinositide-3-kinase-α (PI3K-α) inhibitory activity. In addition, the invention relates to methods of using compounds for treating or preventing various cancers such as pancreatic, prostate, breast and melanoma.

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"6-ARYL-4-PHENYLAMINO-QUINAZOLINE ANALOGS AS PHOSPHOINOSITIDE-3-KINASE INHIBITORS"

FIELD OF THE INVENTION

The present invention relates to 6-aryl-4-phenylamino quinazolines. The present invention particularly relates to synthesis, anticancer and phosphoinositide-3-kinase inhibititory activity of 6-aryl-4-phenylamino quinazoline compounds. More particularly the present invention relates to methods for the treatment of cancer diseases, including those caused by kinase-mediated proliferation of tumor cells. Compounds of the invention can be used for prevention or in the treatment of cancer diseases, such as pancreatic, breast, prostate and melanoma cancers.

BACKGROUND OF THE INVENTION

Cancer is an uncontrolled growth and spread of cells that may affect almost any tissue of the body. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected. The approach to the discovery of new anticancer drugs has recently evolved from a reliance on empiric cell-based screening for anti-proliferative effects to a more mechanistically based approach that targets the specific molecular lesions thought to be responsible for the development and maintenance of the malignant phenotype in various forms of cancer. Through this approach, the kinase inhibitors have emerged as a new class of anticancer drugs that are capable of directly interacting with the catalytic site of the target enzyme and thereby inhibiting kinase function or blocking kinase signaling. In 1994, Parke-Davis scientists reported the first generation of very potent kinase inhibitor with manifold selectivity against other kinases (Fry, D.V. et al., *Science* **1994**, *265*, 1093). This discovery spurred the development of projects throughout the pharmaceutical industry; and as of now 18 kinase inhibitors have been approved by FDA for various diseases, and more than 500 candidates are in active clinical development.

Phosphoinositide 3-kinases (PI3Ks) constitute a family of lipid kinases involved in the regulation of a network of signal transduction pathways that control a range of cellular processes (Ihle, N.T. and Powis, P. *Mol. Cancer Ther.* **2009**, *8*, 1 ; Vivanco, I. and Sawyers, C.L. *Nature Rev. Cancer* **2002**, *2*, 489). The PI3K signaling plays a central role in cellular processes critical for cancer progression, metabolism, growth, survival and motility. The

PI3K family of enzymes is comprised of 15 lipid kinases with distinct substrate specificities, expression patterns, and modes of regulation. In particular, PI3K-α has emerged as an attractive target for cancer therapeutics. Significant efforts have been made to discover inhibitors of the PI3K pathway to treat cancers and several candidates have advanced to clinical studies such as XL-765 and XL-147 (Exelixis), which are class I PI3K inhibitors that have entered Phase I clinical studies for advanced solid tumors. Other PI3K inhibitors in clinical studies include BEZ-235 and BKM-120 (Phase II, Novartis) and GSK-1059615 (Phase I, GSK) for advanced solid tumors. AstraZeneca's AZD-6482, which is a PI3K-β inhibitor, has completed Phase I trials for the treatment of thrombosis. A quinazolinone-based isoform-specific PI3K-δ inhibitor CAL-101 (GS-1101, Gilead Sciences) is in Phase III and IC-87114 (Calistoga) has entered Phase I clinical trial. Other PI3K inhibitors in clinical trials include D106669 and D87503 (Phase I, Aeterna Zentaris), GDC-0941 (Phase I, Genentech) and PKI-587 (Phase I, Pfizer). In addition, several other PI3K inhibitors are in early stages of clinical trials.

Despite of the fact that large number of kinase inhbiitors have received FDA-approval, the target selectivity remains a formidable challenge in drug development because almost all approved kinase inhibitor drugs works by competing with ATP for the ATP binding site of the enzyme. Hence, there is a great need for next-generation kinase inhibitors that work through alternative mechanisms such as allosteric inhibition. While recently approved kinase inhibitor drugs offer benefits for cancer treatment, further advances are required to effect tumor selective cell killing, avoid off-target related toxicities and improve survival rates (Bharate, S.B. *et al.*, *Chem. Rev.* **2013**, *113*, 6761). Amongst the four isoforms of phosphoinositide 3-kinases, particularly the α-isoform has been found to be activated by mutation in several cancers; and therefore discovery of α-isoform selective inhibitor is highly important. BEZ-235 (Novartis molecule) is a pan-PI3K inhibitor inhibiting all four isoforms with IC_{50} values of 4, 76, 7 and 5 nM respectively; thus showing very poor selectivity towards α-isoform compared with β, γ and δ isoforms (19, 17.5 and 1.25 fold selectivity).

OBJECTIVES OF THE INVENTION

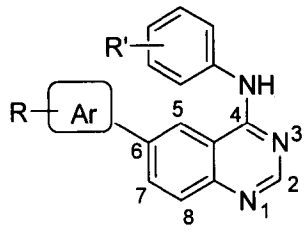
The main object of the present invention is to provide 6-aryl-4-phenylamino quinazolines.

Another object of the present invention is to provide novel anticancer compounds for the treatment of various types of cancers, such as pancreatic, breast, prostate and melanoma cancer.

One more objective of the invention is to provide a process for preparation of 6-aryl-4-phenylamino quinazolines.

SUMMARY OF THE INVENTION

Accordingly, the present invention relates to a compound of formula I,



I

wherein, R is selected from the group comprising of hydrogen, alkyl, nitro, halogens (fluoro, chloro, bromo and iodo), formyl, allyl, vinyl, benzyl, acetyl, hydroxy, phenyl, substituted phenyl, fused aromatics;

R′ is selected from the group consisting of hydrogen, cyanomethyl, or alkyls.

Ar is selected from the group comprising of aryl or heteroaryl, which is unsubstituted or substituted with an alkyl, nitro, halogens, formyl, allyl, vinyl, benzyl, acetyl, hydroxy, phenyl, substituted phenyl, fused aromatics.

In an embodiment of the invention wherein, aryl is selected from the group consisting of phenyl, biphenyl which is unsubstituted or substituted with different R groups, which is selected from the group comprising of alkyl, nitro, halogens (fluoro, chloro, bromo and iodo), formyl, allyl, vinyl, benzyl, acetyl, hydroxy, phenyl, substituted phenyl, fused aromatics.

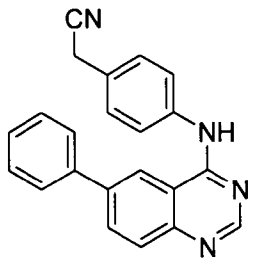
In another embodiment of the invention wherein Alkyl group is selected from the group consisting of (C1-C6)-alkyl, (C1-C4)-haloalkyl, (C1-C4)-alkoxy, (C1-C4)-haloalkoxy; or is (C5-C8)-cycloalkyl, (C5-C8)-cycloalkenyl, (C6-C10)-bicycloalkyl, (C6-C10)-bicycloalkenyl.

In yet another embodiment of the invention wherein, substituted phenyl is selected from the group consisting of alkylphenyls, alkoxyphenyls.

In one more embodiment of the invention wherein, fused aromatics is selected from the group consisting of naphthalene, 2,3-dihydrobenzo[b][1,4]dioxin, benzo[d][1,3]dioxol, benzofuran, benzo[b]thiophene, dibenzo(b,d)furan, dibenzo(b,d)thiophene, 1H-indole, quinoline, isoquinoline.

In still another embodiment of the invention wherein, heteroaryl is selected from the group consisting of pyridine, quinoline, isoquinoline, 2,3-dihydrobenzo[b][1,4]dioxin, benzo[d][1,3]dioxol, benzofuran, benzo[b]thiophene, dibenzo(b,d)furan, dibenzo(b,d)thiophene, 1H-indole.

In a further embodiment of the invention wherein, the structural formulae of the said compounds comprising:



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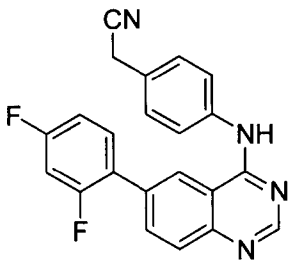

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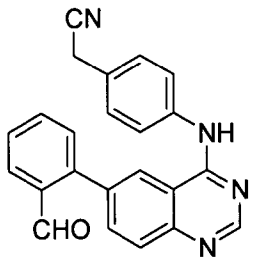

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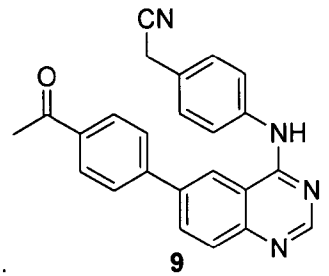

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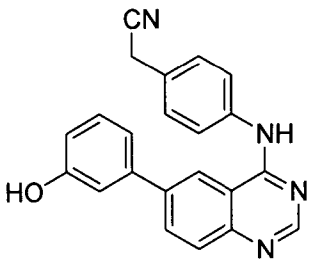

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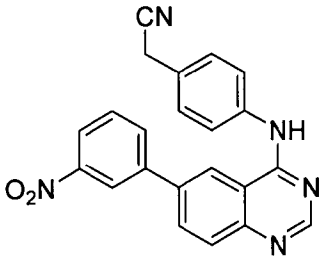

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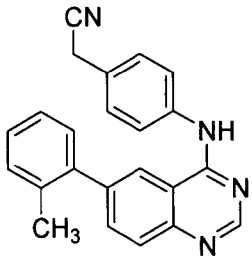

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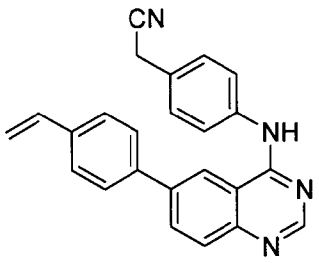

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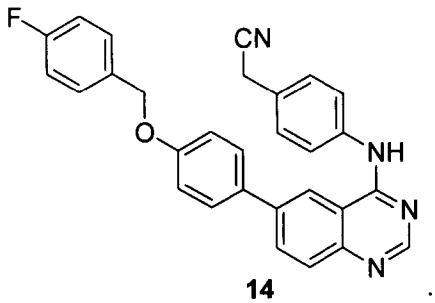
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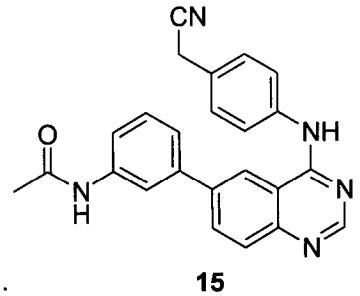
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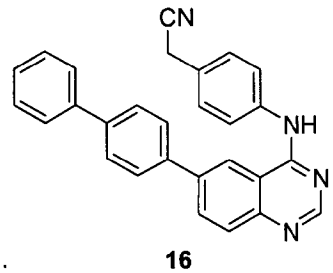
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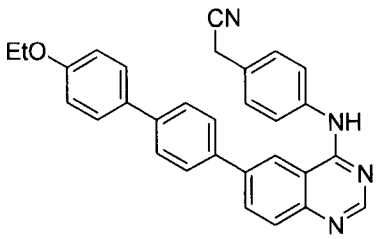
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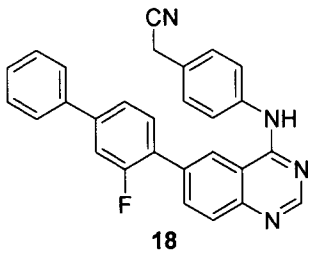
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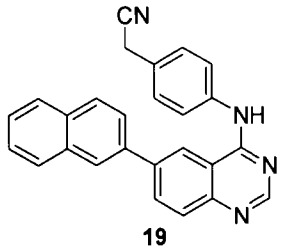
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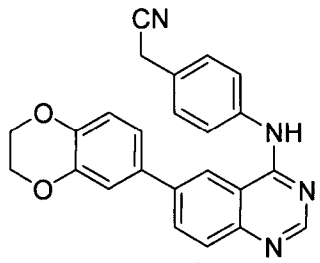
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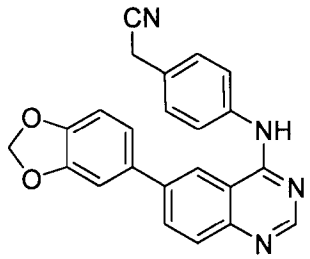
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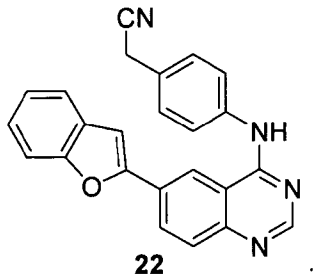
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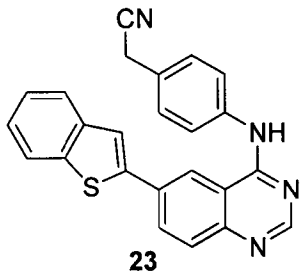
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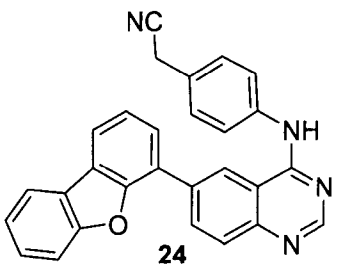
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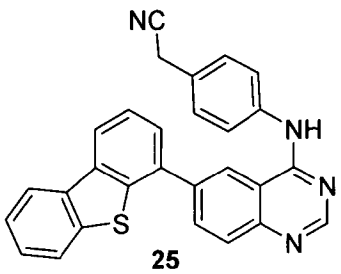
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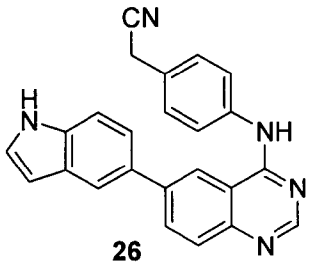
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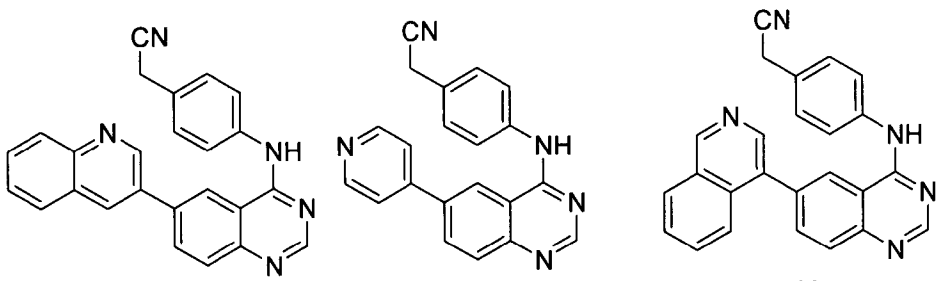


27 ; **28** ; and **29**

In still one more embodiment of the invention wherein, the compounds are useful for the treatment of cancer.

In an embodiment of the invention wherein, the compounds are phosphoinositide-3-kinase inhibitors.

In yet one more embodiment of the invention wherein the compounds are active against cancer cell lines selected from a group consisting of HL-60, A375, MCF-7, Panc-1, PC-3.

In an embodiment of the invention wherein the compounds are phosphoinositide-3-α kinase inhibitors upto about 70% at 0.5 μM concentration.

Accordingly, the present invention provides a process for preparation of the compounds of general formula I, wherein the process steps comprising:

a) reacting anthralinic acid (**1**) with bromine in glacial acetic acid at a temperature in the range of 10-25 °C for the time period of ranging between 15-30 min, followed by diluting with dilute HCl to obtain monobromo anthranilic acid (**2**);

b) adding formamide to monobromo anthranilic acid obtained in step (a) followed by reflux at a temperature ranging between 100-150 °C for a time period ranging between 4-10 h to obtain compound **3**;

c) adding $POCl_3$ to the solution of compound **3** as obtained in step (b) followed by reflux at a temperature ranging between 100-150 °C for a time period ranging between 4-10 h to obtain compound **4**;

d) adding 4-amino benzylcyanide to the solution of compound 4 as obtained in step (c) forming a mixture which is dissolved in isopropanol followed by stirring for a time period of ranging between 2-6 h under reflux at a temperature ranging between 80-100 °C to obtain compound **5**;

e) reacting aryl boronic acid in suitable solvent with compound **5** as obtained in step (d)

followed by addition of $Pd(PPh_3)_4$ followed by stirring of the resultant mixture for the time period ranging between 12-24 h at a temperature ranging between 80-100 °C to yield compound of formula **I**.

In an embodiment of the invention wherein the aryl boronic acid used in step (e) is selected form the group consisting of substituted phenyls, substituted biphenyls, substituted naphthyls, substituted heteroaryls.

In a further embodiment of the invention wherein, the solvent used in step (e) is selected from toluene or dioxane.

In the present invention, we have identified 6-aryl-4-phenylamino quinazolines as PI3K-α isoform selective inhibitors showing selectivity fold up to >133, 56 and >49.7 versus β, γ and δ isoforms, respectively. Furthermore, the 6-aryl-4-phenylamino quinazoline scaffold has never been reported in literature as PI3K-alpha inhibitor

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a diagram illustrating the chemical synthesis of the 6-aryl 4-phenylamino-quinazolines of the invention.

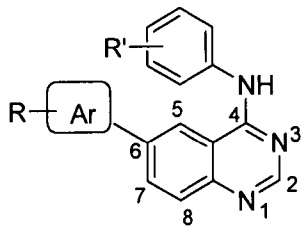
Synthetic scheme for preparation of 6-aryl-4-phenylamino-quinazoline analogs. Reagents and conditions: (a) Br_2 (1.2 equiv.), AcOH (10 mL), 10- 25 °C; followed by dil.HCl (20 mL), reflux, 85%; (b) NH_2CHO (4 equiv.), 150 °C, 6 h, 70% (c) $POCl_3$ (5 mL), reflux at 100 °C, 6 h, 92%; (d) 4-amino benzylcyanide (1.3 equiv), isopropanol (5 mL), reflux, 3 h, 82%; (e) $ArB(OH)_2$ (1.2 equiv.), $Pd(PPh_3)_4$ (0.05 equiv), 2 M K_2CO_3 solution (3 mL), dioxane (3 mL), reflux, 12 h, 43-92%.

Figure 2 is a diagram showing interactions of 6-aryl-4-phenylamino quinazoline **10** and **29** with the active site of phosphoinositide-3-kinase-α.

The 2D and 3D-representation of binding interactions of compounds **10** (A and C) and **29** (B and D) with PI3Kα. Red arrows and dotted line indicates sites of hydrogen bonding and solid green line indicates aromatic π-π interactions.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to 6-aryl-4-phenylamino quinazoline compounds of general formula I as promising anticancer agents.



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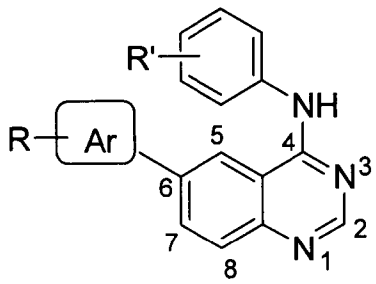
The present invention relates to novel compounds that shows promising anti-cancer activity against various cancer cell lines *viz.* Panc-1 (pancreatic cancer), MCF-7 (breast cancer), PC-3 (prostate cancer), HL-60 (leukemia) and A-375 (melanoma) and inhibition of phosphoinositide-3-kinase (PI3K-α) which is implicated in proliferation of tumor cells. The anticancer activity of 6-aryl-4-phenylamino quinazolines **10** (IC_{50} values: 36 μM for panc-1, 15 μM for MCF-7, 37 μM for PC-3, 24 μM for HL-60 and 28 μM for A375) and **29** (IC_{50} values: 9 μM for Panc-1, 12 μM for MCF-7, 9 μM for PC-3, 10 μM for HL-60 and 12 μM for A375) on various cancer cell lines is shown in Table 1 and 2. The compounds **10** and **29** showed promising inhibition of PI3K-α with IC_{50} values of 0.115 and 0.150 μM, showing excellent selectivity towards α-isoform *versus* other isoforms of PI3K. Simialrly, compound **26** displayed excellent selectivity towards α-isoform versus β- and δ-isoforms. Unlike the known structurally similar PI3K-α inhibitor NVP-BEZ-235, which inhibits all isoforms of PI3K at low nanomolar concentrations, the compound **29** exhibited greater selectivity towards PI3K-α versus other isoforms. In particular, the compound **29** did not inhibit (0% inhibition) PI3K-β up to 20 μM. The isoform selectivity of compounds towards PI3K-α is provided in the Table 2. The promising activity of 6-aryl-4-phenylamino quinazolines **10, 26** and **29** against PI3K-α clearly indicates their potential to develop as anticancer agents. The complimentary fit of compounds **10** and **29** into the active site of PI3K-α is shown by the key H-bonding and π-π interactions of these compounds with active site residues of enzyme are shown in **Figure 2**. The growth inhibitory properties of compounds of the invention against various cancer cell lines and their inhibitory activity against PI3K-α can therefore be used to treat or prevent diseases, disorders, conditions, or symptoms in a patient (e.g. human) that involve, directly, or indirectly, proliferation of cell growth or over-expression of PI3K-α kinase.

A class of 6-aryl-4-phenylamino quinazolines is presented and defined by structural formula I:



I

wherein, the position 6 may contain various substituted aryl rings; and phenylamino moiety located at position 4 may be substituted; wherein

Ar is aryl or heteroaryl, which is unsubstituted or substituted with an alkyl, nitro, halogens, formyl, allyl, vinyl, benzyl, acetyl, hydroxy, phenyl, substituted phenyl, fused aromatics.

wherein, aryl is selected from phenyl, biphenyl which is unsubstituted or substituted with different R groups.

Alkyl group is selected from (C1-C6)-alkyl, (C1-C4)-haloalkyl, (C1-C4)-alkoxy, (C1-C4)-haloalkoxy; or is (C5-C8)-cycloalkyl, (C5-C8)-cycloalkenyl, (C6-C10)-bicycloalkyl, (C6-C10)-bicycloalkenyl.

Substituted phenyl is selected from alkylphenyls, alkoxyphenyls.

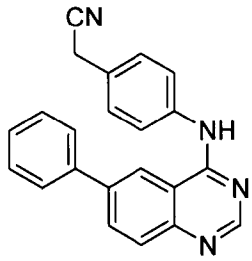
Fused aromatics is selected from naphthalene, 2,3-dihydrobenzo[b][1,4]dioxin, benzo[d][1,3]dioxol, benzofuran, benzo[b]thiophene, dibenzo(b,d)furan, dibenzo(b,d)thiophene, 1H-indole, quinoline, isoquinoline.

Heteroaryl is selected from pyridine, quinoline, isoquinoline, 2,3-dihydrobenzo[b][1,4]dioxin, benzo[d][1,3]dioxol, benzofuran, benzo[b]thiophene, dibenzo(b,d)furan, dibenzo(b,d)thiophene, 1H-indole.

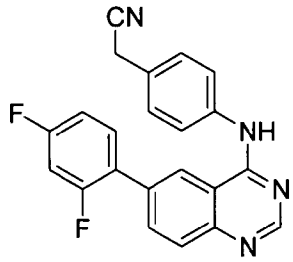
R is selected from hydrogen, alkyl, nitro, halogens, formyl, allyl, vinyl, benzyl, acetyl, hydroxy, phenyl, substituted phenyl, fused aromatics.

R′ is selected from the group consisting of hydrogen, cyanomethyl, or any carbon atom which may be optionally substituted.

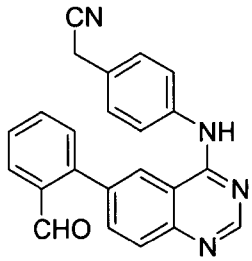
Compounds of the invention derived from Formula I include, but are not limited to, the following chemical structures:



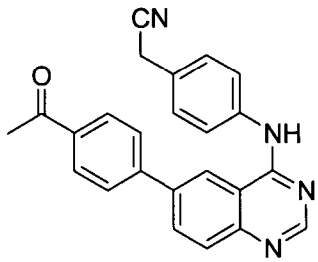
6-phenyl-4-(4-cyanomethyl)phenylamino quinazoline (**6**);



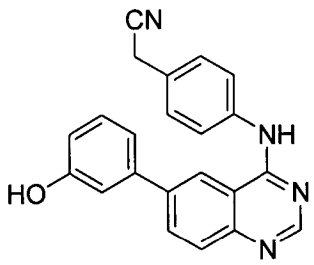
6-(2,4-difluorophenyl)-4-(4-cyanomethyl)phenylamino quinazoline (**7**);



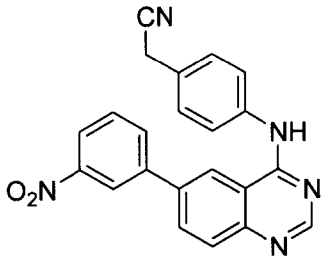
6-(2-formylphenyl)-4-(4-cyanomethyl)phenylamino quinazoline (**8**);



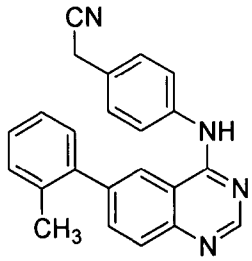
6-(4-acetylphenyl)-4-(4-cyanomethyl)phenylamino quinazoline (**9**);



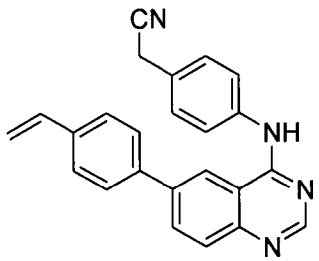
6-(3-hydroxyphenyl)-4-(4-cyanomethyl)phenylamino quinazoline (**10**);



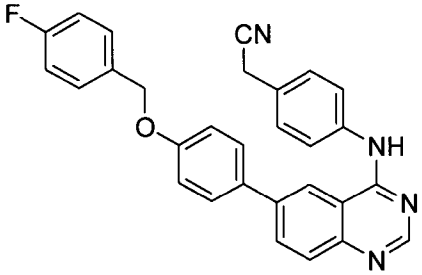
6-(3-nitrophenyl)-4-(4-cyanomethyl)phenylamino quinazoline (**11**);



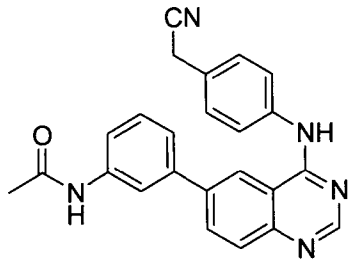
6-(2-methylphenyl)-4-(4-cyanomethyl)phenylamino quinazoline (**12**);



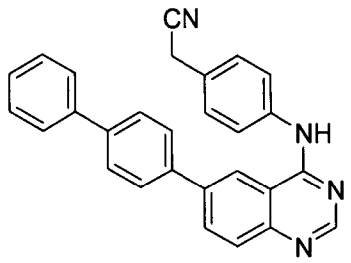
6-(4-vinylphenyl)-4-(4-cyanomethyl)phenylamino quinazoline (**13**);



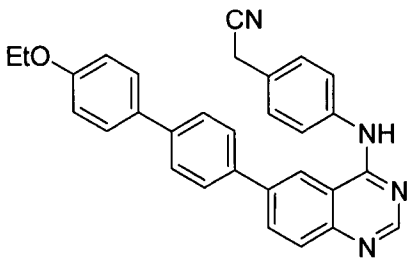
6-(4-fluorobenzyloxyphen-4-yl)-4-(4-cyanomethyl)phenylamino quinazoline (**14**);



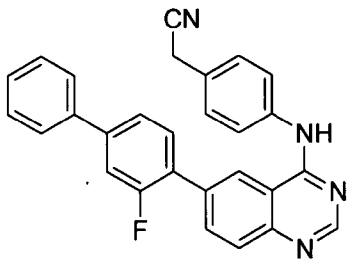
6-(3-acetylaminophenyl)-4-(4-cyanomethyl)phenylamino quinazoline (**15**);



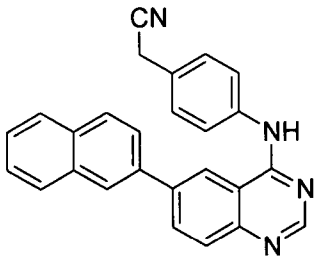
6-(4-phenylphenyl)-4-(4-cyanomethyl)phenylamino-quinazoline (**16**);



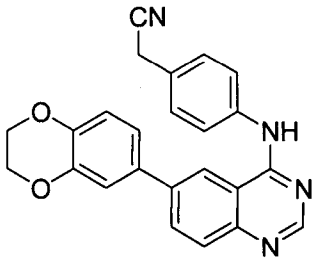
6-(4-(4-ethoxyphenyl)phenyl)-4-(4-cyanomethyl)phenylamino-quinazoline (**17**);



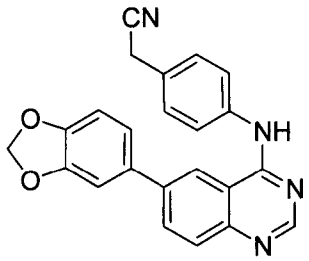
6-(4-phenyl-2-fluorophenyl)-4-(4-cyanomethyl)phenylamino-quinazoline (**18**);



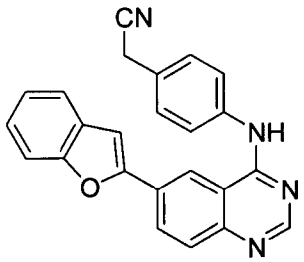
6-(naphthalen-2-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (**19**);



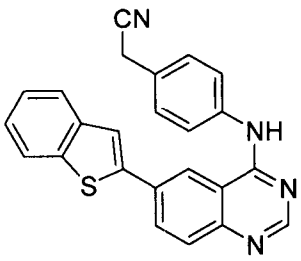
6-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (**20**);



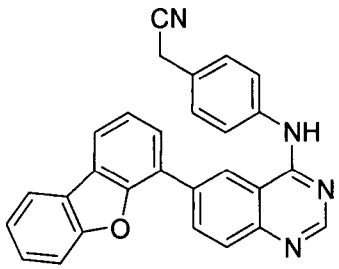
6-(benzo[d][1,3]dioxol-5-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (**21**);



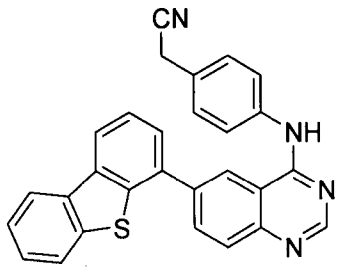
6-(benzofuran-2-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (**22**);



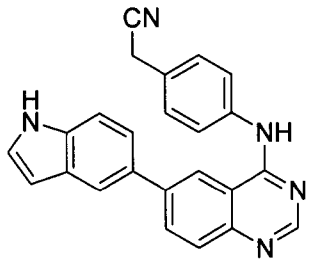
6-(benzo[b]thiophen-2-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (**23**);



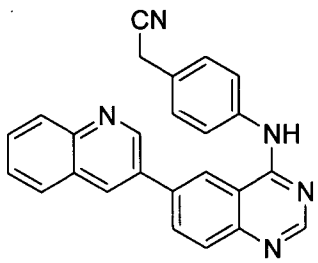
6-(dibenzo(b,d)furan-4-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (**24**);



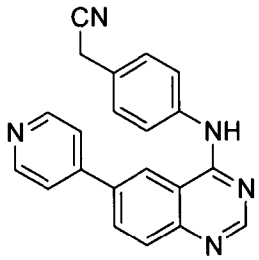
6-(dibenzo(b,d)thiophene-4-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (**25**);



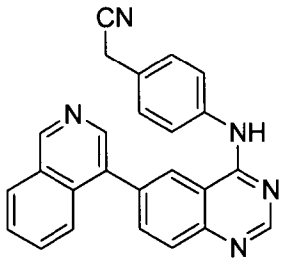
6-(1H-indol-5-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (**26**);



6-(quinolin-3-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (**27**);



6-(pyridin-4-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (**28**); and



6-(isoquinolin-4-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (**29**)

As used herein, the terms below have the meanings indicated.

The term "alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, optionally substituted wherein the term alkyl is as defined below. Examples of alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

The term "alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical optionally substituted containing from 1 to 20 and including 20, preferably 1 to 10, and more preferably 1 to 6, carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, nonyl and the like.

The term "alkylamino" as used herein, alone or in combination, refers to an alkyl group optionally substituted attached to the parent molecular moiety through an amino group. Alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

The term "amino," as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently selected from the group consisting of hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted.

The term "aryl" as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused optionally substituted with at least one halogen, an alkyl containing from 1 to 3 carbon atoms, an alkoxyl, an aryl radical, a nitro function, a polyether radical, a heteroaryl radical, a benzoyl radical, an alkyl ester group, a carboxylic acid, a hydroxyl optionally protected with an acetyl or benzoyl group, or an amino function optionally protected with an acetyl or benzoyl group or optionally substituted with at least one alkyl containing from 1 to 12 carbon atoms.

Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

The term "optionally substituted" means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, arylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylsulfinyl, arylsulfonyl, arylthio, sulfonate, sulfonic acid, trisubstitutedsilyl, N_3, SH, SCH_3, $C(O)CH_3$, $CO2CH_3$, CO_2H, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of

optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

The term "cancer" as used herein refers to any disease, disorder, condition, or symptom characterized by over-expression of kinases. Cancer diseases include pancreatic, breast, prostate and melanoma cancer.

As used herein, reference to "treatment" of a patient is intended to include prophylaxis. The term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, rabbits, and rodents (e.g., rats, mice, and guinea pigs).

Cancer diseases. One or more compounds of the invention can be used to treat a patient (e.g. a human) at a risk of developing or already suffering from cancer disease, such as prostate, breast, pancreatic and melanoma cancer.

Methods of prevention and treatment. The compounds of the invention can be used to treat a patient (e.g. a human) that suffers from or is at a risk of suffering from a disease, disorder, condition, or symptom described herein. The compounds of the invention can be used alone or in combination with other agents and compounds in methods of treating or preventing e.g. a cancer disease (e.g. prostate cancer). Each such treatment described above includes the step of administering to a patient in need thereof a therapeutically effective amount of the compound of the invention described herein to delay, reduce or prevent such a disease, disorder, condition, or symptom. The compounds of the invention presented herein may be also useful in reducing growth inhibition of tumors.

It is understood that the foregoing examples are merely illustrative of the present invention. Certain modifications of the articles and/or methods employed may be made and still achieve the objectives of the invention. Such modifications are contemplated as within the scope of the claimed invention.

EXAMPLES

Example 1. Synthesis of 2-amino-5-bromobenzoic acid (2): Anthranilic acid (**1**, 1 g, 7.3 mmol) was dissolved in glacial acetic acid (10 mL) and cooled below 15 °C. Then bromine (0.45 mL, 8.76 mmol) was added dropwise to the reaction mixture. The reaction mixture was converted to a thick mass of white glistening crystals consisting of the hydrobromides of the mono and dibromo anthranilic acids. The product was filtered off, washed with benzene and dried. It was then refluxed with dilute hydrochloric acid (20 mL) and filtered while hot under

suction. The insoluble residue was extracted twice with boiling water (500 ml). The filtrate upon cooling yielded precipitate of the required monobromo anthranilic acid **2**. Yield: 55%; light brown solid; m. p. 209-211 °C; ^{1}H NMR (CD_3OD, 500 MHz): δ 7.87 (t, 1H, *J* = 5.2 Hz), 7.31-7.28 (m, 1H), 6.67 (dd, 1H, *J* = 5.0 Hz); ESI-MS: *m/z* 215 $[M+H]^+$.

Example 2. Synthesis of 6-bromoquinazolin-4-ol (3): To the solution of 2-amino-5-bromo-benzoic acid (**2**, 1 g, 4.63 mmol), formamide (0.74 mL, 18.52 mmol) was added and the resultant mixture was allowed to reflux at 150 °C for 6 h. After completion of reaction, the reaction mixture was filtered through Whatman filter paper and dried under vacuum to get the desired product **3** as a white solid. Yield: 70%, white solid, m. p. 209-211 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.20 (d, 1H, *J* = 2.3 Hz), 8.17 (d, 1H, *J* = 6.1 Hz), 7.98-7.95 (m, 1H), 7.63 (d, 1H, *J* = 8.7 Hz); HRMS: *m/z* 224.9633 calcd for $C_8H_6BrN_2O+H^+$ (224.9664).

Example 3. Synthesis of 6-bromo-4-chloroquinazoline (4): To the solution of 6-bromoquinazolin-4-ol (**3**, 1 g, 4.44 mmol) in phosphoryl chloride (5 mL) was refluxed for 6 h at 120 °C. The mixture was cooled to room temperature and poured into ice-water containing sodium bicarbonate to quench excess phosphoryl chloride. The mixture was extracted with dichloromethane (3 x 100 ml) and the solvent was evaporated to get the 6-bromo-4-chloroquinazoline **4** as a light yellow solid. Yield: 92%, light yellow solid, m. p. 273-275 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.07 (s, 1H), 8.44 (d, 1H, *J* = 2.0 Hz), 8.04 (d, 1H, *J* = 2.0 Hz), 7.96 (d, 1H, *J* = 8.9 Hz); HRMS: *m/z* 224.9633 calcd for $C_8H_6BrN_2O + H^+$ (224.9664).

Example 4. Synthesis of 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline (5): The mixture of 6-bromo-4-chloroquinazoline (**4**, 0.2 g, 0.83 mmol.) and 4-amino benzyl cyanide (0.142 g, 1.07 mmol) was dissolved in isopropanol (5 mL) and allowed to stir for 3 h under reflux at 80 °C. After completion of reaction, the mixture was filtered through Whatman filter paper and dried under vacuum to get the desired product **5** as brown solid. Yield: 82%; brown solid; mp. 275-277 °C, ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.20 (s, 1H), 8.93 (s, 1H), 8.30-8.23 (m, 1H), 7.96-7.89 (m, 1H), 7.83-7.76 (m, 2H), 7.48 (d, 2H, *J* = 7.2 Hz), 4.10 (s, 2H).^{13}C NMR (DMSO-d_6, 100 MHz): δ 158.71, 151.16, 138.71, 138.18, 135.91, 129.56, 128.43, 127.17, 124.96, 122.15, 120.86, 119.05, 115.01, 21.98. HRMS: m/z 339.0243 calcd for $C_{16}H_{12}BrN_4+ H^+$ (339.0245).

Example 5. Synthesis of 6-phenyl-4-(4-cyanomethyl)phenylamino quinazoline (6) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and phenylboronic acid: The solution of 2 M K_2CO_3 (3 ml) in dioxane (3 ml) in round bottom flask was purged with nitrogen

gas for 5 min at 25 °C. To this solution, 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline (**5**, 0.1 g, 1 mmol.) and phenylboronic acid (1.2 mmol) were added followed by addition of $Pd(PPh_3)_4$ (0.05 equiv.). The resulting reaction mixture was then stirred at 90 °C for 12 h. After completion of reaction, product was extracted with ethyl acetate (2 x 50 ml) and the combined organic layers were dried over anhydrous sodium sulphate to get crude product **6**, which was purified by silica gel column chromatography. Yield: 81%, brick red solid, m.p. 253-255 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.01 (s, 1H), 8.85 (s, 1H), 8.60 (s, 1H), 8.21 (d, 1H, *J* = 8.5 Hz), 7.91-7.87 (m, 4H), 7.62-7.58 (m, 3H), 7.57-7.39 (m, 2H), 4.04 (s, 2H); IR (CHCl3): vmax 3400, 2924, 2853, 1609, 1437, 1192, 1119 cm-1; HRMS: *m/z* 337.1452 calcd for $C_{22}H_{17}N_4 + H^+$ (337.1453).

Example 6. Synthesis of 6-(2,4-difluorophenyl)-4-(4-cyanomethyl)phenylamino quinazoline (7) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 2,4-difluorophenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 45%; yellow solid; m. p. 186-188 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.74 (s, 1H), 8.15 (s, 1H), 7.98-7.92 (m, 1H), 7.80 (d, 2H, *J* = 8.8 Hz), 7.55-7.46 (m, 2H), 7.38 (d, 2H, *J* = 8.4 Hz), 7.06-6.97 (m, 2H), 3.78 (s, 2H). ^{13}C NMR (101 MHz, MeOD): δ 158.31, 154.55, 148.49, 138.13, 133.43, 132.12, 131.46, 128.40, 125.78, 123.13, 121.90, 117.86, 115.30, 111.76, 104.52, 104.26, 104.00, 22.72; IR ($CHCl_3$): ν_{max} 3391, 2955, 2923, 2854, 1606, 1574, 1532, 1515, 1495, 1424, 1401, 1269, 1142, 1101, 1020 cm^{-1}; HRMS: *m/z* 373.1258 calcd for $C_{22}H_{15}F_2N_4 + H^+$ (373.1265).

Example 7. Synthesis of 6-(2-formylphenyl)-4-(4-cyanomethyl)phenylamino quinazoline (8) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 2-formylphenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 67%; brick red solid; m. p. 177-179 °C; ^{1}H NMR ($CDCl_3$ + 1 drop of CD_3OD, 400 MHz): δ 9.99 (s, 1H), 8.80 (s, 1H), 8.32 (s, 1H), 8.12 (d, 1H, *J* = 1.6 Hz), 8.01-8.97 (t, 2H, *J* = 8.8 Hz), 7.84-7.76 (m, 3H), 7.71-7.62 (m, 1H), 7.56-7.46 (m, 2H), 7.43-7.39 (m, 1H), 7.36-7.30 (m, 1H), 3.74 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$ + 1 drop of CD_3OD): δ 192.32, 154.88, 148.58, 144.54, 136.48, 134.82, 134.00, 133.56, 131.95, 131.85, 131.14, 128.73, 128.60, 128.45, 128.42, 128.22, 127.45, 123.72, 123.41, 22.88; IR ($CHCl_3$): ν_{max} 3367, 2956, 2924, 2854, 2250, 1689, 1626, 1596, 1571, 1529, 1515, 1479, 1422, 1402, 1360, 1306, 1252, 1194, 1173, 1120, 1070, 1020 cm^{-1}; HRMS: m/z 365.1397 calcd for $C_{23}H_{17}N_4O + H^+$ (365.1402).

Example8. Synthesis of 6-(4-acetylphenyl)-4-(4-cyanomethyl)phenylamino quinazoline (9) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 4-acetylphenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 45%; pale yellow solid; m. p. 157-159 °C; ^{1}H NMR ($CDCl_3$ + 1 drop of CD_3OD, 400 MHz): δ 8.65 (d, 2H, *J* = 9.0 Hz), 8.13-8.11 (t, 3H, *J* = 1.6 Hz), 7.97-7.91 (m, 3H), 7.82 (d, 2H, *J* = 8.0 Hz), 7.42 (s, 1H), 7.42 (m, 3H), 3.84 (s, 2H), (m, 2H), 2.70 (s, 3H); ^{13}C NMR (126 MHz, DMSO): δ 197.59, 157.93, 154.87, 149.53, 143.38, 138.36, 136.63, 135.90, 132.05, 131.50, 131.42, 128.95, 128.80, 128.71, 128.26, 127.27, 126.57, 123.08, 121.20, 119.41, 115.33, 26.85, 21.90; IR ($CHCl_3$): v_{max} 3369, 2953, 2924, 2855, 2250, 1738, 1678, 1603, 1572, 1532, 1515, 1423, 1362, 1265, 1020 cm^{-1}; HRMS: m/z 379.1555 calcd for $C_{24}H_{19}N_4O$ + H^+ (379.1559).

Example 9. Synthesis of 6-(3-hydroxyphenyl)-4-(4-cyanomethyl)phenylamino quinazoline (10) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 3-hydroxyphenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 62%; pale yellow solid; m. p. 222-224 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.01 (s, 1H), 9.65 (s, 1H), 8.81 (d, 1H, *J* = 1.6 Hz), 8.59 (s, 1H), 8.14-8.11 (dd, 1H , *J* = 2.0 & 1.6 Hz), 7.90-7.84 (m, 2H), 7.65-7.55 (m, 4H), 7.41-7.26 (m, 2H), 6.87-6.85 (m, 1H), 4.06 (s, 2H); ^{13}C NMR (126 MHz, DMSO): δ 157.89, 154.35, 140.56, 138.49, 138.27, 132.04, 131.50, 131.42, 130.02, 128.79, 128.70, 128.21, 126.39, 122.97, 120.35, 119.41, 117.94, 115.28, 114.86, 114.02, 79.15, 21.89; IR ($CHCl_3$): v_{max} 3400, 3055, 2955, 2924, 2854, 1731, 1591, 1484, 1437, 1400, 1275, 1219, 1189, 1119, 1072 cm^{-1}; HRMS: m/z 353.1402 calcd for $C_{22}H_{17}N_4O$ + H^+ (353.1402).

Example 10. Synthesis of 6-(3-nitrophenyl)-4-(4-cyanomethyl)phenylamino quinazoline (11) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 3-nitrophenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 57%; pale yellow solid; m. p. 216-218 °C; ^{1}H NMR ($CDCl_3$ + 1 drop of CD_3OD, 400 MHz): δ 8.69 (d, 1H, *J* = 15.2 Hz), 8.28 (d, 1H, *J* = 8.0 Hz), 8.14-8.27 (t, 1H, *J* = 4.8 Hz), 7.97 (d, 1H, *J* = 8.4 Hz), 7.83 (d, 1H, *J* = 8.4 Hz), 7.75-7.71 (t, 1H, *J* = 8.0 Hz), 7.65-7.58 (m, 2H), 7.53-7.49 (m, 2H), 7.42-7.36 (m, 3H), 3.83 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.99, 154.97, 148.57, 140.80, 135.57, 133.66, 131.99, 131.79, 131.50, 131.40, 130.63, 128.78, 128.66, 128.26, 123.21, 122.59, 121.47, 121.36, 119.33, 21.92; IR ($CHCl_3$): v_{max} 3400, 2955, 2923, 2853, 1733, 1606, 1536, 1423, 1384, 1157, 1021 cm^{-1}; HRMS: m/z 382.1302 calcd for $C_{22}H_{16}N_5O_2$ + H^+ (382.1304).

Example 11. Synthesis of 6-(2-methylphenyl)-4-(4-cyanomethyl)phenylamino quinazoline (12) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 2-methylphenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 57%; orange solid; m. p. 173-175 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.83-8.81 (t, 1H, *J* = 2.4 Hz), 8.03-8.00 (t, 1H, *J* = 9.6 Hz), 7.98-7.96 (t, 4H, *J* = 6.0 Hz), 7.55 (s, 1H), 7.43-7.27 (m, 6H), 3.78 (d, 2H, *J* = 6.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.63, 154.73, 148.95, 140.83, 140.54, 138.33, 135.42, 134.63, 130.60, 129.79, 128.64, 128.37, 128.09, 126.06, 125.66, 122.52, 120.74, 117.97, 115.07, 23.14, 20.47; IR ($CHCl_3$): ν_{max} 3368, 2955, 2924, 2853, 2252, 1626, 1604, 1572, 1527, 1515, 1486, 1421, 1403, 1360, 1307, 1242, 1190, 1020 cm^{-1}; HRMS: m/z 351.1602 calcd for $C_{23}H_{19}N_4 + H^+$ (351.1610).

Example 12. Synthesis of 6-(4-vinylphenyl)-4-(4-cyanomethyl)phenylamino quinazoline (13) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 4-vinylphenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 71%, pale yellow solid, m. p. 216-218 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (s, 1H), 8.42 (d, 1H, *J* = 1.6 Hz), 8.07 (s, 1H), 7.92 (d, 1H, J = 8.6 Hz), 7.82 (d, 2H, J = 8.5 Hz), 7.73 (d, 2H, J = 8.2 Hz), 7.56 (d, 3H, J = 8.2 Hz), 7.40-7.34 (t, 1H, J = 8.5 Hz), 6.80-6.77 (t, 1H, *J* = 6.7 Hz), 5.85 (d, 1H, J = 17.7 Hz), 5.33 (d, 1H, J = 11.0 Hz), 3.81 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 158.30, 154.92, 149.57, 138.96, 138.87, 137.93, 137.19, 136.56, 132.05, 131.97, 128.89, 128.70, 127.72, 127.27, 126.90, 123.48, 120.64, 119.87, 115.83, 115.30, 22.39; IR ($CHCl_3$): ν_{max} 3368, 2951, 2923, 2857, 2248, 1741, 1623, 1603, 1571, 1514, 1497, 1423, 1360, 1020 cm^{-1}; HRMS: m/z 363.1605 calcd for $C_{24}H_{19}N_4 + H^+$ (363.1610).

Example 13. Synthesis of 6-(4-fluorobenzyloxyphen-4-yl)-4-(4-cyanomethyl)phenylamino quinazoline (14) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 4-((4-fluorobenzyl)oxy)phenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 81%, pale yellow solid, m. p. 230-232 °C; ^{1}H NMR ($CDCl_3$ + 1 drop of CD_3OD, 400 MHz): δ 8.65 (s, 1H), 8.45 (s, 1H), 8.04 (d, 1H, *J* = 1.6 Hz), 7.88 (d, 1H, *J* = 8.8 Hz), 7.81 (d, 2H, *J* = 8.4 Hz), 7.73-7.70 (t, 2H, *J* = 6.8 Hz), 7.48-7.38 (m, 5H), 7.13-7.08 (m, 4H), 5.12 (s, 2H), 3.82 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 158.70, 158.20, 154.60, 149.14, 139.03, 138.17, 132.18, 131.94, 130.45, 130.39, 128.77, 128.69, 126.82, 123.41, 119.93, 119.87, 115.84, 115.66, 69.04, 22.41; IR ($CHCl_3$): ν_{max} 3400, 2954, 2923, 2854, 1605, 1573, 1498, 1514, 1423, 1401, 1384, 1225, 1157, 1020 cm^{-1}; HRMS: m/z 461.1777 calcd for $C_{29}H_{22}FN_4O + H^+$ (461.1778).

Example 14. Synthesis of 6-(3-acetylaminophenyl)-4-(4-cyanomethyl)phenylamino quinazoline (15) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 3-acetylaminophenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 81%, pale yellow solid, m. p. 195-197 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.01 (s, 2H), 8.80 (s, 1H), 8.60 (s, 1H), 8.10-8.07 (dd, 1H, *J* = 1.6 & 0.8 Hz), 8.00 (s, 1H), 7.90-7.87 (dd, 3H, *J* = 1.6 & 1.6 Hz), 7.66-7.46 (m, 4H), 7.39 (d, 2H, *J* = 8.4 Hz), 4.04 (s, 2H), 2.07 (d, 3H, J = 0.8 Hz); ^{13}C NMR (126 MHz, DMSO-d_6): δ 168.40, 157.79, 154.38, 148.98, 139.85, 139.80, 138.43, 138.23, 131.42, 131.34, 129.30, 128.71, 128.61, 128.38, 128.14, 126.32, 122.87, 122.05, 120.57, 119.31, 118.50, 117.79, 115.26, 23.95, 21.83; IR ($CHCl_3$): v_{max} 3368, 2921, 1676, 1608, 1534, 1515, 1480, 1426, 1119 cm^{-1}; HRMS: m/z 394.1668 calcd for $C_{24}H_{20}N_5O$ + H^+ (394.1668).

Example 15. Synthesis of 6-(4-phenylphenyl)-4-(4-cyanomethyl)phenylamino-quinazoline (16) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 4-phenylphenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 57%, yellow solid, m. p. 214-216 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.03 (s, 1H), 8.92 (d, 1H, *J* = 1.6 Hz), 8.61 (s, 1H), 8.29-8.27 (m, 1H), 8.03 (d, 2H, *J* = 8.4 Hz), 7.92-7.87 (m, 4H), 7.80-7.77 (t, 2H , *J* = 1.2 Hz), 7.54-7.50 (t, 2H, *J* = 7.6 Hz), 7.43-7.7.40 (m, 3H), 4.07-4.01 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 157.84, 154.47, 149.11, 139.59, 139.41, 138.46, 138.01, 137.98, 137.44, 131.64, 129.02, 128.47, 128.25, 127.69, 127.62, 127.25, 126.65, 123.03, 120.27, 119.42, 115.38, 21.90; IR ($CHCl_3$): v_{max} 3401, 2953, 2927, 1604, 1567, 1515, 1486, 1423, 1358, 1021 cm^{-1}; HRMS: m/z 413.1769 calcd for $C_{28}H_{21}N_4$; found, 413.1766. HRMS: m/z 381.1357 calcd for $C_{23}H_{17}N_4O_2$ + H^+ (381.1352).

Example 16. Synthesis of 6-(4-(4-ethoxyphenyl)phenyl)-4-(cyanomethyl)phenylamino-quinazoline (17) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 4-(4-ethoxyphenyl)phenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 47%, yellow solid, m. p. 195-197 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.75 (s, 1H), 8.64 (s, 1H), 8.52 (s, 1H), 7.93 (d, 1H, *J* = 8.8 Hz), 7.84-7.82 (m, 4H), 7.72 (d, 2H, J = 8.4 Hz), 7.63-7.60 (t, 4H, J = 4.4 Hz), 7.02 (d, 2H, J = 8.4 Hz), 4.30 (d, 2H, J = 6.8 Hz), 1.35-1.21 (m, 3H); IR ($CHCl_3$): v_{max} 3306, 2956, 2925, 2855, 1729, 1604, 1568, 1515, 1494, 1424, 1401, 1360, 1252, 1190, 1082, 1019 cm^{-1}; HRMS: m/z 457.2012 calcd for $C_{30}H_{25}N_4O$ + H^+ (457.2028).

Example 17. Synthesis of 6-(4-phenyl-2-fluorophenyl)-4-(4-cyanomethyl)phenylamino-quinazoline (18) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 4-phenyl-2-fluorophenylboronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 57%, pale yellow solid, m. p. 229-231 °C; ^{1}H NMR ($CDCl_3$ + 1 drop of CD_3OD, 400 MHz): δ 8.60 (d, 2H), 8.10 (d, 1H), 7.98-7.88 (m, 1H), 7.83 (d, 2H, J = 8.4 Hz), 7.68-7.57 (m, 5H), 7.55-7.49 (m, 2H), 7.47-7.40 (m, 3H), 3.89 (s, 2H); ^{13}C NMR (101 MHz, DMSO): δ 157.89, 154.72, 149.41, 140.38, 138.39, 136.01, 134.61, 131.46, 131.28, 128.76, 128.73, 128.68, 128.50, 128.24, 128.01, 126.55, 123.35, 123.08, 120.63, 119.33, 115.32, 21.93; IR ($CHCl_3$): vmax 3392, 2951, 2924, 2853, 2250, 1604, 1573, 1515, 1483, 1424, 1021 cm^{-1}; HRMS: m/z 431.1666 calcd for $C_{28}H_{20}FN_4$ + H^+ (431.1672).

Example 18. Synthesis of 6-(naphthalen-2-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (19) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and naphthalen-2-yl boronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 57%, pale yellow solid, m. p. 204-206 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.04 (s, 1H), 8.97 (s, 1H), 8.64-8.59 (m, 1H), 8.47-8.33 (m, 1H), 8.14-7.87 (m, 6H), 7.60-7.53 (m, 3H), 7.45-7.37 (m, 2H), 4.08-4.03 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 157.85, 154.48, 149.12, 136.42, 133.24, 132.34, 132.00, 131.46, 131.38, 128.75, 128.66, 128.56, 128.47, 128.20, 127.55, 126.59, 126.42, 126.39, 125.78, 125.28, 123.03, 120.69, 115.40, 21.89; IR ($CHCl_3$): ν_{max} 3369, 3053, 2955, 2924, 2854, 2250, 1733, 1603, 1572, 1529, 1515, 1468, 1422, 1404, 1385, 1360, 1245, 1175, 1119, 1070, 1020 cm^{-1}; HRMS: m/z 387.1611 calcd for $C_{26}H_{19}N_4$ + H^+ (387.1610).

Example 19. Synthesis of 6-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (20) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 2,3-dihydrobenzo[b][1,4]dioxin-6-yl boronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 81%, pale yellow solid, m. p. 207-209 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.95 (s, 1H), 8.76 (d, 1H, *J* = 1.6 Hz), 8.57 (s, 1H), 8.16-8.13 (dd, 1H, *J* = 1.6 & 2.0 Hz), 7.89 (d, 2H, *J* = 8.4 Hz), 7.82 (d, 1H, *J* = 8.8 Hz), 7.65-7.53 (m, 1H), 7.46 (d, 1H, *J* = 2.0 Hz), 7.41-7.37 (m, 3H), 7.03 (d, 1H, *J* = 8.4 Hz), 4.32 (s, 4H), 4.05 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.72, 154.18, 148.75, 143.78, 143.55, 138.51, 137.46, 132.26, 131.49, 131.42, 128.78, 128.69, 128.20, 126.38, 123.00, 119.97, 119.50, 117.57, 115.60, 115.31, 64.23, 64.15, 21.90; IR ($CHCl_3$): ν_{max} 3854, 3745, 3400, 2922, 2853, 1602, 1514, 1495,

1422, 1307, 1249, 1068, 1021 cm^{-1}; HRMS: m/z 395.1508 calcd for $C_{24}H_{19}N_4O_2$ + H^+ (395.1508).

Example 20. Synthesis of 6-(benzo[d][1,3]dioxol-5-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (21) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and benzo[d][1,3]dioxol-5-yl boronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 57%, yellow solid, m. p. 241-243 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.90 (s, 1H), 8.76 (d, 1H, *J* = 1.6 Hz), 8.58 (s, 1H), 8.23-8.15 (m, 2H), 7.99-7.81 (m, 2H), 7.53 (d, 1H, *J* = 1.6 Hz), 7.41-7.39 (t, 1H, *J* = 6.4 Hz), 7.13-7.10 (t, 1H, *J* = 6.4 Hz), 6.12 (s, 2H), 4.04 (s, 2H); ^{13}C NMR (101 MHz, DMSO): δ 157.74, 154.21, 148.78, 148.13, 147.26, 138.52, 137.73, 133.28, 131.58, 131.50, 131.40, 128.78, 128.66, 128.25, 128.20, 126.38, 122.95, 120.85, 119.71, 119.33, 115.29, 108.74, 107.42, 101.32, 21.91; IR ($CHCl_3$): v_{max} 3400, 2923, 1603, 1514, 1419, 1220, 1039 cm^{-1}; HRMS: m/z 381.1357 calcd for $C_{23}H_{17}N_4O_2$ + H^+ (381.1352).

Example 21. Synthesis of 6-(benzofuran-2-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (22) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and benzofuran-2-yl boronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 62%, pale yellow solid, m. p. 245-247 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.14 (s, 1H), 9.09 (d, 1H, *J* = 1.6 Hz), 8.61 (s, 1H), 8.41-8.38 (m, 1H), 7.93-7.88 (m, 2H), 7.75 (d, 1H, *J* = 7.2 Hz), 7.71-7.69 (t, 1H, *J* = 8.0 Hz), 7.65-7.7.60 (m, 1H), 7.58-7.53 (m, 1H), 7.42-7.39 (m, 2H), 7.32-7.30 (m, 1H), 4.06 (s, 2H); ^{13}C NMR (126 MHz, DMSO): δ 157.84, 154.88, 154.57, 154.46, 149.84, 138.42, 132.77, 131.83, 131.46, 128.79, 128.70, 128.23, 125.09, 123.06, 119.29, 118.65, 114.73, 111.15, 103.34, 21.91; IR ($CHCl_3$): v_{max} 3400, 2955, 2923, 2853, 1605, 1572, 1515, 1422, 1384, 1020 cm^{-1}; HRMS: m/z 377.1399 calcd for $C_{24}H_{17}N_4O$ + H^+ (377.1402).

Example 22. Synthesis of 6-(benzo[b]thiophen-2-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (23) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and benzo[b]thiophen-2-yl boronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 65%, yellow solid, m. p. 263 °C, decomposed; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.04 (s, 1H), 8.91 (s, 1H), 8.58 (s, 1H), 8.26-8.23 (dd, 1H, *J* = 2.0 & 2.0 Hz), 8.05-8.02 (t, 2H , *J* = 6.8 Hz), 7.91-7.84 (m, 3H), 7.44-7.38 (m, 4H), 4.04-4.00 (t, 2H, *J* = 8.0 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ 157.69, 154.65, 149.52, 142.35, 140.22, 138.89, 138.30, 131.42, 130.88, 128.63, 128.14, 126.51, 124.90, 124.86, 123.76, 123.09, 122.45, 121.09, 119.89, 119.25, 115.36, 21.85; IR ($CHCl_3$): v_{max} 3392, 2951, 2922,

2852, 1602, 1572, 1514, 1419, 1403, 1361, 1157, 1020, cm^{-1}; HRMS: m/z 393.1163 calcd for $C_{24}H_{17}N_4S + H^+$ (393.1174).

Example 23. Synthesis of 6-(dibenzo(b,d)furan-4-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (24) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and dibenzo(b,d)furan-4-yl boronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 42%, pale yellow solid, m. p. 207-209 °C; ^1H NMR (DMSO-d_6, 400 MHz) : δ 10.03 (s, 1H), 9.02 (d, 1H, J = 1.6 Hz), 8.66 (s, 1H), 8.47-8.45 (dd, 1H, J = 1.6 & 2.0 Hz), 8.26-8.23 (m, 2H), 7.99 (d, 1H , J = 8.8 Hz), 7.91 (d, 3H, J = 8.0 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.65-7.55 (m, 3H), 7.48-7.39 (m, 2H), 4.05 (s, 2H); ^{13}C NMR (126 MHz, DMSO): δ 157.86, 155.49, 154.75, 152.58, 149.16, 138.47, 133.90, 133.61, 132.03, 131.49, 131.42, 128.78, 128.69, 128.23, 127.84, 127.58, 126.44, 124.47, 124.31, 123.72, 123.41, 123.32, 122.97, 122.62, 121.30, 120.92, 119.39, 115.36, 111.96, 21.91; IR ($CHCl_3$): v_{max} 3392, 2955, 2923, 2853, 1604, 1573, 1530, 1515, 1490, 1451, 1402, 1362, 1189, 1120, 1020 cm^{-1}; HRMS: m/z calcd for $C_{28}H_{19}N_4O$, 427.1553 + H^+ (427.1559).

Example 24. Synthesis of 6-(dibenzo(b,d)thiophene-4-yl)-4-(4-cyanomethyl) phenylamino-quinazoline (25) from 6-bromo-4-(4-cyanomethyl) phenylamino quinazoline and dibenzo(b,d)thiophene-4-yl boronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 45%, pale yellow solid, m. p. 199-201 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.80 (s, 1H), 8.36 (d, 1H, *J* = 1.6 Hz), 8.19-8.11 (m, 3H), 8.03 (d, 1H, *J* = 8.8 Hz), 7.80-7.77 (t, 1H, *J* = 3.6 Hz), 7.57-7.46 (m, 4H), 7.36-7.30 (m, 2H), 3.72 (s, 2H). IR ($CHCl_3$): v_{max} 3392, 2922, 2853, 1605, 1571, 1537, 1514, 1421, 1026 cm^{-1}; HRMS: m/z 443.1320 calcd for $C_{28}H_{19}N_4S + H^+$ (443.1330).

Example 25. Synthesis of 6-(1H-indol-5-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (26) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and 1H-indol-5-yl boronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 81%, dark yellow solid, m. p. 267-269 °C; ^1H NMR (DMSO-d_6, 400 MHz): δ 11.23 (s, 1H), 9.99 (s, 1H), 8.83 (d, 1H, *J* = 17.6 Hz), 8.57 (d, 1H, *J* = 17.6 Hz), 8.24-8.22 (dd, 1H, *J* = 2.0 & 1.6 Hz), 8.08 (s, 1H), 7.93-7.84 (dd, 3H, *J* = 8.4 & 8.4 Hz), 7.66-7.53 (m, 3H), 7.44-7.39 (m, 2H), 6.54 (d, 1H, *J* = 17.6 Hz), 4.05 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.70, 153.86, 148.37, 139.94, 138.63, 135.70, 131.50, 131.42, 130.21, 128.79, 128.70, 128.27, 128.19, 126.39, 126.25, 122.94, 120.72, 119.57, 119.43, 118.79, 111.91, 101.61, 21.90; IR ($CHCl_3$): v_{max} 3787, 3212, 2923, 2853, 1603, 1572, 1529, 1514, 1436, 1421, 1309, 1175, 1119, 1070 cm^{-1}; HRMS: m/z 376.1564 calcd for $C_{24}H_{18}N_5 + H^+$ (376.1562).

Example 26. Synthesis of 6-(quinolin-3-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (27) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and quinolin-3-yl boronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 62%, off-white solid, m. p. °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.06 (s, 1H), 9.52 (d, 1H, *J* = 2.0 Hz), 9.10 (d, 1H, *J* = 1.6 Hz), 8.86 (d, 1H, *J* = 2.0 Hz), 8.64 (s, 1H), 8.45-8.42 (m, 1H), 8.12 (d, 2H, *J* = 8.4 Hz), 7.97 (d, 3H, *J* = 8.4 Hz), 7.91 (d, 1H, *J* = 8.4 Hz), 7.83 (d, 1H, *J* = 1.2 Hz), 7.42 (d, 2H, *J* = 8.8 Hz), 4.05 (s, 2H); IR ($CHCl_3$): v_{max} 3400, 2922, 1617, 1423, 1130 cm^{-1}; HRMS: m/z 388.1559 calcd for $C_{25}H_{18}N_5 + H^+$ (388.1562).

Example 27. Synthesis of 6-(pyridin-4-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (28) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and pyridin-4-yl boronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 81%, pale yellow solid, m. p. 234-236 °C; ^{1}H NMR ($CDCl_3$ + 1 drop of CD_3OD, 400 MHz): δ 8.62 (s, 3H), 8.11-8.09 (t, 1H, *J* = 6.8 Hz), 7.97 (d, 1H, *J* = 8.4 Hz), 7.83 (d, 4H, *J* = 8.4 Hz), 7.41-7.32 (m, 3H), 3.81 (s, 2H). ^{13}C NMR ($CDCl_3$ + 1 drop of CD_3OD, 126 MHz): δ 158.51, 154.91, 149.30, 147.56, 137.93, 135.52, 131.31, 128.13, 127.95, 125.94, 123.18, 121.70, 120.98, 117.80, 115.54, 22.50; IR ($CHCl_3$): v_{max} 3392, 2957, 2923, 2850, 1606, 1573, 1532, 1493, 1425, 1020 cm^{-1}; HRMS: m/z 338.1365 calcd for $C_{21}H_{16}N_5 + H^+$ (338.1406).

Example 28. Synthesis of 6-(isoquinolin-4-yl)-4-(4-cyanomethyl)phenylamino-quinazoline (29) from 6-bromo-4-(4-cyanomethyl)phenylamino quinazoline and isoquinolin-4-yl boronic acid: This compound was synthesized using the similar procedure as described in example 5. Yield: 57%, pale yellow solid, m. p. 237-239 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.90 (s, 1H), 9.45 (s, 1H), 8.81 (s, 1H), 8.69 (s, 1H), 8.63 (s, 1H), 8.30 (d, 1H, *J* = 8.0 Hz), 8.07-8.05 (dd, 1H, *J* = 1.6 & 1.6 Hz), 7.97 (d, 1H, *J* = 8.8 Hz), 7.92-7.77 (m, 4H), 7.38 (d, 2H, *J* = 8.8 Hz), 3.36 (s, 2H); ^{13}C NMR (126 MHz, DMSO): δ 157.76, 154.84, 152.44, 149.23, 142.99, 138.46, 134.75, 134.55, 133.22, 131.71, 131.45, 128.20, 128.20, 128.04, 127.97, 127.73, 126.36, 124.17, 124.10, 122.72, 119.35, 115.26, 21.89; IR ($CHCl_3$): v_{max} 3400, 2923, 2853, 1624, 1423, 1042 cm^{-1}; HRMS: m/z 388.1564 calcd for $C_{25}H_{18}N_5 + H^+$ (388.1562).

All examples disclosed in formula I, are prepared by employing the similar method containing different Ar, R, and R' groups, as described for preparation of compound **6** (example 5).

Example 29. Cytotoxicity of compounds of the invention: Compounds proposed in present invention were evaluated for their cytotoxic effect against panel of 5 cancer cell line *viz*. Panc-1 (pancreatic cancer), MCF-7 (breast cancer), PC-3 (prostate), HL-60 (leukemia) and A-375 (melanoma) using MTT assay. In each well of a 96-well plate, 3×10^3 cells were grown in 100 µL of medium. After 24 h, each test molecules were added to achieve a final concentration of 10 to 0.01 µmol/L, respectively. After 48 h of treatment, 20 µL of 2.5 mg/mL MTT (Organics Research, Inc.) solution in phosphate buffer saline was added to each well. After 48h, supernatant was removed and formazan crystals were dissolved in 200 µL of DMSO. Absorbance was then measured at 570 nm using an absorbance plate reader (Bio-Rad Microplate Reader). Data are expressed as the percentage of viable cells in treated relative to non-treated conditions. Each experiment was repeated thrice and data was expressed as mean ± SD of three independent experiments (Mordant, P. et al., *Mol. Cancer Ther.* **2010**, *9*, 358). Compounds showed promising cytotoxivity in panel of cell lines. Cytotoxicity results are shown in Table 1.

Example 30. Phosphoinositide-3-kinase assay: Compounds proposed in present invention were evaluated for their inhibitory activity on phosphoinositide-3-kinase-alpha and other isoforms (beta, gamma and delta). The preliminary screening was performed at 0.5 µM concentration. The protocols used for these bioassays are as follows:

PI3K-α assay: PI3K alpha (diluted in 12.5mM Glycine-NaOH (pH 8.5), 50 mM KCl, 2.5 mM $MgCl_2$, 1 mM DTT, 0.05% CHAPS) is assayed in total volume of 20 ul containing 12.5 mM glycine-NaOH (pH 8.5), 50 mM KCl, 2.5 mM $MgCl_2$, 1 mM DTT, 0.05% CHAPS, 0.01 mM ATP and 0.05 mM diC8 PIP2. The enzyme is assayed for 80 min after which 20 ul of ADP-Glo reagent is added. After a further incubation of 40 min, 40 ul of Kinase Detection Buffer is added. The assays are incubated for 40 min and then read on PerkinElmer Envision for 1sec/well.

PI3K-β assay: PI3K beta (diluted in 12.5 mM glycine-NaOH (pH 8.5), 50 mM KCl, 2.5mM $MgCl_2$, 1 mM DTT, 0.05% CHAPS) is assayed in total volume of 20 ul containing 12.5mM Glycine-NaOH (pH 8.5), 50 mM KCl, 2.5 mM $MgCl_2$, 1 mM DTT, 0.05% CHAPS, 0.01 mM ATP and 0.05 mM diC8 PIP2. The enzyme is assayed for 60 min after which 20 ul of ADP-Glo reagent is added. After a further incubation of 40 min, 40 ul of kinase detection Buffer is added. The assays are incubated for 40 min and then read on PerkinElmer Envision for 1 sec/well.

PI3K-δ assay: PI3K delta (diluted in 12.5mM Glycine-NaOH (pH 8.5), 50 mM KCl, 2.5mM $MgCl_2$, 1 mM DTT, 0.05% CHAPS) is assayed in total volume of 20 ul containing 12.5 mM Glycine-NaOH (pH 8.5), 50 mM KCl, 2.5mM $MgCl_2$, 1 mM DTT, 0.05% CHAPS, 0.01 mM ATP and 0.05 mM diC8 PIP2. The enzyme is assayed for 120 min after which 20ul of ADP-Glo reagent is added. After a further incubation of 40 min, 40 ul of Kinase Detection Buffer is added. The assays are incubated for 40 min and then read on PerkinElmer Envision for 1 sec/well.

PI3K-γ assay: PI3K gamma (diluted in 12.5 mM Glycine-NaOH (pH 8.5), 50 mM KCl, 2.5 mM $MgCl_2$, 1 mM DTT, 0.05% CHAPS) is assayed in total volume of 20 ul containing 12.5mM glycine-NaOH (pH 8.5), 50 mM KCl, 2.5 mM $MgCl_2$, 1 mM DTT, 0.05% CHAPS, 0.01 mM ATP and 0.05 mM diC8 PIP2. The enzyme is assayed for 75 min after which 20 ul of ADP-Glo reagent is added. After a further incubation of 40 min, 40 ul of Kinase Detection Buffer is added. The assays are incubated for 40 min and then read on PerkinElmer Envision for 1sec/well.

The results of preliminary screening are shown in **Table 1**. The 6-aryl-4-phenylamino quinazolines **10**, **21**, **26**, **28**, and **29** showed >40% inhibition of PI3K-α at 0.5 μM. The IC_{50} was determined for best compounds and results are shown in **Table 2**. The fold-selectivity of these compounds for PI3K-α isoform is also shown in **Table 2**.

Table 1.

Anticancer activity of 6-aryl-4-phenylamino quinazolines against pancreatic, breast, prostate, leukemia and melanoma cells; and inhibition of phosphoinositide-3-kinase-α (PI3K-α) by these compounds

Compound		**Anticancer activity IC_{50} (μM)**						**% Inhibition of PI3K-α at 0.5 μM**
		HL-60	**A375**	**MCF-7**	**Panc-1**	**PC-3**		
6		32	24	23	40	27		16.4
7		7	9	10	21	28		17
8		42	39	91	90	21		1.3
9		28	32	45	13	24		44
10		24	28	15	36	37		69.9
11		15	23	12	7	29		38.1
12		36	32	>100	68	38		4.1

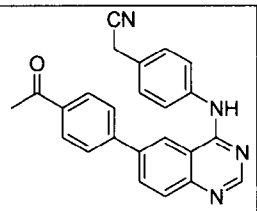
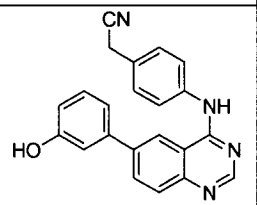
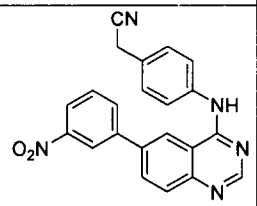
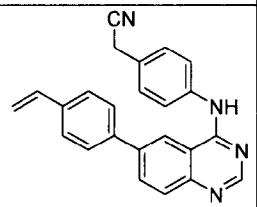
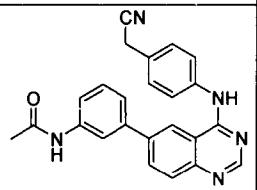
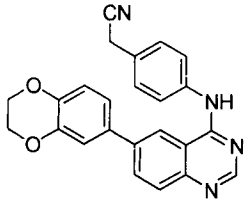
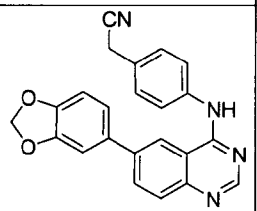
13		16	27	11	32	34		36.4
14		14	16	12	13	13		11
15		23	38	14	38	26		36.8
16		16	13	29	30	10		NI
17		16	30	26	33	17		NI
18		16	32	13	33	14		20.3
19		25	31	16	48	22		8.2
20		21	27	34	32	34		33
21		27	24	34	33	7		48.6
22		17	10	9	28	8		29.8
23		14	14	8	24	13		2.7
24		12	36	27	31	16		1.5
25		31	34	34	33	18		NI
26		18	31	7	16	24		47.5
27		44	89	32	90	23		NI
28		32	35	32	39	76		45.6
29		10	12	12	9	9		48.8

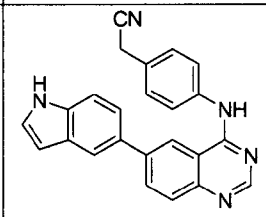
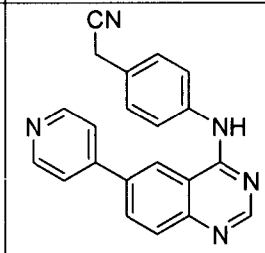
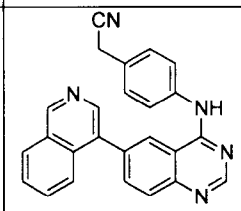
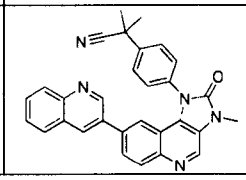
NI, no inhibition at tested concentration; Panc-1: Human pancreatic carcinoma cell line; MCF-7: Human breast adenocarcinoma cell line; PC-3: human prostate cancer cell line; A-375: Human malignant melanoma cells; HL-60: Human leukemia cells; nd, not determined.

Table 2.

The IC_{50} values for 6-aryl-4-phenylamino quinazolines against four isoforms of phosphoinositide-3-kinase and the fold-selectivity for PI3K-α isoform

Entry	Structure		PI3K inhibition (IC_{50} values in μM)					Fold-selectivity for PI3K-α with respect to other isoforms		
			-α	-β	-γ	- δ		-β	-γ	- δ

9			0.270	>10	0.15	>10		>37	0.5	>37
10			0.115	0.67	1.84	0.27		5.8	16	2.3
11			0.451	>10	0.85	>10		>22.2	1.9	>22.2
13			>10	>10	0.52	>10		1	>0.05	1
15			0.475	>10	6.95	>10		>21	14.6	>21
20			0.342	>10	1.37	>10		>29.2	4	>29.2
21			0.321	>10	0.19	>10		>31.1	0.6	>31.1

26			0.201	>10	0.75	>10		>49.7	3.7	>49.7
28			0.704	>10	0.36	>10		>14.2	0.5	>14.2
29			0.150	>20	8.44	0.88		>133	56	5.9
BEZ2 35			0.004	0.076	0.007	0.005		19	17.5	1.25

Among the examples depicted in Table 2, compound **29** displayed promising selectivity towards α-isoform versus β-isoform (>133 fold selectivity). Compound **29** also displayed 56-fold selectivity for α-isoform versus γ-isoform. Similarly, another compound **26** displayed >49.7 fold selectivity towards α-isoform versus β- and δ-isoforms. However, the Novartis molecule BEZ-235 has very weak selectivity towards α-isoform versus other three isoforms: β, γ and δ (19, 17.5 and 1.25 fold selectivity, respectively).

Example 31. Molecular modeling studies of 6-aryl-4-phenylamino quinazolines 10 and 29 with phosphoinositide-3-kinase-α: The conformation, orientation and interactions of compounds **10** and **29** with phosphoinositide-3-kinase was determined by Glide module of Schrodinger molecular modeling package using PI3Kα (PDB: 2RD0) crystal structure (Huang, C.-H et al., *Science* **2007**, *318*, 1744). The interactions of inhibitors **10** and **29** with PI3Kα were studied by incorporating missing residues in the apo-form of PI3Kα (PDB: 2RD0). Protein was prepared by removing solvent, adding hydrogens and by minimizing

energy using protein preparation wizard. Missing residues (Tyr307-Thr324, Ala415-Ala423, Phe506-Asp527 and Lys941-Glu950) were incorporated in the apo-form of PI3K-α (PDB: 2rD0) using Prime module (version 3.0) of Schrodinger Inc. LLC, NewYork, USA. Compounds were docked using Glide in extra-precision mode with up to three poses saved per molecule.

As depicted in Figure 2, the compound **10** showed typical H-bonding interaction with the Val 851 residue of the hinge region and Tyr 836 residue of the ATP binding site. The phenolic ring of Tyr 836 residue stablizes the quinazoline ring via π-π interactions. Compound **29** showed H-bonding with the Gln859 residue of the PI3K-α catalytic domain instead of the Val851. Similar to compound **10**, the phenolic Tyr-836 and indolyl Trp-780 stabilizes the quinazoline and phenolic ring of the compound **29** by aromatic π-π interactions. Both molecules fits into the hydrophobic cleft formed by Trp780, Tyr 836, Val 850, Val851, Ile 848, Phe 930, Ile932, Asp933 and Phe934 residues. The interaction map of compounds **10** and **29** in the active site of PI3K-α is shown in **Figure 2.**

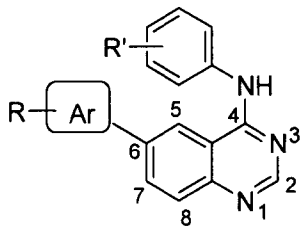
ADVANTAGES OF THE INVENTION

The main advantages of the present invention are:

- Compounds of the invention show promising anticancer activity against various cancer cell lines and inhibit phosphoinositide-3-kinase-alpha, a key target in cancer at low micromolar to nanomolar concentrations.
- Compounds of the invention are stable.

The Claims:

1. A compound of formula I,



I

wherein, R is selected from the group comprising of hydrogen, alkyl, nitro, halogens (fluoro, chloro, bromo and iodo), formyl, allyl, vinyl, benzyl, acetyl, hydroxy, phenyl, substituted phenyl, fused aromatics;

R′ is selected from the group consisting of hydrogen, cyanomethyl, or alkyls.

Ar is selected from the group comprising of aryl or heteroaryl, which is unsubstituted or substituted with an alkyl, nitro, halogens, formyl, allyl, vinyl, benzyl, acetyl, hydroxy, phenyl, substituted phenyl, fused aromatics.

2. A compound of formula I as claimed in claim 1 wherein, aryl is selected from the group consisting of phenyl, biphenyl which is unsubstituted or substituted with different R groups, which is selected from the group comprising of alkyl, nitro, halogens (fluoro, chloro, bromo and iodo), formyl, allyl, vinyl, benzyl, acetyl, hydroxy, phenyl, substituted phenyl, fused aromatics.

3. A compound of formula I as claimed in claim 1 wherein Alkyl group is selected from the group consisting of (C1-C6)-alkyl, (C1-C4)-haloalkyl, (C1-C4)-alkoxy, (C1-C4)-haloalkoxy; or is (C5-C8)-cycloalkyl, (C5-C8)-cycloalkenyl, (C6-C10)-bicycloalkyl, (C6-C10)-bicycloalkenyl.

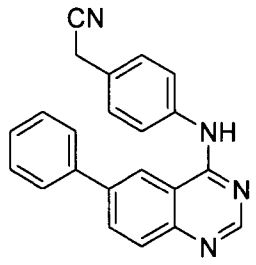
4. A compound of formula I as claimed in claim 1 wherein, substituted phenyl is selected from the group consisting of alkylphenyls, alkoxyphenyls.

5. A compound of formula I as claimed in claim 1 wherein, fused aromatics is selected from the group consisting of naphthalene, 2,3-dihydrobenzo[b][1,4]dioxin, benzo[d][1,3]dioxol, benzofuran, benzo[b]thiophene, dibenzo(b,d)furan, dibenzo(b,d)thiophene, 1H-indole, quinoline, isoquinoline.

6. A compound of formula I as claimed in claim 1 wherein, heteroaryl is selected from the group consisting of pyridine, quinoline, isoquinoline, 2,3-dihydrobenzo[b][1,4]dioxin,

benzo[d][1,3]dioxol, benzofuran, benzo[b]thiophene, dibenzo(b,d)furan, dibenzo(b,d)thiophene, 1H-indole.

7. A compound of formula I as claimed in claim 1 wherein, the structural formulae of the said compounds comprising:



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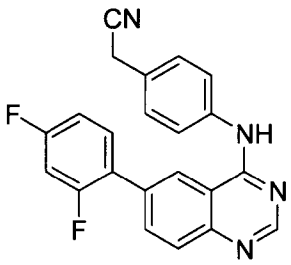

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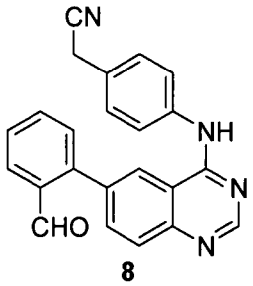

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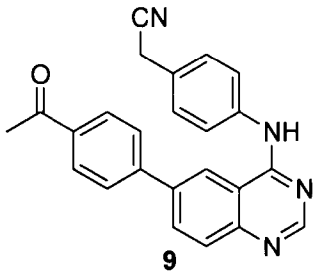

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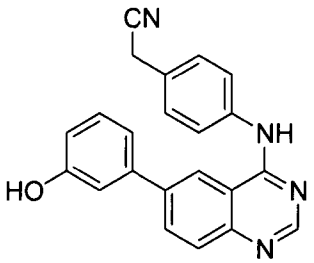

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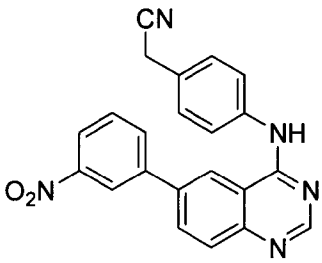

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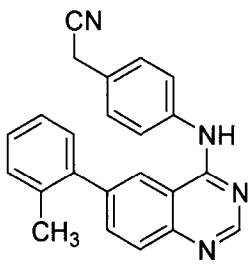

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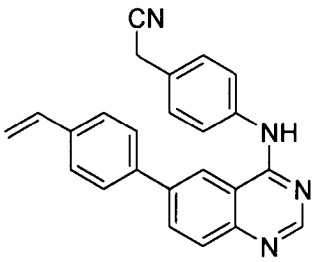

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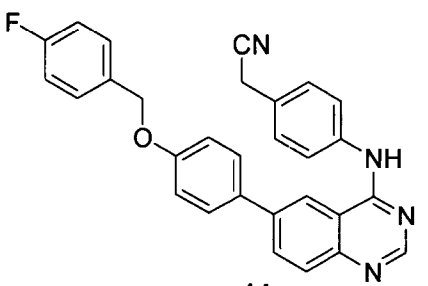

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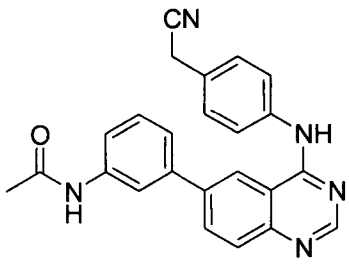

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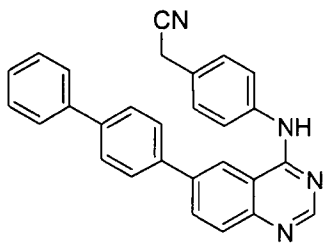

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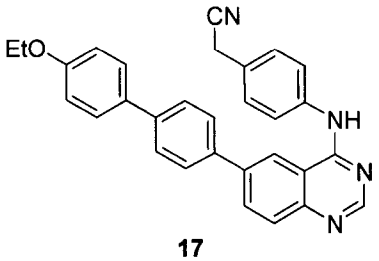
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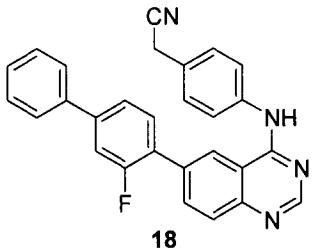
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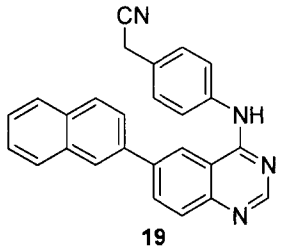
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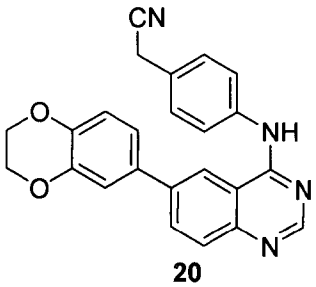
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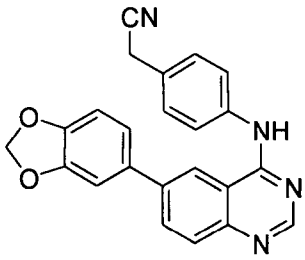
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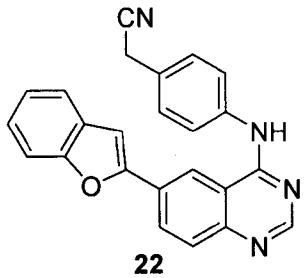
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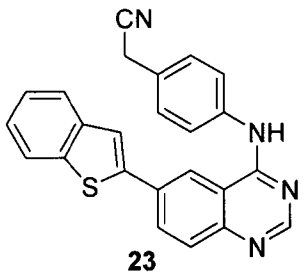
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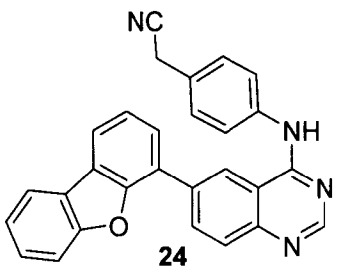
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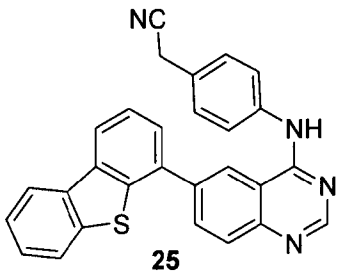
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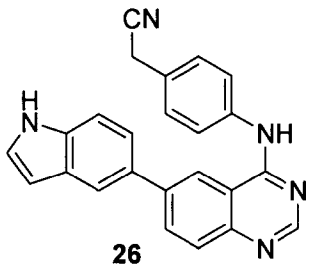
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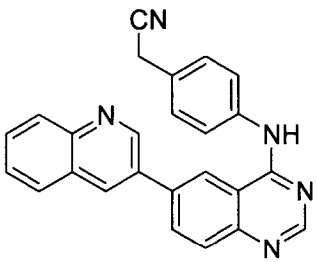
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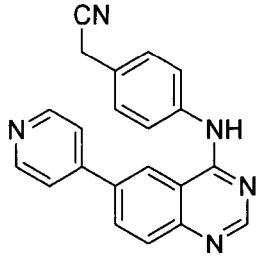
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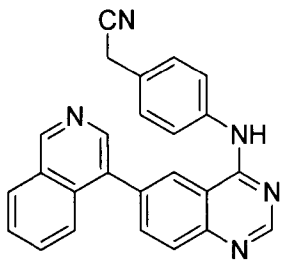

29

8. A compound of formula I as claimed in claim 1 wherein, the compounds are useful for the treatment of cancer.

9. A compound of formula I as claimed in claim 1 wherein, the compounds are

phosphoinositide-3-kinase inhibitors.

10. A compound as claimed in claim 1, wherein the compounds are active against cancer cell lines selected from a group consisting of HL-60, A375, MCF-7, Panc-1, PC-3.

11. A compound as claimed in claim 1, wherein the compounds are phosphoinositide-3-α kinase inhibitors upto about 70% at 0.5 μM concentration

12. A process for preparation of the compounds of general formula I as claimed in claim 1 wherein the process steps comprising:

a) reacting anthralinic acid (**1**) with bromine in glacial acetic acid at a temperature in the range of 10-25 °C for the time period of ranging between 15-30 min, followed by diluting with dilute HCl to obtain monobromo anthranilic acid (**2**);

b) adding formamide to monobromo anthranilic acid obtained in step (a) followed by reflux at a temperature ranging between 100-150 °C for a time period ranging between 4-10 h to obtain compound **3**;

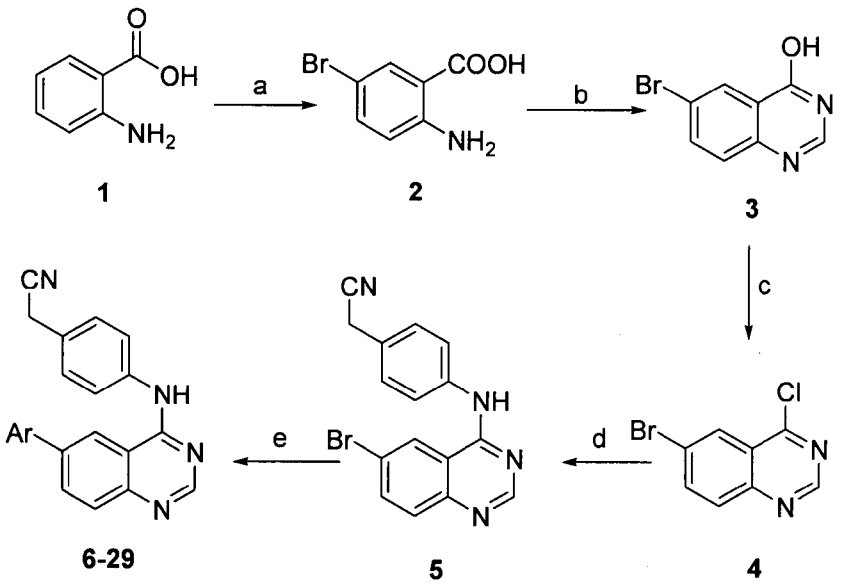
c) adding $POCl_3$ to the solution of compound **3** as obtained in step (b) followed by reflux at a temperature ranging between 100-150 °C for a time period ranging between 4-10 h to obtain compound **4**;

d) adding 4-amino benzylcyanide to the solution of compound 4 as obtained in step (c) forming a mixture which is dissolved in isopropanol followed by stirring for a time period of ranging between 2-6 h under reflux at a temperature ranging between 80-100 °C to obtain compound **5**;

e) reacting aryl boronic acid in suitable solvent with compound **5** as obtained in step (d) followed by addition of $Pd(PPh_3)_4$ followed by stirring of the resultant mixture for the time period ranging between 12-24 h at a temperature ranging between 80-100 °C to yield compound of formula **I**.

13. A process as claimed in claim 12 wherein, the aryl boronic acid used in step (e) is selected form the group consisting of substituted phenyls, substituted biphenyls, substituted naphthyls, substituted heteroaryls.

14. A process as claimed in claim 12, wherein, the solvent used in step (e) is selected from toluene or dioxane.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4

FIGURE 1

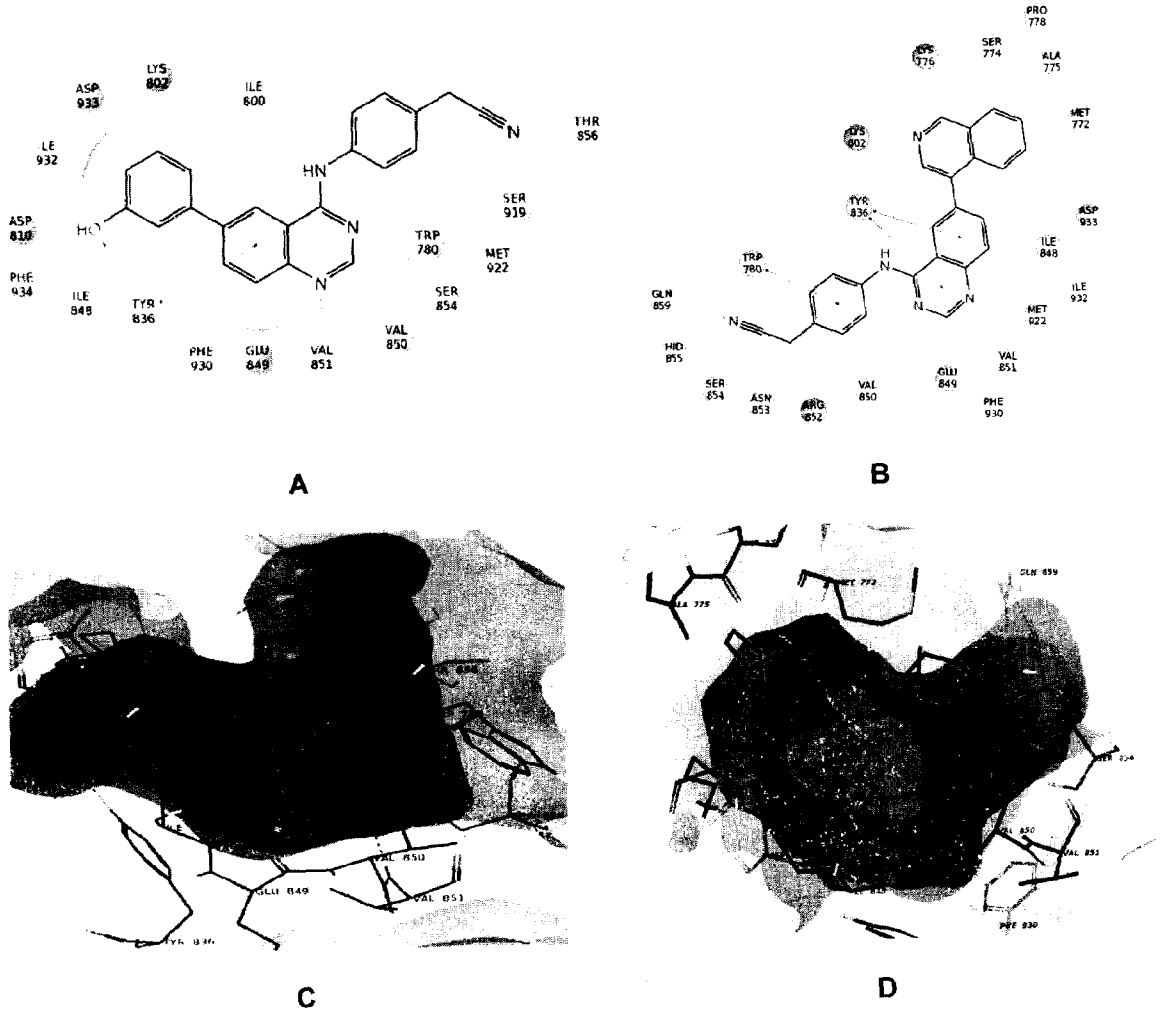

Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2015/000088

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D403/04 C07D405/04 C07D409/04 C07D239/94
A61K31/517 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/157191 A2 (SMITHKLINE BEECHAM CORP [US]; ADAMS NICHOLAS D [US]; BURGESS JOELLE LO) 24 December 2008 (2008-12-24) page 9, line 13; claim 1; examples 1-92	1-14
X	WO 2008/009078 A2 (GILEAD SCIENCES INC [US]; GAO LING-JIE [BE]; HERDEWIJN PIET ANDRE MAUR) 24 January 2008 (2008-01-24) claim 1; example 38	1-6
X	WO 96/16960 A1 (ZENECA LTD [GB]; BARKER ANDREW JOHN [GB]) 6 June 1996 (1996-06-06) claim 1; examples 1,2	1-6
X	WO 97/30034 A1 (ZENECA LTD [GB]) 21 August 1997 (1997-08-21) claim 1; example 2	1-6

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2015	13/07/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Seelmann, Ingo

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2015/000088

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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