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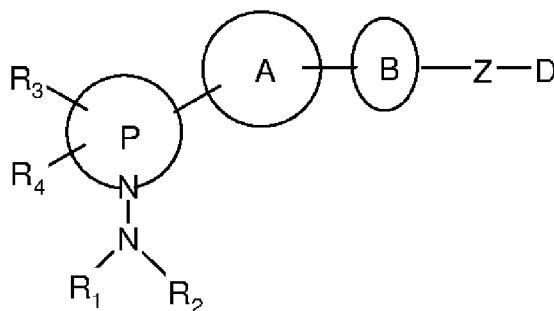
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[Continued on next page]

(54) **Title:** NOVEL HYDRAZINO COMPOUNDS AS BTK INHIBITORS

(I)

(57) **Abstract:** The present invention relates to novel hydrazino compounds of Formula (I) as Bruton tyrosine kinase inhibitors, process of preparation thereof, and to the use of the compounds in the preparation of pharmaceutical compositions for the therapeutic treatment of disorders involving mediation of Bruton tyrosine kinase in humans.



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NOVEL HYDRAZINO COMPOUNDS AS BTK INHIBITORS

RELATED APPLICATIONS

- 5 This application claims the benefit of Indian Patent Application no. IN 201621003737 filed on February 02, 2016 which is hereby incorporated by reference.

FIELD OF THE INVENTION

- 10 The present invention relates to novel hydrazino compounds as Bruton tyrosine kinase (BTK) inhibitors, process of preparation thereof, and to the use of the compounds in the preparation of pharmaceutical compositions for the therapeutic treatment of disorders involving mediation of Bruton tyrosine kinase in humans.

15 BACKGROUND OF THE INVENTION

- Involvement of BTK in signal transduction pathways regulating B-cell proliferation, differentiation and survival has been a ground breaking discovery and has led to developments of drugs for the treatment of B-cell malignancies. Improper /auto activated
20 BTK signaling is considered to be the major cause in several haematological malignancies such as chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL) etc. (Li *et al.* Journal of Med. Chem., 2014, 57(12), 5112-5128; Seng-Lai Tan *et al.*, Pharmacology and Therapeutics, 2013, 138, 294-309).

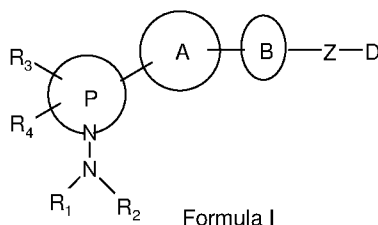
- 25 First in class BTK inhibitor, Ibrutinib, which is disclosed in US patent number 7514444 is presently marketed for the treatment of mantle cell lymphoma and chronic lymphocytic leukemia under the trade name Imbruvica[®]. The clinical and commercial success of Ibrutinib has led to discovery of newer BTK inhibitors. WIPO publication number WO 2015002894A1, WO 2014188173A1, WO 2014188173A1, WO 2014100748A1,
30 WO2011031896, WO2013155347, WO2014130856, WO2015165279A1; US patent numbers 7169791, 6596746, 6002008, 8114874, 7728131 and US publication US 2015 0005277, US20140079690 discloses various compounds as BTK inhibitors.

The present inventors have found novel hydrazine compounds which have shown potent BTK inhibitory activity.

SUMMARY OF THE INVENTION

5

The present invention provides a compound of Formula I and pharmaceutically acceptable salts thereof



10 wherein, R_1 is selected from a group consisting of hydrogen, $-C_{1-4}$ alkyl, $-C_{3-4}$ alkenyl, $-C_{3-4}$ alkynyl, $-C_{1-4}$ haloalkyl, $-C_{2-4}$ haloalkenyl, $-C_{3-4}$ haloalkylalkynyl, $-C_{1-4}$ cyanoalkyl, $-C_{2-4}$ cyanoalkenyl, $-C_{2-4}$ cyanoalkynyl, $-C_{2-5}$ O-alkyl, $-C_{2-5}$ O-haloalkyl, $-C_{3-6}$ cycloalkyl, $-C_{4-6}$ heterocycloalkyl containing 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with $-C_{1-4}$ alkyl or $-CO-C_{1-}$
 15 4 alkyl group; and when R_1 is alkenyl or alkynyl, the double and triple bond, respectively, is not on the carbon directly attached to the nitrogen atom;

R_2 is selected from hydrogen, $-C_{1-4}$ alkyl, $-C_{3-4}$ alkenyl, $-C_{3-4}$ alkynyl, $-C_{1-4}$ haloalkyl, $-C_{2-4}$ haloalkenyl, $-C_{3-4}$ haloalkylalkynyl, $-C_{1-4}$ cyanoalkyl, $-C_{2-4}$ cyanoalkenyl, $-C_{2-4}$ cyanoalkynyl, $-$
 20 C_{2-5} O-alkyl, $-C_{2-5}$ O-haloalkyl, $-C_{3-6}$ cycloalkyl, $-CN$, $-C(O)R_5$, $-C(S)R_5$, $-SO_2R_5$, $-SOR_5$, $-CONHSO_2R_5$, $-CSNHSO_2R_5$, $-CONHCOR_5$, $-CSNHCOR_5$, $-CON(C_{1-4} \text{ alkyl})COR_5$, $-$, $-C(S)N(C_{1-4} \text{ alkyl})COR_5$, $-CON(C_{1-4} \text{ alkyl})SO_2R_5$, $-CSN(C_{1-4} \text{ alkyl})SO_2R_5$, $-C(=NR_6)R_5$, $-C(=NR_6)N(R_6)C(O)R_5$, $-C_{4-6}$ heterocycloalkyl containing 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further
 25 substituted with $-C_{1-4}$ alkyl and $-CO-C_{1-4}$ alkyl group, and when R_2 is alkenyl or alkynyl, the double and triple bond, respectively, is not on the carbon directly attached to the nitrogen atom;

wherein R_5 is selected from a group comprising R_5' , hydrogen, $-NH_2$, $-NHOH$, $-NR_1(C_{1-4}$
 30 alkyl)-, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-6}$ cycloalkenyl, $-C_{1-3}$

heterocycloalkenylalkyl, -C₃₋₆ heterocycloalkyl, -NH C₆₋₁₀ aryl, C₅₋₁₀ heteroaryl containing 1-3 heteroatoms selected from oxygen, nitrogen or sulfur; wherein alkyl, cycloalkenyl, cycloalkyl are optionally further substituted with CN group; and aryl, heteroaryl and heterocycloalkenylalkyl are optionally substituted with one or more halogen; and R₅ is selected from a group consisting of -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ alkenylaryl, -C₃₋₆ alkenylheteroaryl, -C₃₋₆ alkynylaryl, -C₃₋₆ alkynylheteroaryl, -CH=CH-(CH₂)_n-COOR₆, -C(=CH₂)CH₂COOR₆, -C≡C-(CH₂)_n-COOR₆, -CH=CH-(CH₂)_n-CN, -C≡C-(CH₂)_n-CN, -CH=CH-(CH₂)_n-OR₆, -C≡C-(CH₂)_n-OR₆, -CH=CH-(CH₂)_n-NR₆R₇ and -C≡C-(CH₂)_n-NR₆R₇;

n is an integer and at each occurrence is selected from 0 to 3; m is an integer and at each occurrence is selected from 1 to 3; R₆ and R₇ at each occurrence are independently selected from hydrogen, -C₁₋₃ alkyl and -C₄₋₆ cycloalkyl or R₆ and R₇ together forms a 4-6 membered ring optionally containing one additional heteroatom selected from oxygen, nitrogen, or sulfur;

or R₂ is an aryl group substituted with at least one halogen atom and at least one group at *ortho* or *para* position with respect to halogen atom selected from -CN, -COOH, -COO-C₁₋₃ alkyl, -CON(-C₁₋₃ alkyl), -NO₂, -SO₂C₁₋₃ alkyl, -SO₂NH₂, -SO₂NH-C₁₋₃ alkyl, -SO₂N(C₁₋₃ alkyl)₂, -CO-C₁₋₃ alkyl, -CONH₂, -CONH(C₁₋₃ alkyl), -CON(C₁₋₃ alkyl)₂;

or R₂ is a 6 membered heteroaryl ring containing 1-3 nitrogen atoms or 5 membered ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur wherein the 6 membered or 5 membered ring is substituted with at least one group selected from halogen, C₃₋₆ alkenyl, C₃₋₆ alkynyl, -COOH and -SH group; and optionally further substituted with one or more groups selected from -CN, S-C₂₋₄ alkenyl, -COOH, -OC₁₋₆ alkyl, -COO-C₁₋₃ alkyl, -CON(-C₁₋₃ alkyl), -NO₂, -SO₂C₁₋₃ alkyl, -SO₂NH₂, -SO₂NH-C₁₋₃ alkyl, -SO₂N(C₁₋₃ alkyl)₂, -CO-C₁₋₃ alkyl, -CONH₂, -CONH(C₁₋₃ alkyl), -CON(C₁₋₃ alkyl)₂;

or R₂ is a group selected from moieties provided in Figure 1

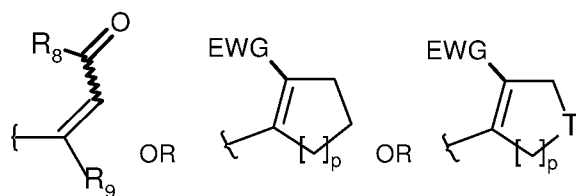


Figure 1

wherein, R_8 and R_9 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl or R_8 and R_9 together forms 4 to 10 membered mono or bicyclic carbocyclic ring optionally substituted with one or more C_{1-3} alkyl group or a 5 to 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with $-C_{1-4}$ alkyl or $-CO-C_{1-4}$ alkyl group;

EWG is an electron withdrawing group selected from $-COOR_{10}$, $-CON(R_{10})_2$, $-CN$, $-NO_2$, $-SO_3H$, $-SO_2N(R_{10})_2$, $-SO_2R_{10}$ wherein R_{10} is selected from hydrogen, $-C_{1-3}$ alkyl and $-C_{4-6}$ cycloalkyl;

T is a heteroatom selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with $-C_{1-4}$ alkyl or $-CO-C_{1-4}$ alkyl group;

p is an integer selected from 1 and 2;

'{' is the point of attachment of R_2 with nitrogen atom;

or

R_1 and R_2 together forms a group selected from the groups provided in Figure 2

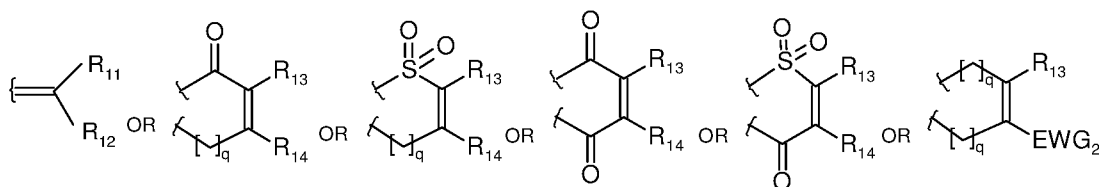


Figure 2

wherein, R_{11} and R_{12} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, $-COOR$, $-CON(R)_2$, $-CH=CHCOOR$, $-CH=CHCONRR'$, $-C_{4-6}$ heteroaryl containing 1-3 heteroatoms selected from oxygen, nitrogen or sulfur, the heteroaryl is optionally substituted with one or more halogen atoms; wherein R and R' are selected from

hydrogen or C₁₋₆ alkyl or R and R' together with the nitrogen to which they are attached forms a 5-6 membered saturated or unsaturated ring;

or R₁₁ and R₁₂ together forms 4 to 10 membered mono or bicyclic saturated or unsaturated carbocyclic ring or a 5 to 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from oxygen, nitrogen and sulfur and when the heteroatom is nitrogen it is optionally further substituted with -C₁₋₄ alkyl or -CO-C₁₋₄ alkyl group; the carbocyclic and the heterocyclic rings are optionally further substituted with one or more halogen atoms;

R₁₃ and R₁₄ are independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl or R₁₃ and R₁₄ together forms 4 to 10 membered mono or bicyclic carbocyclic ring or a 5 to 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with -C₁₋₄ alkyl or -CO-C₁₋₄ alkyl group;

EWG₂ is an electron withdrawing group selected from -COOR₁₅, -CON(R₁₅)₂, -CN, -NO₂, -SO₃H, -SO₂N(R₁₅)₂, -SO₂R₁₅ wherein R₁₅ at each occurrence is independently selected from hydrogen, -C₁₋₃ alkyl and -C₄₋₆ cycloalkyl;

q is an integer selected from 1 and 2;

'{' is the point of attachment of R₁ and R₂ with nitrogen atom;

R₃ and R₄ are independently selected from hydrogen, halogen, C₁₋₆ alkyl and C₃₋₆ cycloalkyl;

ring P is 4 to 13 membered saturated or unsaturated monocyclic, bicyclic or tricyclic ring optionally containing one additional heteroatom selected from oxygen, nitrogen and sulfur;

ring A is a heterocycle selected from moieties provided in Figure 3

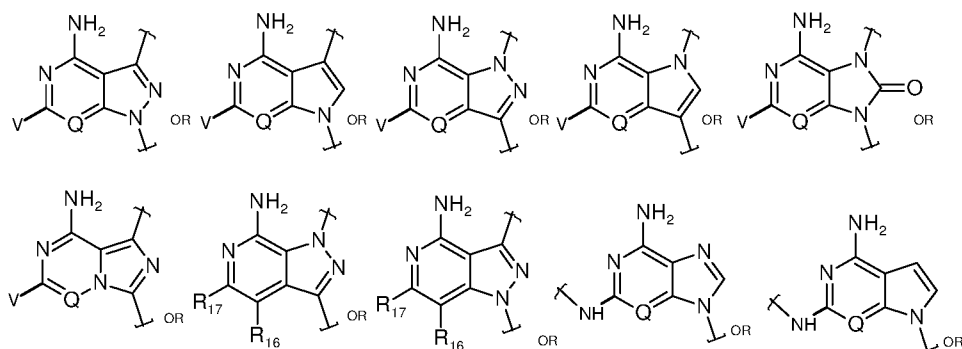


Figure 3

wherein Q is selected from CH or nitrogen;

R₁₆ and R₁₇ together forms a phenyl ring optionally substituted with halogen, -O-C₁₋₃ alkyl, -
5 COOH, -COOC₁₋₃ alkyl, -C₁₋₃ alkyl, -OH;

or R₁₆ and R₁₇ together forms a 5 to 6 membered heterocyclic ring containing 1 to 2
heteroatoms selected from oxygen, nitrogen and sulfur;

10 V independently selected from R₁₈, halogen, -C₁₋₄ haloalkyl, -C₂₋₄ alkenyl, -C₂₋₄ alkynyl, -
SR₁₈, -OR₁₈, -SOR₁₈, -SO₂R₁₈, -N(R₁₈)₂, -NHCHO, -NHCOCH₃, -C₄₋₆ hetrocycloalkyl, -C₄₋₆
cycloalkenyl, -CO-R₁₈, -CN and -CHO wherein R₁₈ at each occurrence is independently
selected from hydrogen, -C₁₋₄ alkyl and -C₃₋₆ cycloalkyl;

15 ‘{’ represents the attachment to ring B;

‘[’ represents the attachment to ring P;

ring B is selected from moieties provided in Figure 4

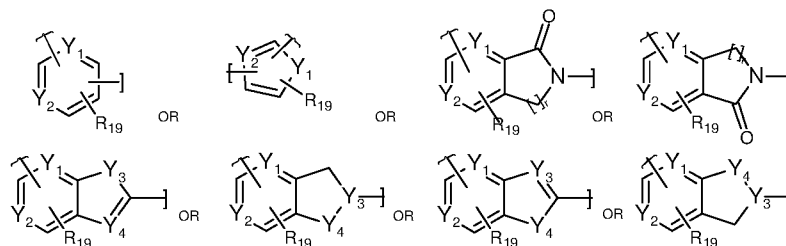


Figure 4

wherein, R₁₉ is selected from hydrogen, halogen, hydroxyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), -C₁₋₆ haloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ alkyl, -O C₃₋₆ alkenyl, -O C₃₋₆ alkynyl, -S-C₁₋₆ alkyl, -CN, -CO-C₁₋₄ alkyl, -CO—C₃₋₆ cycloalkyl, -COOH, -CONH₂, -CON(C₁₋₆ alkyl)₂, -CONH(C₁₋₆ alkyl), -NHC(O) -C₁₋₄ alkyl, -N(C₁₋₄ alkyl)C(O) C₁₋₄ alkyl and when R₁₉ is -OC₃₋₆ alkenyl or -O C₃₋₆ alkynyl the double and triple bond, respectively, is not on the carbon directly attached to the oxygen atom;

Y₁, Y₂, Y₃ and Y₄ are independently and appropriately selected from CH, NR₂₀, O, or S; wherein, R₂₀ is selected from hydrogen, -C₁₋₃ alkyl and -C₄₋₆ cycloalkyl;

10 r is an integer selected from 1 to 3;

'{' represents the position of attachment to ring A;

'[' represents the position of attachment to Z;

Z is a bond or is selected from -O-, -S-, -NH-, -N(C₁₋₄ alkyl)-, -N(C₁₋₆ alkyl)CO-, -C(O)NH-, -C(C₁₋₂ alkyl)₂-, -C(O)-, -S(O)-, -S(O)₂-, -CH₂O-, -OCH₂-, -CH=CH-, -CH₂-, -N(CH₂CN)- and -NHC(O)-;

15

D is a ring containing 5 to 13 membered aryl, fused aryl, heteroaryl, fused heteroaryl, saturated or unsaturated monocyclic, bicyclic or tricyclic carbocyclic ring containing 0-3 heteroatoms selected from nitrogen, oxygen and sulfur; optionally substituted with C₁₋₃ alkyl;

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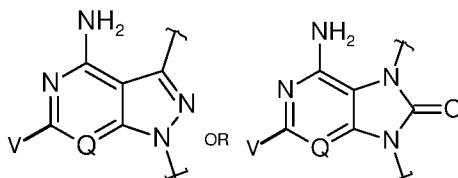
or D is selected from -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₄ alkyl-O-C₂₋₄ alkyl, -C₃₋₆ cycloalkyl-O-C₂₋₄ alkyl, -C₁₋₄ alkyl-O-C₃₋₆ cycloalkyl, -C₁₋₄ haloalkyl-O-C₂₋₄ alkyl, -C₁₋₄ haloalkyl-S-C₂₋₄ alkyl and -C₁₋₄ alkyl-S-C₂₋₄ alkyl;

25 with the proviso that when:

ring B and D are phenyl;

Z is selected from -O-, -S-, -NH-, -N(C₁₋₄ alkyl)- or -C(O)-;

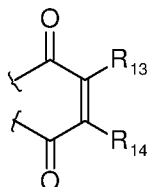
Ring A is selected from



30 and V is hydrogen then:

R_2 is not selected from $-C(O)R_5$, $-C(S)R_5$, $-SO_2R_5$, $-SOR_5$ wherein R_5 is R_5 ; and

R_1 and R_2 together does not form the following group



- 5 The compounds of the present invention were found to be potent and selective BTK inhibitors and can be useful in treatment of the diseases mediated by BTK receptors.

DEFINITION

- 10 “**Salts**” according to the invention include those formed with either organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulfuric, citric, tartaric, phosphoric, acetic, trifluoroacetic, triphenylacetic, phenylacetic, succinic, oxalic, fumaric, maleic, glutamic, aspartic, oxalacetic, methanesulphonic, ethanesulphonic, *p*-toluenesulphonic, benzenesulphonic,
- 15 naphthalenesulphonic or naphthalenedisulphonic, salicylic, glutaric, gluconic, mandelic, cinnamic, ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic acids and butane-1,4-disulfonic acid. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline
- 20 earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexylamine and *N*-methyl-D-glucamine.

- The term “**alkyl**” refers to a saturated hydrocarbon chain radical that includes solely carbon and hydrogen atoms in the backbone, either linear or branched and which is attached to the
- 25 rest of the molecule by a single bond, e.g., methyl, ethyl, *n*-propyl, 1-methylethyl (isopropyl), *n*-butyl, *n*-pentyl, and 1,1-dimethylethyl (*t*-butyl). The alkyl chain may have 1 to 13 carbon atoms unless specified otherwise. Unless set forth or recited to the contrary, all alkyl groups described or claimed herein may be unsubstituted or substituted with groups selected from halogen, $-OC_{1-6}$ alkyl, $-OC_{3-6}$ cycloalkyl, CN, $-COOH$, $-COO-C_{1-3}$ alkyl, $-CON(-C_{1-3}$ alkyl), $-$
- 30 NO_2 , $-SO_2C_{1-3}$ alkyl, $-SO_2N-C_{1-3}$ alkyl, $-CO-C_{1-3}$ alkyl.

The numerical in phrases like “C₁₋₄ alkyl”, refers that there are 1 to 4 carbon atoms in the alkyl chain.

The term "**alkenyl**" refers to a hydrocarbon chain containing at least one carbon-carbon double bond, and may have (*E*) or (*Z*) configuration. An alkenyl group may contain 2 to 8 carbon atoms unless specified otherwise. Non-limiting examples of alkenyl groups include 2-propenyl (allyl), 2-methyl-2-propenyl, and (*Z*)-2-butenyl. Unless set forth or recited to the contrary, all alkenyl groups described or claimed herein may be straight chain or branched, unsubstituted or substituted with groups selected from halogen, -OC₁₋₆ alkyl, -OC₃₋₆ cycloalkyl, CN, -COOH, -COO-C₁₋₃ alkyl, -CON(-C₁₋₃ alkyl), -NO₂, -SO₂C₁₋₃ alkyl, -SO₂N-C₁₋₃ alkyl, -CO-C₁₋₃ alkyl.

The term "**alkynyl**" refers to a hydrocarbon chain having at least one carbon-carbon triple bond. An alkynyl group may contain 2 to 8 carbon atoms unless specified otherwise. Non-limiting examples of alkynyl groups include 2-propynyl and 3-butynyl. Unless set forth or recited to the contrary all alkynyl groups described or claimed herein may form part of a straight or branched, substituted or unsubstituted chains. The alkynyl group may be unsubstituted or substituted with the groups selected from halogen, -OC₁₋₆ alkyl, -OC₃₋₆ cycloalkyl, CN, -COOH, -COO-C₁₋₃ alkyl, -CON(-C₁₋₃ alkyl), -NO₂, -SO₂C₁₋₃ alkyl, -SO₂N-C₁₋₃ alkyl, -CO-C₁₋₃ alkyl.

The term "**halo**", as used herein includes chloro, fluoro, bromo and iodo. Similarly the terms "**haloalkyl**", "**haloalkenyl**" and "**haloalkynyl**" refers to halo substituted alkyl, alkenyl and alkynyl chain, respectively.

The term "**cycloalkyl**" denotes a non-aromatic mono-, or multicyclic ring system of 3 to about 13 carbon atoms. Monocyclic rings include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Examples of simple multicyclic cycloalkyl groups include perhydronaphthyl, perhydroindenyl etc; bridged multicyclic groups include adamantyl and norbornyl etc, and spiro multicyclic groups for e.g., spiro(4,4)non-2-yl. Unless set forth or recited to the contrary, all cycloalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "**heterocycloalkyl**" refers to a cycloalkyl ring containing a heteroatom. Unless specifically specified, the heteroatom is selected from N, O and S.

5 The term "**cycloalkenyl**" refers to a monocyclic or bicyclic, 3 to 14 membered ring system, which is unsaturated. Representative examples of cycloalkenyl include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl.

The terms "**alkenylaryl**" and "**alkynylaryl**" refers to alkenyl and alkynyl group, respectively, are further substituted with an aryl group. Similarly, "**alkenylheteroaryl**" and
10 "**alkynylheteroaryl**" refers to alkenyl chain is substituted with a heteroaryl group.

The term "**aryl**" as used herein, include aromatic mono or bi-cyclic compound having 5-10 atoms which may be optionally fused with a cycloalkyl ring. The non-limiting examples of aryl group are phenyl and naphthyl.

15 The term "**heteroaryl**" as used herein, refers to an aryl group containing 1-4 heteroatoms. Unless specifically specified, the heteroatom is selected from N, O and S. The non-limiting examples of heteroaryl group are oxazolyl, isoxazolyl, imidazolyl, furyl, pyrrolyl, triazolyl, triazinyl, tetrazolyl, thienyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyrazinyl,
20 pyridazinyl, benzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothienyl, benzopyranyl, quinolinyl, isoquinolinyl, quinazolinyl, pyrazolo[3,4-*d*]pyrimidin and pyrrolo[2,3-*d*]pyrimidin.

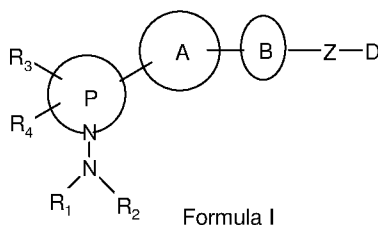
The term "**heterocyclic**" or "**heterocyclyl**" unless otherwise specified refers to substituted or
25 unsubstituted non-aromatic 3 to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from nitrogen, oxygen and sulfur. The heterocyclic ring radical may be a mono-, bi- or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition,
30 the nitrogen atom may be optionally quarternized; also, unless otherwise constrained by the definition the heterocyclic ring or heterocyclyl may optionally contain one or more olefinic bond(s) thus forming heterocycloalkenyl group. Examples of such heterocyclic ring radicals include, but are not limited to azepinyl, azetidiny, benzodioxolyl, benzodioxanyl, chromanyl, dioxolanyl, dioxaphospholanyl, isoxazolidinyl, morpholinyl, oxazolinyl, oxazolidinyl,

oxadiazolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, octahydroindolyl, octahydroisoindolyl, perhydroazepinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, piperidinyl, phenothiazinyl, phenoxazinyl, quinuclidinyl, tetrahydroisquinolyl, tetrahydrofuryl, tetrahydropyranyl, thiazolynyl, thiazolidinyl, thiamorpholinyl, thiamorpholinyl sulfoxide and thiamorpholinyl sulfone. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure. Unless set forth or recited to the contrary, all heterocyclyl groups described or claimed herein may be substituted or unsubstituted.

The term “**heterocycloalkenylalkyl**” refers to alkyl chain substituted with a heterocycloalkenyl ring.

DESCRIPTION

In one aspect, the present invention provides a compound of Formula I and pharmaceutically acceptable salts thereof



wherein, R₁ is selected from a group consisting of hydrogen, -C₁₋₄ alkyl, -C₃₋₄ alkenyl, -C₃₋₄ alkynyl, -C₁₋₄ haloalkyl, -C₂₋₄ haloalkenyl, -C₃₋₄ haloalkylalkynyl, -C₁₋₄ cyanoalkyl, -C₂₋₄ cyanoalkenyl, -C₂₋₄ cyanoalkynyl, -C₂₋₅ O-alkyl, -C₂₋₅ O-haloalkyl, -C₃₋₆ cycloalkyl, -C₄₋₆ heterocycloalkyl containing 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with -C₁₋₄ alkyl or -CO-C₁₋₄ alkyl group; and when R₁ is alkenyl or alkynyl, the double and triple bond, respectively, is not on the carbon directly attached to the nitrogen atom;

R₂ is selected from hydrogen, -C₁₋₄ alkyl, -C₃₋₄ alkenyl, -C₃₋₄ alkynyl, -C₁₋₄ haloalkyl, -C₂₋₄ haloalkenyl, -C₃₋₄ haloalkylalkynyl, -C₁₋₄ cyanoalkyl, -C₂₋₄ cyanoalkenyl, -C₂₋₄ cyanoalkynyl, -C₂₋₅ O-alkyl, -C₂₋₅ O-haloalkyl, -C₃₋₆ cycloalkyl, -CN, -C(O)R₅, -C(S)R₅, -SO₂R₅, -SOR₅, -CONHSO₂R₅, -CSNHSO₂R₅, -CONHCOR₅, -CSNHCOR₅, -CON(C₁₋₄ alkyl)COR₅, -

C(S)N(C₁₋₄ alkyl)COR₅, -CON(C₁₋₄ alkyl)SO₂R₅, -CSN(C₁₋₄ alkyl)SO₂R₅ -C(=NR₆)R₅, -C(=NR₆)N(R₆)C(O)R₅, -C₄₋₆ heterocycloalkyl containing 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with -C₁₋₄ alkyl and -CO-C₁₋₄ alkyl group, and when R₂ is alkenyl or alkynyl, the double and triple bond, respectively, is not on the carbon directly attached to the nitrogen atom;

wherein R₅ is selected from a group comprising R₅, hydrogen, -NH₂, -NHOH, -NR₁(C₁₋₄ alkyl)-, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ haloalkyl, -C₃₋₆ cycloalkenyl, -C₁₋₃ heterocycloalkenylalkyl, -C₃₋₆ heterocycloalkyl, -NH C₆₋₁₀ aryl, C₅₋₁₀ heteroaryl containing 1-3 heteroatoms selected from oxygen, nitrogen or sulfur; wherein alkyl, cycloalkenyl, cycloalkyl are optionally further substituted with CN group; and aryl, heteroaryl and heterocycloalkenylalkyl are optionally substituted with one or more halogen; and R₅ is selected from a group consisting of -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ alkenylaryl, -C₃₋₆ alkenylheteroaryl, -C₃₋₆ alkynylaryl, -C₃₋₆ alkynylheteroaryl, -CH=CH-(CH₂)_n-COOR₆, -C(=CH₂)CH₂COOR₆, -C≡C-(CH₂)_n-COOR₆, -CH=CH-(CH₂)_n-CN, -C≡C-(CH₂)_n-CN, -CH=CH-(CH₂)_n-OR₆, -C≡C-(CH₂)_n-OR₆, -CH=CH-(CH₂)_n-NR₆R₇ and -C≡C-(CH₂)_n-NR₆R₇;

n is an integer and at each occurrence is selected from 0 to 3; m is an integer and at each occurrence is selected from 1 to 3; R₆ and R₇ at each occurrence are independently selected from hydrogen, -C₁₋₃ alkyl and -C₄₋₆ cycloalkyl or R₆ and R₇ together forms a 4-6 membered ring optionally containing one additional heteroatom selected from oxygen, nitrogen, or sulfur;

or R₂ is an aryl group substituted with at least one halogen atom and at least one group at *ortho* or *para* position with respect to halogen atom selected from -CN, -COOH, -COO-C₁₋₃ alkyl, -CON(-C₁₋₃ alkyl), -NO₂, -SO₂C₁₋₃ alkyl, -SO₂NH₂, -SO₂NH-C₁₋₃ alkyl, -SO₂N(C₁₋₃ alkyl)₂, -CO-C₁₋₃ alkyl, -CONH₂, -CONH(C₁₋₃ alkyl), -CON(C₁₋₃ alkyl)₂;

or R₂ is a 6 membered heteroaryl ring containing 1-3 nitrogen atoms or 5 membered ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur wherein the 6 membered or 5 membered ring is substituted with at least one group selected from halogen, C₃₋₆ alkenyl, C₃₋₆ alkynyl, -COOH and -SH group; and optionally further substituted with one or more groups selected from -CN, S-C₂₋₄ alkenyl, -COOH, -OC₁₋₆ alkyl, -COO-C₁₋₃ alkyl, -

CON(-C₁₋₃ alkyl), -NO₂, -SO₂C₁₋₃ alkyl, -SO₂NH₂, -SO₂NH-C₁₋₃ alkyl, -SO₂N(C₁₋₃ alkyl)₂, -CO-C₁₋₃ alkyl, -CONH₂, -CONH(C₁₋₃ alkyl), -CON(C₁₋₃ alkyl)₂;

or R₂ is a group selected from moieties provided in Figure 1

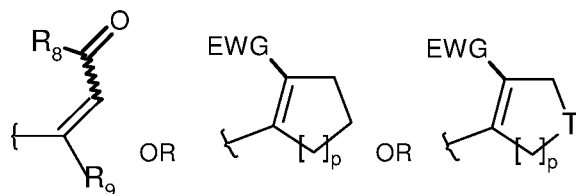


Figure 1

5

wherein, R₈ and R₉ are independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl or R₈ and R₉ together forms 4 to 10 membered mono or bicyclic carbocyclic ring optionally substituted with one or more C₁₋₃ alkyl group or a 5 to 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with -C₁₋₄ alkyl or -CO-C₁₋₄ alkyl group;

10

EWG is an electron withdrawing group selected from -COOR₁₀, -CON(R₁₀)₂, -CN, -NO₂, -SO₃H, -SO₂N(R₁₀)₂, -SO₂R₁₀ wherein R₁₀ is selected from hydrogen, -C₁₋₃ alkyl and -C₄₋₆ cycloalkyl;

15

T is a heteroatom selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with -C₁₋₄ alkyl or -CO-C₁₋₄ alkyl group;

20 p is an integer selected from 1 and 2;

'{' is the point of attachment of R₂ with nitrogen atom;

or

R₁ and R₂ together forms a group selected from the groups provided in Figure 2

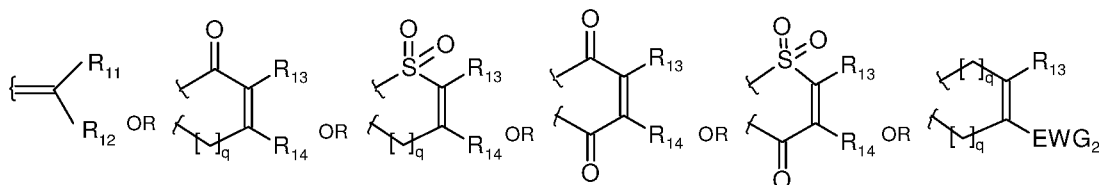


Figure 2

25

wherein, R_{11} and R_{12} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, $-\text{COOR}$, $-\text{CON}(\text{R})_2$, $-\text{CH}=\text{CHCOOR}$, $-\text{CH}=\text{CHCONRR}'$, $-\text{C}_{4-6}$ heteroaryl containing 1-3 heteroatoms selected from oxygen, nitrogen or sulfur, the heteroaryl is optionally substituted with one or more halogen atoms; wherein R and R' are selected from
5 hydrogen or C_{1-6} alkyl or R and R' together with the nitrogen to which they are attached forms a 5-6 membered saturated or unsaturated ring;

or R_{11} and R_{12} together forms 4 to 10 membered mono or bicyclic saturated or unsaturated carbocyclic ring or a 5 to 6 membered heterocyclic ring containing 1 to 2 heteroatoms
10 selected from oxygen, nitrogen and sulfur and when the heteroatom is nitrogen it is optionally further substituted with $-\text{C}_{1-4}$ alkyl or $-\text{CO}-\text{C}_{1-4}$ alkyl group; the carbocyclic and the heterocyclic rings are optionally further substituted with one or more halogen atoms;

R_{13} and R_{14} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl
15 or R_{13} and R_{14} together forms 4 to 10 membered mono or bicyclic carbocyclic ring or a 5 to 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with $-\text{C}_{1-4}$ alkyl or $-\text{CO}-\text{C}_{1-4}$ alkyl group;

20 EWG_2 is an electron withdrawing group selected from $-\text{COOR}_{15}$, $-\text{CON}(\text{R}_{15})_2$, $-\text{CN}$, $-\text{NO}_2$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{N}(\text{R}_{15})_2$, $-\text{SO}_2\text{R}_{15}$ wherein R_{15} at each occurrence is independently selected from hydrogen, $-\text{C}_{1-3}$ alkyl and $-\text{C}_{4-6}$ cycloalkyl;

q is an integer selected from 1 and 2;

25

'{' is the point of attachment of R_1 and R_2 with nitrogen atom;

R_3 and R_4 are independently selected from hydrogen, halogen, C_{1-6} alkyl and C_{3-6} cycloalkyl;

30 ring P is 4 to 13 membered saturated or unsaturated monocyclic, bicyclic or tricyclic ring optionally containing one additional heteroatom selected from oxygen, nitrogen and sulfur;

ring A is a heterocycle selected from moieties provided in Figure 3

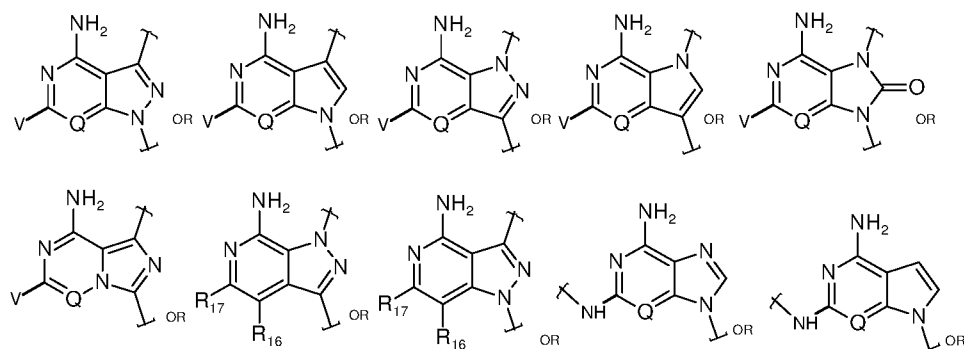


Figure 3

wherein Q is selected from CH or nitrogen;

R₁₆ and R₁₇ together forms a phenyl ring optionally substituted with halogen, -O-C₁₋₃ alkyl, -
5 COOH, -COOC₁₋₃ alkyl, -C₁₋₃ alkyl, -OH;

or R₁₆ and R₁₇ together forms a 5 to 6 membered heterocyclic ring containing 1 to 2
heteroatoms selected from oxygen, nitrogen and sulfur;

10 V independently selected from R₁₈, halogen, -C₁₋₄ haloalkyl, -C₂₋₄ alkenyl, -C₂₋₄ alkynyl, -
SR₁₈, -OR₁₈, -SOR₁₈, -SO₂R₁₈, -N(R₁₈)₂, -NHCHO, -NHCOCH₃, -C₄₋₆ hetrocycloalkyl, -C₄₋₆
cycloalkenyl, -CO-R₁₈, -CN and -CHO wherein R₁₈ at each occurrence is independently
selected from hydrogen, -C₁₋₄ alkyl and -C₃₋₆ cycloalkyl;

15 ‘{’ represents the attachment to ring B;

‘[’ represents the attachment to ring P;

ring B is selected from moieties provided in Figure 4

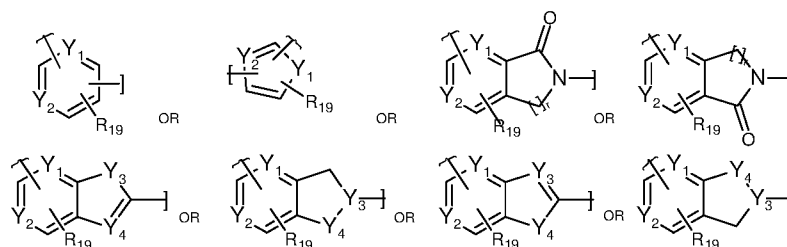


Figure 4

20

wherein, R₁₉ is selected from hydrogen, halogen, hydroxyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), -C₁₋₆ haloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ alkyl, -O C₃₋₆ alkenyl, -O C₃₋₆ alkynyl, -S-C₁₋₆ alkyl, -CN, -CO-C₁₋₄ alkyl, -CO—C₃₋₆ cycloalkyl, -COOH, -CONH₂, -CON(C₁₋₆ alkyl)₂, -CONH(C₁₋₆ alkyl), -NHC(O) -C₁₋₄ alkyl, -N(C₁₋₄ alkyl)C(O) C₁₋₄ alkyl and when R₁₉ is -OC₃₋₆ alkenyl or -O C₃₋₆ alkynyl the double and triple bond, respectively, is not on the carbon directly attached to the oxygen atom;

Y₁, Y₂, Y₃ and Y₄ are independently and appropriately selected from CH, NR₂₀, O, or S; wherein, R₂₀ is selected from hydrogen, -C₁₋₃ alkyl and -C₄₋₆ cycloalkyl;

r is an integer selected from 1 to 3;

'{' represents the position of attachment to ring A;

'[' represents the position of attachment to Z;

Z is a bond or is selected from -O-, -S-, -NH-, -N(C₁₋₄ alkyl)-, -N(C₁₋₆ alkyl)CO-, -C(O)NH-, -C(C₁₋₂ alkyl)₂-, -C(O)-, -S(O)-, -S(O)₂-, -CH₂O-, -OCH₂-, -CH=CH-, -CH₂-, -N(CH₂CN)- and -NHC(O)-;

D is a ring containing 5 to 13 membered aryl, fused aryl, heteroaryl, fused heteroaryl, saturated or unsaturated monocyclic, bicyclic or tricyclic carbocyclic ring containing 0-3 heteroatoms selected from nitrogen, oxygen and sulfur; optionally substituted with C₁₋₃ alkyl;

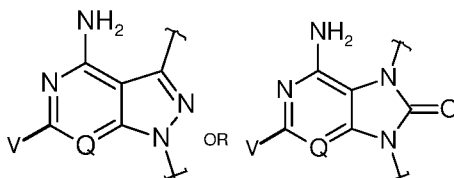
or D is selected from -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₄ alkyl-O-C₂₋₄ alkyl, -C₃₋₆ cycloalkyl-O-C₂₋₄ alkyl, -C₁₋₄ alkyl-O-C₃₋₆ cycloalkyl, -C₁₋₄ haloalkyl-O-C₂₋₄ alkyl, -C₁₋₄ haloalkyl-S-C₂₋₄ alkyl and -C₁₋₄ alkyl-S-C₂₋₄ alkyl;

with the proviso that when:

ring B and D are phenyl;

Z is selected from -O-, -S-, -NH-, -N(C₁₋₄ alkyl)- or -C(O)-;

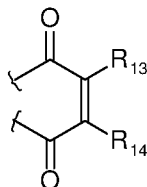
Ring A is selected from



and V is hydrogen then:

R_2 is not selected from $-C(O)R_5$, $-C(S)R_5$, $-SO_2R_5$, $-SOR_5$ wherein R_5 is R_5 ; and

R_1 and R_2 together does not form the following group



In an embodiment the present invention provides a compound of Formula I; wherein

5 R_1 is hydrogen;

R_2 is selected from $-CN$, $-C(O)R_5$, $-C(S)R_5$, $-SO_2R_5$ wherein,

R_5 is selected from a group comprising R_5 , $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-3}$ heterocycloalkenylalkyl, NH C_{6-10} aryl, C_{5-10} heteroaryl containing 1-3 heteroatoms selected from oxygen, nitrogen or sulfur, wherein

10 alkyl and cycloalkyl are optionally further substituted with CN group; and aryl, heteroaryl and heterocycloalkenylalkyl are optionally substituted with one or more halogen;

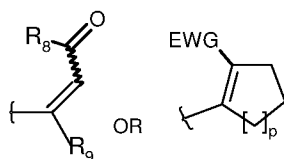
R_5 is selected from a group consisting of $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-CH=CH-(CH_2)_n-COOR_6$ and $-C(=CH_2)CH_2COOR_6$;

n is an integer and at each occurrence is selected from 0 to 3;

15 R_6 is selected from hydrogen, $-C_{1-3}$ alkyl;

or R_2 is a 6 membered heteroaryl ring substituted with at least one group selected from halogen, C_{3-6} alkenyl, C_{3-6} alkynyl and $-SH$ group; and optionally further substituted with one or more groups selected from $S-C_{2-4}$ alkenyl, $-COOH$, $-OC_{1-6}$ alkyl, $-CON(-C_{1-3}$ alkyl), $-NO_2$
20 and $-CONH_2$;

or R_2 is a group selected from following moieties

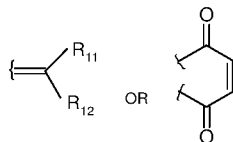


wherein, R_8 and R_9 are independently selected from hydrogen and C_{1-6} alkyl, or R_8 and R_9
25 together forms 4 to 10 membered mono-cyclic ring optionally substituted with one or more C_{1-3} alkyl group;

EWG is $-C(O)OC_{1-3}$ alkyl;

OR

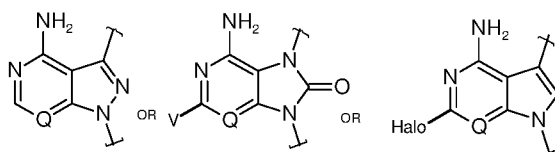
R₁ and R₂ together forms a group selected from following groups



wherein, R₁₁ and R₁₂ are independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, -COOR and -C₄₋₆ heteroaryl containing 1-3 heteroatoms selected from oxygen, nitrogen or sulfur; wherein R is hydrogen or C₁₋₆ alkyl and the heteroaryl is optionally substituted with one or more halogen atoms;

or R₁₁ and R₁₂ together forms substituted or unsubstituted 5 to 6 membered saturated or unsaturated mono carbocyclic ring or a 5 to 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from oxygen and nitrogen; and the carbocyclic and the heterocyclic rings are optionally further substituted with one or more halogen atoms; ring P is 4 to 6 membered saturated monocyclic, ring containing one additional heteroatom selected from nitrogen;

ring A is a heterocycle selected from following moieties



wherein Q is selected from CH or nitrogen;

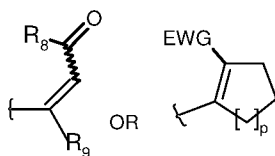
ring B is phenyl;

Z is selected from -O-, -C(O)NH- and -NHC(O)-;

D is phenyl or pyridine ring unsubstituted or substituted with C₁₋₃ alkyl.

In another preferred embodiment the present invention provides a compound of Formula I, wherein R₁ is hydrogen; R₂ is -C(O)R₅ or a 6 membered heteroaryl ring substituted with one or more halogen radical;

or R₂ is a group selected from following moieties



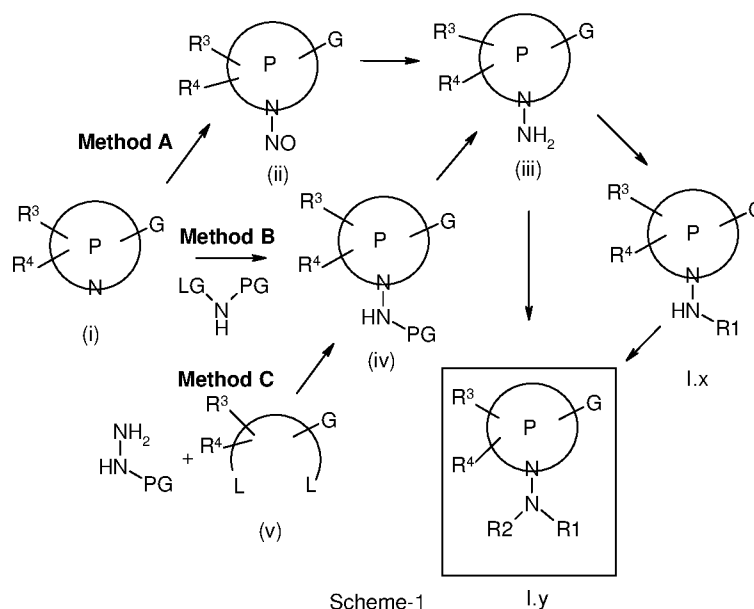
wherein, R_8 and R_9 are independently selected from hydrogen and C_{1-6} alkyl, or R_8 and R_9 together forms 4 to 10 membered mono-cyclic ring optionally substituted with one or more C_{1-3} alkyl group;

EWG is $-C(O)OC_{1-3}$ alkyl;

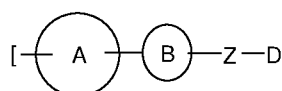
5 ring A is a heterocycle selected from following moieties.

The compounds of the present invention can be used as selective agents as inhibitors of BTK either alone or in combination with other related kinases inhibitors, or any other appropriate drugs. Thus the compound of present invention finds use in treating cancer, particularly in
 10 haematological malignancies such as chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL), follicular lymphoma (FL) or even disorder such as diffused large B-cell lymphoma (DLBCL) etc., in which the activated B-cell need to be controlled or the proliferation needs to be down regulated.

15 In an embodiment the compounds of present invention can be prepared by any of the following methods as described in the general scheme-1.



wherein G represents the following moiety



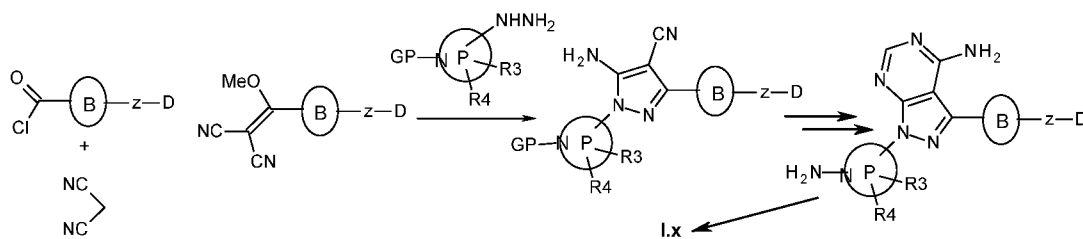
PG represents an amino protecting group such as a Boc, Fmoc or CBZ which can be cleaved easily under acidic, basic or neutral conditions to the substituted hydrazines of interest. L is leaving group such as halogen or a alkyl-sulfonate.

- 5 In method A, cyclic amines represented by (i) are treated with alkali nitrites under acidic condition or by the use of an alkyl nitrite, to obtain the nitroso derivatives such as (ii), which on further reduction results in some of the hydrazines of interest as in (iii).

Hydrazines (iii) can also be prepared by direct displacement of a leaving group (LG) on
 10 nitrogen such as mesylate, tosylate, brosylate, triflates or nonaflates to give protected hydrazino derivatives such as (iv) which on deprotection render compounds represented by (iii) as depicted in Method B

In Method C, some of the hydrazines are prepared by treatment of acyclic compounds such
 15 as (v) with mono-*N*-protected hydrazides to obtained directly the cyclic product represented by (iv) which on de-protection under suitable conditions result in required hydrazines (iii). The hydrazines of Formula iii can be converted into compound of Formula I by reacting them with $LG-R^1$ and/or $LG-R^2$ groups wherein LG is a leaving group.

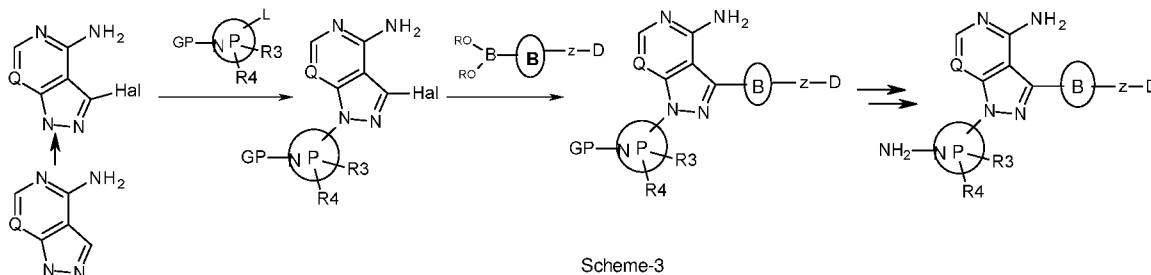
- 20 The required hydrazines on different A-ring moieties can be synthesized as per the general methods outlined in Scheme-2-7 as given below.



Scheme-2

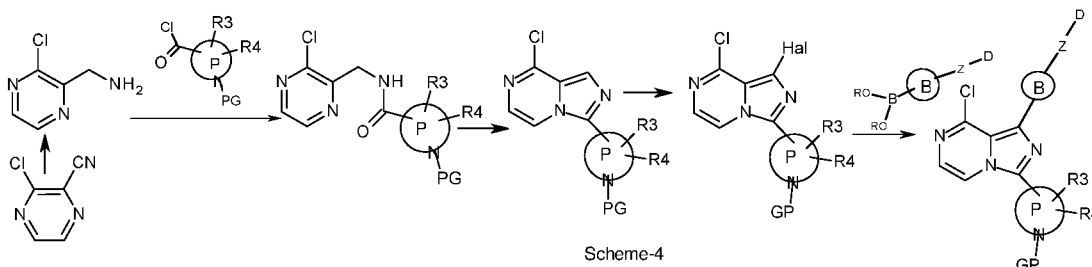
- Accordingly, 'A' ring as a pyrazinopyrimidine can be prepared by a sequence starting with
 25 condensation of melanonitrile with properly substituted acid chlorides and the condensation product on treatment with hydrazines can give the cyclized amino-pyrazoles as shown. When pyrazolo compound on treatment with formaldehyde and ammonia results in the central A ring of requirement.

In another embodiment 'A' ring as a starting material can be elaborated to the required hydrazines by functional transformations as outlined in Scheme-3.



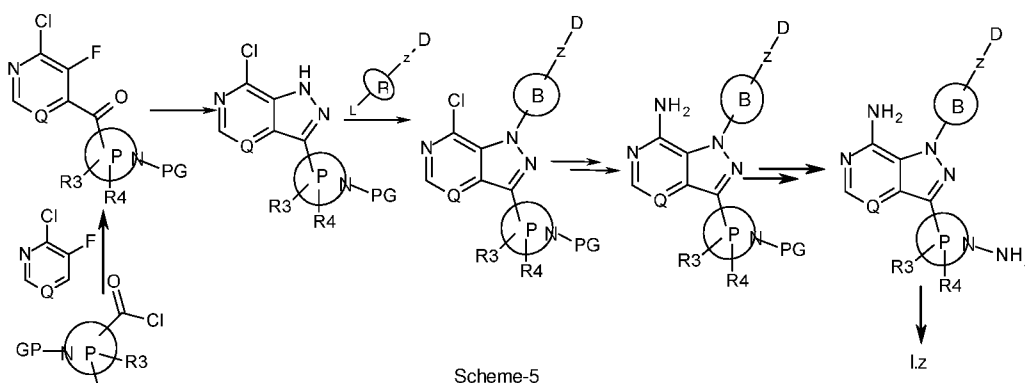
- As shown in Scheme-3 pyrazolo-pyrimidines (Q=N) or pyrazolo-pyridines (Q=CH) can be halogenated at 3-position and then can be treated with nitrogen hetero-cycle of the choice from 4-7 membered ring containing a leaving group 'L' such as halogen or a alkyl-sulfonate at appropriate position to form a C-N bond. Alternatively, 'L' can be a hydroxyl group which participate in Mitsunobu reaction to form C-N bond. Later the halogenated derivative can further be elaborated by treating with a boronate under Suzuki coupling condition to obtain the skeletons of the requirement which can be transformed to the hydrazines of choice.

In another embodiment 'A' ring is an imidazole-pyrazine envisioned can be synthesized as per the brief Scheme-4 outlined hereunder.



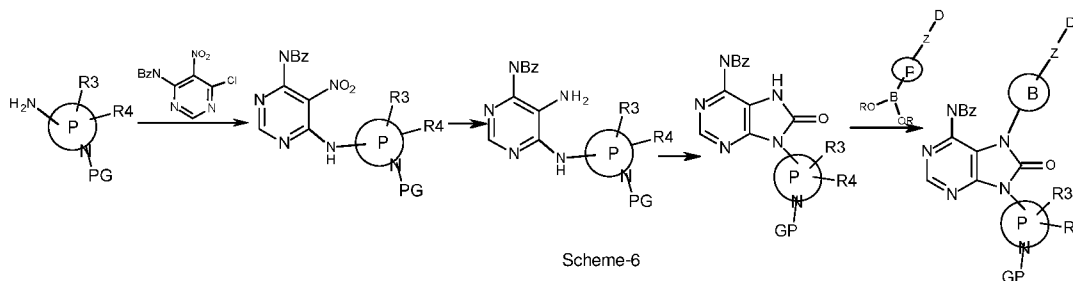
- Accordingly, a commercially available 2-chloro-3-cyanopyrazole can be reduced either by known hydrogenation method or by involving reducing agents such as lithium aluminium hydride to convert into an amine which can be treated with an acid chloride or appropriately activated acid to form an amide bond as shown in Scheme-4. The amide intermediate can ring closed to obtain the 'A' ring as an imidazole-pyrazine scaffold of choice. Which can be further elaborated to the hydrazines by the known methods known in the art.

In a fourth embodiment as outlined in Scheme-5, 'A' ring can be modified as pyrazolo-pyrimidine or pyrazolo-pyridine scaffolds which are differently disposed from the earlier described embodiments.



- 5 Commercially available chlorofluoropyrimidine or chlorofluoropyridine can be acylated with suitable acid chloride moiety and then treated with hydrazine to form the scaffold of interest. Further elaboration can result in some of the hydrazines of current interest.

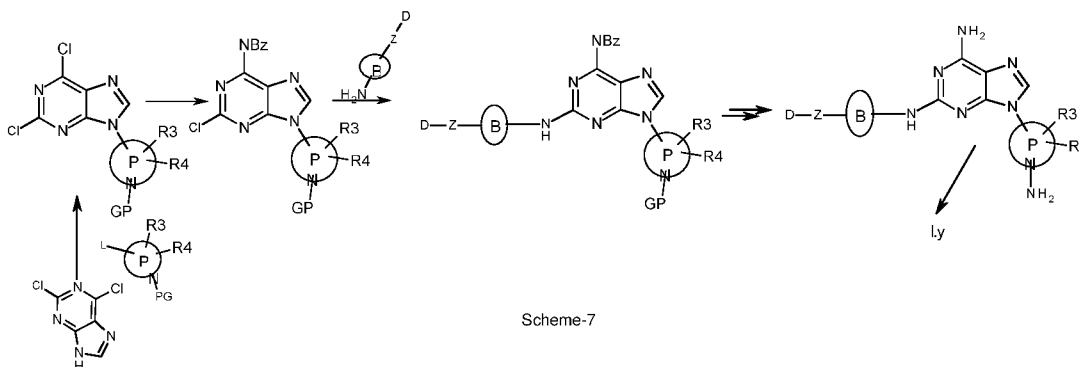
In yet another embodiment the 'A' ring scaffold can be modified to a 2-imidazalone fused pyrimidine/pyridine as described in the Scheme-6



- 15 Bz in Scheme-6 is a benzyl group which may be substituted or unsubstituted. From the known dichloronitropyrimidine, the A-ring can be synthesized by successive substitutions with different amines of choice followed by the reduction of the nitro group to obtain a 1,2-diamino function which can be ring closed to form the urea linkage by either CDI or 4-nitrophenyl chloroformate. These intermediates can be further elaborated by a Suzuki or by Buchwald coupling methods to obtain the needed disposition of groups and the hydrazines of choice.

- 20 The linkage of the groups is not confined to one of the fused heterocyclic rings such as pyrazole or imidazole but can be viewed as a substituents attached in both the rings as given

in some of the scaffolds of Figure-3. Scheme-7 given below outlines the synthesis of such hydrazines.



Accordingly, substituted dichloropurine can be functionalized to obtain the required hydrazine in few steps. Hydrazines prepared as per the above methods described in Scheme-1 to Scheme-7, can be treated with suitable electrophilic compounds to afford the compounds of Formula I. Some of the representative electrophilic compounds are provided in Figure-5. The electrophilic compound may require some functional modifications depending upon the type of the substitution on them which are under the purview of a person skilled in the art.

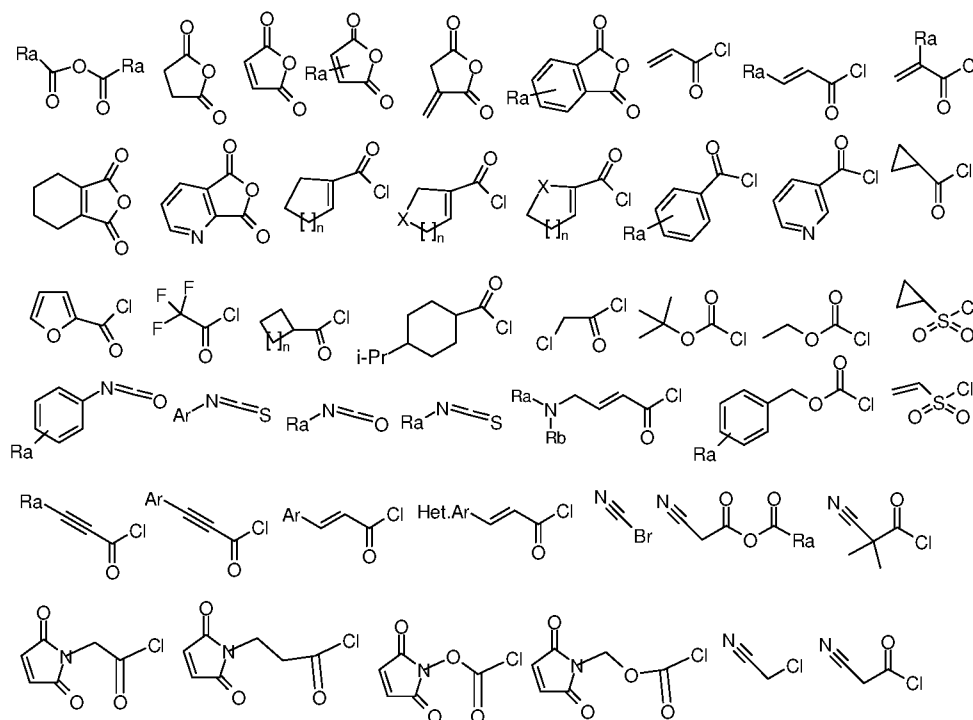


Figure-5

Ar in Figure-5 is an aryl group and Het.Ar is a heteroaryl group. R_a and R_b are independently H, alkyl C_{1-6} , cycloalkyl C_{3-6} .

In another embodiment the hydrazines prepared as per the process provided in Scheme-1 to Scheme-7 were treated with aromatic electrophiles. Some of the representative aromatic electrophilic compounds are provided in Figure-6. The aromatic electrophilic compound may also require some functional modifications depending upon the type of the substitution on them and such modifications are under the purview of a person skilled in the art.

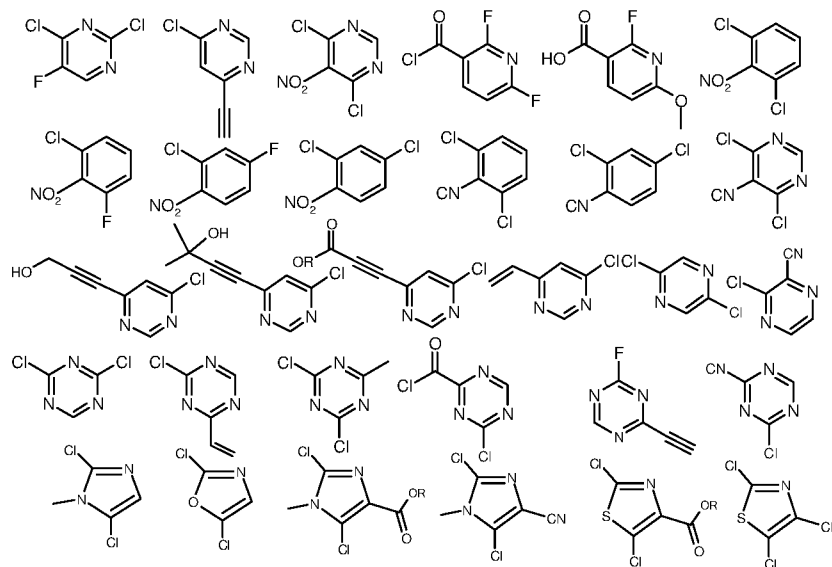


Figure-6

In yet another embodiment, the hydrazines prepared according to the methods described above can be treated with substrates containing aldehydes and ketones containing either saturated or unsaturated functionalities as condensing agents to obtain the compound of Formula I. Representative aldehydes and ketones are provided in Figure-7.

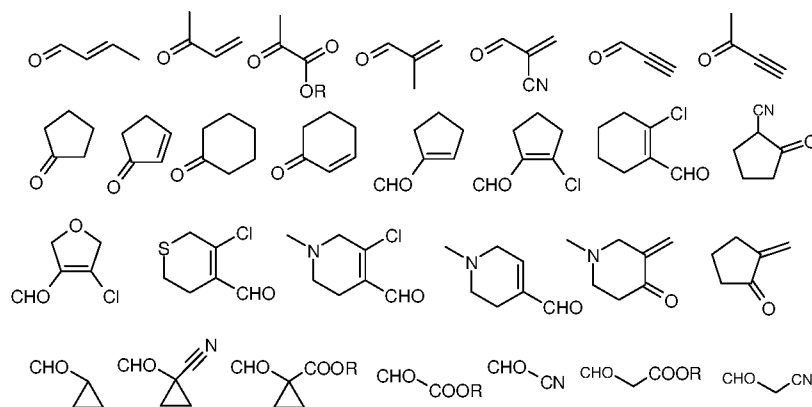


Figure-7

Similarly hydrazines prepared according to the methods described above can be treated with 1,3 diketones, 1,3 ketoesters or 1,2 ketoesters to afford compound of Formula I having ene-

amide, ene-ester etc. linked substitution. The representative 1,3 diketones, 1,3 ketoesters or 1,2 ketoesters are provided in Figure-8

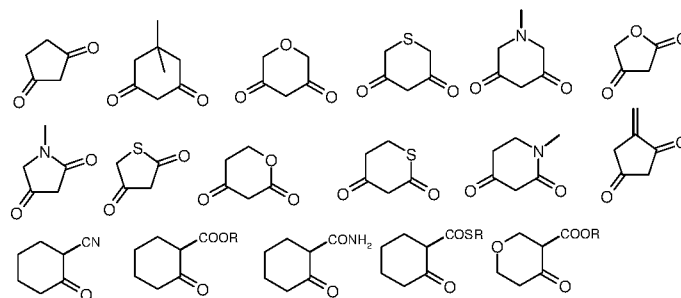


Figure-8

Representative compounds of Formula I are presented in Table 1.

5 **Table 1**

#	Name	¹ H-NMR (D6)-DMSO
I.1	Cyclopropanecarboxylic acid{4-[4-amino-3-(4-phenoxy-phenyl)pyrazolo-[3,4- <i>d</i>]pyrimidine-1-yl]-amide	9.2(s,1H),8.3(s,1H),7.7(d,2H,J=9Hz),7.3(t,2H,J=8Hz),7.2(m,5H),4.9(m,1H),3.1(m,2H),2.9(m,2H),2.4(m,2H),2.0(m,2H),1.5(m,1H), 0.9(m,4H).
I.2	Cyclopropanecarboxylic acid{3-[4-amino-3-(4-phenoxy-phenyl)pyrazolo-[3,4- <i>d</i>]pyrimidine-1-yl]-amide	8.32 (s, 1H); 7.72 (d, 2H, J = 8.6 Hz); 7.49 (t, 2H, J = 7.9 Hz); 7.26-7.17 (m, 5H); 4.76-4.72 (m, 1H); 4.16 (d, J = 10.4 Hz); 3.95 (d, 1H, J = 13.0 Hz); 2.96 (t, 1H, J = 11.8 Hz); 2.25-2.15 (m, 1H); 1.91-1.81 (m, 2H); 1.67-1.64 (m, 1H); 1.07-1.04 (m, 2H); 0.95-0.94 (m, 2H)
I.3	Cyclopropanesulfonic acid{4-[4-amino-3-(4-phenoxy-phenyl)-pyrazolo[3,4- <i>d</i>]pyrimidine-1-yl]-piperidine-1-yl]-amide	8.5(s,1H),8.3(s,1H),7.7(d,2H,J=8Hz),7.5(t,2H,J=8Hz),7.1-7.3(m,5H),4.7(m,1H),3.3(m,2H),2.8(t,2H,J=11Hz),2.7(m,1H),2.3(m,2H),2.0(m,2H),1.04-1.05(m,4H)
I.4	(<i>E</i>)-3-{4-[4-Amino-3-(4-phenoxy-phenyl)-pyrazolo[3,4- <i>d</i>]pyrimidine-1-yl]-piperidine-1-ylcarbamoyl}-acrylic acid ethyl ester	9.7(s,1H),8.3(s,1H),7.7(m,2H),7.5(t,2H,J=8Hz),7.1-7.3(m,5H),7.0(d,1H,J=15Hz),6.6(D,1H,J=16Hz),4.8(m,2H),4.2(m,2H),3.2(m,2H),2.9(m,2H),2.4(m,2H),2.0(m,2H),1.3(m,3H)
I.5	(<i>Z</i>)-3-{4-[4-Amino-3-(4-Phenoxy-phenyl)-pyrazolo[3,4- <i>d</i>]pyrimidine-1-yl]-piperidine-1-ylcarbamoyl}-acrylic acid	14.3+13.2(br,s,1H),10.1+9.2(s,1H),8.4(s,1H),7.7(m,2H),7.5(t,2H,J=8Hz),7.17(m,5H),6.9+6.1(d,1H,J=12Hz),6.2+6.4(d,1H,J=12Hz),4.6-4.7(m,1H),3.2(m,2H),2.9-2.8(m,2H),2.3-2.4(m,2H),2.0(m,2H)
I.6	3-[4-[4-Amino-3-(4-phenoxy-phenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-ylamino]-cyclopent-2-enone	8.73 (s, 1H), 8.30 (s, 1H), 7.73 (d, J = 8.64Hz, 2H), 7.50 (t, J = 7.48Hz, 2H), 7.15-7.28 (m, 5H), 5.05 (s, 1H), 4.75-4.85 (m, 1H), 3.15-3.25 (m, 2H), 2.70-2.85 (m, 2H), 2.45-2.55 (m, 2H), 2.25-2.45 (m, 2H), 2.10-2.25 (m, 2H), 2.00-2.10 (m, 2H)
I.7	3-[4-[4-Amino-3-(4-phenoxy-phenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-ylamino]-5,5-dimethyl-cyclohex-2-enone	8.31 (s, 1H), 8.09 (s, 1H), 7.74 (d, J = 8.64Hz, 2H), 7.50 (t, J = 7.50Hz, 2H), 7.15-7.30 (m, 5H), 5.33 (s, 1H), 4.70-4.85 (m, 1H), 3.10-3.20 (m, 2H), 2.70-2.80 (m, 2H), 2.30-2.45 (m, 2H), 2.15 (s, 2H), 2.00-2.10 (m, 2H), 2.04 (s, 2H), 1.03 (s, 6H)
I.8	<i>E</i> -4-[4-[4-Amino-3-(4-phenoxy-phenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-ylamino]-pent-3-en-2-one	11.24 (s,1H), 8.30 (s, 1H), 7.72 (d, J = 8.68Hz, 2H), 7.49 (t, J = 7.96Hz, 2H), 7.17-7.20 (m, 5H), 4.97 (s, 1H), 4.75-4.90 (m, 1H), 3.10-3.20 (m, 2H), 2.75-2.90 (m, 2H), 2.30-2.45 (m, 2H), 2.08 (s, 3H), 1.95-2.05 (m, 2H), 1.95 (s, 3H)
I.9	1-{4-[4-Amino-3-(4-phenoxy-phenyl)-pyrazolo[3,4- <i>d</i>]pyrimidine-1-yl]piperidine-1-yl}-pyrrole-2,5-dione	8.4(s,1H), 7.7(d,2H,J=2Hz), 7.2-7.3(m,5H), 7.0(s,2H), 4.8(m,1H), 3.65(t,2H,J=10Hz), 3.2(m,2H), 2.4(m,2H), 2.0(m,2H)
I.10	1-[4-[4-Amino-3-(4-phenoxy-phenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-yl]-3-phenylthiourea	9.77 (s, 1H), 9.26 (s, 1H), 8.23 (s, 1H), 7.63 (d, J = 8.50Hz, 2H), 7.58 (d, J = 7.70Hz, 2H), 7.41 (t, J = 7.90Hz, 2H), 7.30 (t, J = 7.88Hz, 2H), 7.15-7.20 (m, 6H), 4.60-4.70 (m, 1H), 3.30-3.35 (m, 2H), 3.05-3.15 (m, 2H), 2.80-2.90 (m, 2H), 1.90-2.00

		(m, 2H)
I.11	1-Cyano-cyclopropanecarboxylic acid{4-[4-amino-3-(4-phenoxy-phenyl)-pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidine-1-yl}-amide.	9.42(s,0.4H),9.31(s,0.4H),8.31(s,1H),7.7(t,2H,J=8Hz),7.5(m,2H),7.1-7.3(m,5H),4.7-4.8(m,1H),3.2(m,1.5H),2.9-3.1(m,2H),2.85(t,1H,J=12Hz),2.3-2.5(m,2H),1.9-2.1(m,2H),1.5-1.6(m,4H)
I.12	<i>N</i> -{4-[4-Amino-3-(4-phenoxyphenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-yl}-2-cyano-2,2-dimethyl acetamide	9.40+9.21 (s, 1H), 8.31 (s, 1H), 7.74-7.70 (m, 2H), 7.51-7.47 (m, 2H), 7.26-7.19 (m, 5H), 4.80-4.74 (m, 1H), 3.25-3.22 (m, 1H), 3.07 (m, 1H), 2.97 (t, J = 10.84 Hz, 1H), 2.85 (t, J = 11.0 Hz, 1H), 2.38-2.35 (m, 2H), 2.03-1.96 (m, 2H), 1.57 (s, 6H)
I.13	1-[1-[Cyclohex-2-en-(<i>Z</i>)-ylideneamino]piperidin-4-yl]-3-(4-phenoxyphenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-4-ylamine	8.30 (s, 1H), 7.73 (d, J = 8.64Hz, 2H), 7.50 (t, J = 7.96Hz, 2H), 7.10-7.30 (m, 5H), 6.74+6.11(2d, J=10.16Hz 1H), 6.35-6.46 (m, 1H), 4.75-4.90 (m, 1H), 2.95-3.15 (m, 2H), 2.60-2.80 (m, 3H), 2.30-2.50 (m, 3H), 2.15-2.30 (m, 2H), 1.90-2.05 (m, 2H), 1.70-1.90 (m, 2H)
I.14	1-[1-(2-Chloro-5-fluoropyrimidin-4-ylamino)piperidin-4-yl]-3-(4-phenoxyphenyl)-1 <i>H</i> -pyrazolo [3,4- <i>d</i>]pyrimidin-4-ylamine	9.40 (s, 1H), 8.31 (s, 1H), 8.19 (d, J= 3.80 Hz, 1H), 7.76 (d, J= 8.68 Hz, 2H), 7.47-7.53 (m, 2H), 7.17-7.28 (m, 5H), 4.73-4.82 (m, 1H), 3.15-3.27 (m, 2H), 2.96 (t, J=10.80 Hz, 2H), 2.37-2.50 (m, 2H), 2.01-2.09 (m, 2H)
I.15	1-[1-Cyclopentylideneamino-piperidin-4-yl]-3-[4-phenoxy-phenyl]-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-4-ylamine	8.30 (s, 1H), 7.72 (d, J = 8.32Hz, 2H), 7.50 (t, J = 7.70Hz, 2H), 7.15-7.30 (m, 5H), 4.75-4.85 (m, 1H), 3.00-3.15 (m, 2H), 2.65-2.75 (m, 2H), 2.25-2.50 (m, 8H), 1.90-2.10 (m, 2H), 1.60-1.80 (m, 2H)
I.16	3-{4-Amino-3-(4-phenoxy-phenyl)-pyrazolo[3,4- <i>d</i>]pyrimidine-1-yl}-piperidine-1-ylcarbamoyl}but-3-enoic acid	12.5(br,s,1H), 9.2+8.6(br,s,0.5H), 8.4(s,1H), 7.7(d,2H,J=8.4Hz), 7.5(t,2H,J=8Hz), 7.1-7.3(m,5H),5.7+6.2(br,s,1.5H), 4.7(br,s,1H), 3.5(s,2H), 3.0-3.1(m,2H), 2.8-2.9(m,2H), 2.3-2.4(m,2H), 1.9-2.0(m,2H)
I.17	1-[1-[(<i>E</i>)-But-2-en-(<i>Z</i>)-ylidene]amino]-piperidin-4-yl]-3-[4-phenoxy-phenyl]-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-4-ylamine	8.30 (s, 1H), 7.71 (d, J = 8.68Hz, 2H), 7.49 (t, J = 7.98Hz, 2H), 7.41 (d, J = 8.76Hz, 1H), 7.24 (t, J = 7.42Hz, 2H), 7.21 (d, J = 8.88Hz, 2H), 7.18 (d, J = 7.72Hz, 1H), 6.15-6.25 (m,1H), 5.90-6.02 (m, 1H), 4.83-4.95 (m, 1H), 3.70-3.80 (m, 2H), 2.75-2.90 (m, 2H), 2.20-2.45 (m, 2H), 1.95-2.10 (m, 2H), 1.80-1.90 (m, 3H)
I.18	1-[1-[1-Methyl-prop-2-en-(<i>Z</i>)-ylideneamino]-piperidin-4-yl]-3-(4-phenoxy-phenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-4-ylamine	8.38 (s, 1H), 7.60-7.70 (m, 2H), 7.35-7.45 (m, 2H), 7.15-7.20 (m, 3H), 7.05-7.10 (m, 2H), 6.42-6.55 + 5.60-5.75 (2m, 1H), 5.45-5.60 (m, 2H), 4.85-4.95 (m, 1H), 2.95-3.15 (m, 2H), 2.75-2.85 (m, 2H), 2.55-2.68 (m, 3H), 2.22-2.45 (m, 1H), 2.05-2.19 (m, 3H).
I.19	<i>N</i> -{4-[4-Amino-3-[4-phenoxy-phenyl]-pyrazolo[3,4- <i>d</i>]pyrimidine-1-yl]-piperidine-1-yl}-3-[2,5-dioxo-2,5-dihydropyrrol-1-yl]-propionamide	9.1+8.7+8.6(s,1H), 8.3(s,1H), 7.7(d,2H,J=8.6Hz), 7.5(t,2H,J=7.5Hz), 7.2-7.3(m,5H), 7.17(d,2H,J=7.8Hz), 4.7(br,s,1H), 3.6-3.7(m,2H), 3.0-3.2(m,4H), 2.7-2.9(m,3H), 2.3-2.4(m,3H), 1.9-2.0(m,2H)
I.20	Ethyl (2 <i>Z</i>)-2-[[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]-1-piperidyl]imino]acetate	8.31 (s, 1H), 7.70-7.78 (m, 2H), 7.46-7.55 (m, 2H), 7.15-7.30 (m, 5H), 6.92 (s, 1H), 5.00-5.15 (m, 1H), 4.21 (q, J = 7.08Hz, 2H), 3.95-4.05 (m, 2H), 3.25-3.35 (m, 2H), 2.25-2.35 (m, 2H),2.05-2.15 (m, 2H),1.28 (t, J = 7.10Hz, 3H).
I.21	4-[4-Amino-3-(4-phenoxyphenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-yl-cyanamide	8.67 (s, 1H), 8.40 (s, 1H), 7.72 (d, J = 13.95Hz, 2H), 7.49 (t, J= 7.92Hz, 2H), 7.16-7.28 (m, 5H), 4.72- 4.80 (m, 1H), 3.20-3.28 (m, 2H), 2.78 (t, J= 10.60Hz, 2H), 2.28-2.42 (m, 2H), 2.0-2.10 (m, 2H)
I.22	<i>N</i> -{4-[4-Amino-3-(4-phenoxyphenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-yl}-2-(2,5-dioxo-2,5-dihydropyrrol-1-yl)acetamide	9.38+9.08 (s, 1H), 8.31+8.30 (s, 1H), 7.72 (d, J = 8.52 Hz, 2H), 7.49 (t, J = 7.90 Hz, 2H), 7.39-7.16 (m, 7H), 4.79-4.73 (m, 1H), 4.43+4.03 (s, 2H), 3.20-3.09 (m, 2H), 2.89-2.72 (m, 2H), 2.44-2.30 (m, 2H), 2.07-1.98 (m, 2H)
I.23	Ethyl (2 <i>Z</i>)-2-[[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]-1-piperidyl]imino]propanoate	8.39 (s, 1H), 7.64-7.69 (m, 2H), 7.36-7.43 (m, 2H), 7.13-7.21 (m, 3H), 7.06-7.15 (m, 2H), 5.40-5.60 (br. s, 2H), 4.85-5.00 (m, 1H), 4.33 (q, J = 7.12Hz, 2H), 3.30-3.45 (m, 2H), 2.95-3.10 (m, 2H), 2.50-2.65 (m, 2H), 2.19 (s, 3H), 2.05-2.15 (m, 2H),1.36 (t, J = 7.12Hz, 3H)

I.24	4-{4-[4-Amino-3-(4-phenoxyphenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-ylamino}-5-fluoropyrimidine-2-thiol	12.22(s, 1H), 9.47(s, 1H), 8.31(s, 1H), 7.71-7.82(m, 3H), 7.49(t, 3H), 7.27-7.37(m, 5H), 4.70-4.82(m, 1H), 3.15-3.25(m, 2H), 2.91-3.05(m, 2H), 2.40-2.50(m, 2H), 2.0-2.10(m, 2H)
I.25	(<i>E,Z</i>)-3-(4-{4-[4-Amino-3-(4-phenoxyphenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-ylamino}-5-fluoropyrimidin-2-ylsulfanyl)acrylic acid ethyl ester	9.35+9.28(bs, 1H), [8.65+8.49(J=16.04Hz,10.16Hz)2d,1H], 8.31 (s, 1H), 8.24 (m, 1H), 7.70-7.80(m, 2H), 7.49 (t, J=7.44Hz, 2H), 7.15-7.30(m, 5H), [6.33+6.22(J=16.04Hz,10.44Hz)2d,1H], 4.72-4.88(m, 1H), 4.22+4.16 (q, 2H), 3.20-3.30 (m, 2H), 2.90-3.08(m, 2H), 2.38-2.52(m, 2H), 2.01-2.15(m, 2H), 1.29+1.13(t, 3H)
I.26	1-Cyano cyclopropanecarboxylic acid {3-[4-amino-3-(4-phenoxy phenyl) pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]azetidin-1-yl}amide	9.87 (s, 1H), 8.32 (s, 1H), 7.75 (d, J = 8.28 Hz, 2H), 7.49 (t, J = 7.84 Hz, 2H), 7.26-7.18 (m, 5H), 5.34 (m, 1H), 4.33-4.19 (m, 4H), 1.58-1.54 (m, 4H)
I.27	1-[1-[(<i>Z</i>)-2-Methylprop-2-enylideneamino]-4-piperidyl]-3-(4-phenoxyphenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-4-amine	8.30 (d, J = 5.00Hz,1H), 7.68-7.74 (m, 2H), 7.46-7.52 (m, 2.5H), 7.15-7.28 (m, 3H), 6.88 (s, 1H), 6.23 (s, 0.5H), 5.25 (d, J = 21.00Hz, 1H), 4.85-4.95 (m, 1H), 3.65-3.90 (m, 2H), 2.75-2.90 (m, 2H), 2.25-2.40 (m, 2H), 1.90-2.10 (m, 2H), 1.53 (s, 1.5H), 1.32 (s, 1.5H)
I.28	1-[1-(6-Chloro-5-nitropyrimidin-4-ylamino)-piperidin-4-yl]-3-(4-phenoxyphenyl)-1 <i>H</i> -pyrazolo [3,4- <i>d</i>]pyrimidin-4-ylamine	10.03 (s, 1H), 8.39 (s, 1H), 8.27 (s, 1H), 7.64 (d, J = 8.55 Hz, 2H), 7.40-7.45 (m, 2H), 7.10-7.19 (m, 5H), 4.62 (m, 1H), 2.97-3.05 (m, 2H), 2.81 (t, J = 10.77 Hz, 2H), 2.0-2.12 (m, 2H), 1.90-1.98 (m, 2H)
I.29	N-[4-[4-Amino-3-(4-phenoxyphenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-yl]-2,6-difluoro nicotinamide	9.73+9.57 (s, 1H), 8.36-8.42 (m, 1H), 8.28+8.31 (s, 1H), 7.67+7.74 (d, J=8.65 Hz, 2H), 7.46-7.53 (m, 2H), 7.29-7.37 (dd, 1H), 7.15-7.28 (m, 5H), 4.6-4.9 (m, 1H), 3.12-3.25 (m, 2H), 2.84-2.96 (m, 2H), 2.39-2.48 (m, 2H), 1.9-2.1 (m, 2H)
I.30	6-Amino-9-[1-(2-chloro-5-fluoropyrimidin-4-ylamino)-piperidin-4-yl]-7-(4-phenoxy-phenyl)-7,9-dihydro-purin-8-one	9.31(S,1H),8.23(S,1H),8.185(d,J=3.7,1H),7.48-7.51(m,4H),7.18-7.27(m,5H),5.81(bs,2H),4.32(m,1H),3.17-3.19(m,2H),2.80-2.88(m,4H),1.86(m,2H)
I.31	4-[4-Amino-1-[1-(2-chloro-5-fluoropyrimidin-4-ylamino)-piperidin-4-yl]-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl]- <i>N</i> -[5- <i>tert</i> -butyl-pyridine-2-yl]-benzamide	10.1(s,1H), 9.4(s,1H), 8.33(s,1H), 8.19(d,1H,J=3.75Hz), 8.0(d,2H,J=8.45Hz),7.62(d,2H,J=8.45Hz),7.55(d,1H,J=7.7Hz), 7.45(t,1H,J=7.7Hz), 7.35(d,1H,J=6.75Hz), 4.7(m,1H), 3.2(d,2H,J=11Hz), 3.0(t,2H,J=11Hz), 2.4(m,2H), 2.2(s,3H), 2.0(m,2H), 1.4(s,9H)
I.32	2-[4-[4-Amino-3-(4-phenoxyphenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-ylamino]-6-methoxy nicotinic acid	12.69 (bs, 1H), 9.22 (s, 1H), 8.31(s, 1H), 8.02 (d, J = 8.45 Hz, 1H), 7.73 (d, J = 8.45 Hz, 2H), 7.45-7.53 (m, 2H), 7.17-7.29 (m, 5H), 6.10 (d, J = 8.40 Hz, 1H), 4.80-4.90 (m, 1H), 3.96 (s, 3H), 3.28-3.35 (m, 2H), 3.0-3.12 (m, 2H), 2.38-2.5 (m, 2H), 2.0-2.10 (m, 2H)
I.33	4-[1-(1-Acryloylamino-piperidin-4-yl)-4-amino-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-3-yl]- <i>N</i> -(4-methylpyridine-2-yl)-benzamide	10.8(s,1H),9.3(s,1H),8.35(s,1H),8.3(d,1H,J=6.3Hz),8.(s,1H), 7.8(d,2H,J=8.35Hz),7.1(d,2H,J=13.45Hz),6.1-6.2(m,2H), 5.6(dd,1H),4.8(m,1H),3.2(m,2H),2.9(m,2H),2.45(s,3H), 2.4(m,1H),2.0(m,2H)
I.34	4-[4-Amino-1-[1-[(2-chloro-5-fluoropyrimidin-4-yl)amino]-4-piperidyl]pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl]- <i>N</i> -[2-pyridyl]benzamide	10.94 (s, 1H), 9.40 (s, 1H), 8.45 - 8.50 (m,1H), 8.35 (s, 1H), 8.25 - 8.30 (m, 3H), 8.19 (d, J= 3.75Hz, 1H), 7.88 - 7.96 (m, 3H), 7.22 - 7.28 (m, 1H), 4.77 - 4.88 (m, 1H), 3.18-3.27 (m, 2H), 2.92-3.10 (m, 2H), 2.40 - 2.50 (m, 2H), 2.05 - 2.15 (m, 2H)
I.35	2-[4-[4-Amino-3-(4-phenoxyphenyl)pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl]piperidin-1-ylamino]-6-fluoro nicotinamide	9.8 (s, 1H), 8.31(s, 1H), 8.19 (t, J = 8.25 Hz, 1H), 8.04 (s, 1H), 7.75 (d, J = 8.60 Hz, 2H), 7.45-7.53 (m, 3H), 7.17-7.28 (m, 5H), 6.35 (dd, J = 8.20 Hz, 1H), 4.79-4.90 (m, 1H), 3.2-3.3 (m, 2H), 2.8-2.9(m, 2H), 2.4-2.52 (m, 2H), 2.0-2.17 (m, 2H).
I.36	4-[1-(1-Acryloylamino-piperidin-4-yl)-4-amino-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidine-3-yl]- <i>N</i> -pyridin-2-yl-benzamide.	10.96(s,1H), 9.3(s,1H), 8.47(d,1H,J=3.8Hz), 8.32(s,1H), 8.2-8.3(m,3H), 7.8-7.9(m,3H), 7.2(m,1H), 6.1-6.3(m,2H), 5.6-5.7(m,1H), 4.7-4.9(m,1H), 3.1-3.2(m,2H), 2.8-2.9(m,2H), 2.3-2.4(m,2H), 1.9-2.1(m,2H).
I.37	4-[4-Amino-1-[1-(but-2-ynoylamino)-4-piperidyl]pyrazolo[3,4- <i>d</i>]pyrimidin-	10.96 (s, 1H), 9.00 + 8.48 (2s, 0.5H+0.5H), 8.45 - 8.50 (m,1H), 8.30 - 8.35 (m, 1H), 8.25 - 8.30 (m, 3H), 7.90 - 7.95 (m, 1H), 7.85 - 7.90 (m, 2H), 7.22 - 7.28 (m, 1H), 4.70 - 4.85 (m, 1H),

	3-yl]-N-[2-pyridyl]benzamide	3.05 - 3.18 (m, 2H), 2.75 - 2.90 (m, 2H), 2.30 - 2.45 (m, 2H), 2.00 - 2.15 (m, 2H), 2.04 + 1.79 (2s, 1.5H+1.5H).
I.38	4-[1-(1-Acryloylamino-piperidine-3-yl)-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-N-(4-methyl-pyridine-2-yl)-benzamide.	10.9(s,1H), 9.4(s,1H), 8.3(m,2H), 8.2(d,2H,J=8.2Hz), 8.15(s,1H), 7.8(d,2H,J=8.3Hz), 7.1(d,1.5H,J=4.8Hz), 6.15(m,2H), 5.6(m,1H), 5.0(m,1H), 3.2(m,1.4H), 3.1(m,1H), 2.7-2.8(m,1H), 2.45(s,3H), 2.1(m,2H), 1.8-2.0(m,2H).
I.39	N-{4-[6-Amino-8-oxo-7-(4-phenoxyphenyl)-7,8-dihydro-purin-9-yl]-piperidin-1-yl}-3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-propionamide	9.05(S,0.5H),8.20(S,0.5H),8.19(S,0.5H),7.42-7.51(m,4H),7.14-7.27(m,5H),7.07-7.12(m,2H),5.82-5.83(bs,2H),4.24-4.27(m,1H),3.61-3.70(m,2H),3.1-3.12(m,1H),3.02-3.03(m,1H),2.61-2.75(m,4H),1.72-1.80(m,2H),1.28-1.29(m,2H)
I.40	N-{4-[1-(1-Acryloylamino-piperidin-4-yl)-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-phenyl}-nicotinamide	10.7(s,1H), 9.3(s,1H), 9.2(s,1H), 8.8(d,1H,J=3.5Hz), 8.4(d,1H,J=8Hz), 8.3(s,1H), 8.05(d,2H,J=8.45Hz), 7.75(d,2H,J=8.5Hz), 7.65(m,1H), 6.1-6.3(m,2H), 5.6-5.7(m,1H), 4.8-4.9(bris,1H), 3.15(m,1H), 3.0(m,0.5H), 2.8-2.9(m,2H), 2.3-2.4(m,2H), 2.0-2.1(m,2H).
I.41	1-[1-[(Z)-2-Furylmethyleneamino]-4-piperidyl]-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-amine	8.31 (s, 1H), 7.70-7.75 (m, 3H), 7.63(s, 1H), 7.45-7.55 (m, 2H), 7.15-7.25 (m, 5H), 6.75-6.65(m,2H), 4.90-5.00 (m, 1H), 3.85-3.95(m, 2H), 2.90-3.00 (m, 2H), 2.30-2.40 (m, 2H), 2.00-2.10 (m, 2H).
I.42	Ethyl (2Z)-2-[[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]imino]cyclopentanecarboxylate	8.30 (s, 1H), 8.06(s, 1H), 7.70 -7.75(m, 2H), 7.46-7.53(m, 2H), 7.16-7.28 (m, 5H), 4.70-4.85 (m, 1H), 4.10(q, J = 7.06Hz, 2H), 3.05-3.20 (m, 2H), 2.65-2.90 (m, 4H), 2.40-2.50 (m, 2H), 2.30-2.40 (m, 2H), 1.95-2.05 (m, 2H), 1.65-1.85(m, 2H), 1.24(t, J = 7.08Hz, 3H).
I.43	1-[1-[(Z)-2-Chloro-4-pyridyl)methyleneamino]-4-piperidyl]-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-amine	8.25-8.35 (m, 1H), 8.35-8.45 (m, 1H), 7.52-7.74 (m, 6H), 7.45-7.52 (m, 2H), 7.15-7.30 (m, 2H), 7.09-7.15 (m, 1H), 6.99-7.05 (m, 1H), 4.95-5.10 (m, 1H), 3.95-4.05 (m, 2H), 3.15-3.25 (m, 2H), 2.25-2.40 (m, 2H), 2.00-2.15 (m, 2H).
I.44	N-[4-[4-Amino-2-chloro-5-(4-phenoxyphenyl)pyrrolo[2,3-d]pyrimidin-7-yl]-1-piperidinyl]prop-2-enamide	9.25 (s, 1H), 7.57 (s, 1H), 7.57-7.45 (m,4H),7.23 (m, 1H),7.16-7.13 (m, 4H), 6.22-6.18 (d, J=16,1H),6.20-6.19 (d, J=13.7,1H),5.67-4.59 (dd,J ₁ =7.0,J ₂ =9.3, 1H), 4.57 (m, 1H), 3.14 (m, 2H), 2.86 (m, 2H), 2.28-2.26 (m, 2H), 2.04 --1.96 (m,2H).

Examples:

A typical synthesis of the product **I.1** presented in Table-1 was accomplished from already known intermediates such as 1-aminopiperidin-4-ol and 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine as described in Miscoria *et al.* [US 2006/0064065] and Hirst *et al.* [US2002/0156081] respectively. Also intermediate 1-nitrosopiperidin-4-ol was prepared as per the procedures described in Bush *et al.* [WO2007/127688A2] which on usual methanesulphonation results in mesylated intermediate (1-nitroso-4-piperidyl) methanesulfonate required for current work.

Other compounds of interest such as I.6, I.11, I.14 and I.17 were also accomplished from the intermediate 1-(1-amino-4-piperidyl)-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-amine as per the procedures described here under and not limited to these compounds only.

Example 1: tert-Butyl N-(4-hydroxy-1-piperidyl)carbamate

To a stirred solution of 1-aminopiperidin-4-ol (9.6 g) in THF (100 mL) in around bottom (RB) flask, triethylamine (16.4 mL) and (Boc)₂O (21.4 mL) were added and stirred for 3 h. The content of the flask was concentrate under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was subjected to column chromatography to afford the title compound as an off-white solid.

Example 2: [1-(*tert*-Butoxycarbonylamino)-4-piperidyl]methanesulfonate

To a cooled (0-5 °C) stirred solution of *tert*-butyl *N*-(4-hydroxy-1-piperidyl)carbamate boc-hydrazide (1.7 g) in dichloromethane (34 ml) under nitrogen, triethylamine (1.3 ml) and methanesulfonyl chloride (0.73 ml) were added, and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was quenched into cold water and the organic layer separated. The organic phase was dried over anh. sodium sulfate, filtered and concentrated to obtain title compound as a pale yellow oily mass, which was used as such in the next step without further purification.

Example 3: *tert*-Butyl *N*-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidyl]carbamate

To a stirred solution of the intermediate 3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.38 g) in DMF (20 ml), potassium carbonate (2.15 g) and a solution of [1-(*tert*-butoxycarbonylamino)-4-piperidyl]methanesulfonate (2.30 g) in DMF (5 ml) were added. The reaction mixture was heated at 80 °C for 16 h and DMF was distilled off under reduced pressure. The crude mass was dissolved in dichloromethane and purified by column chromatography, to obtain the title compound as an off-white solid.

Example 4: 1-(1-Aminopiperidin-4-yl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine

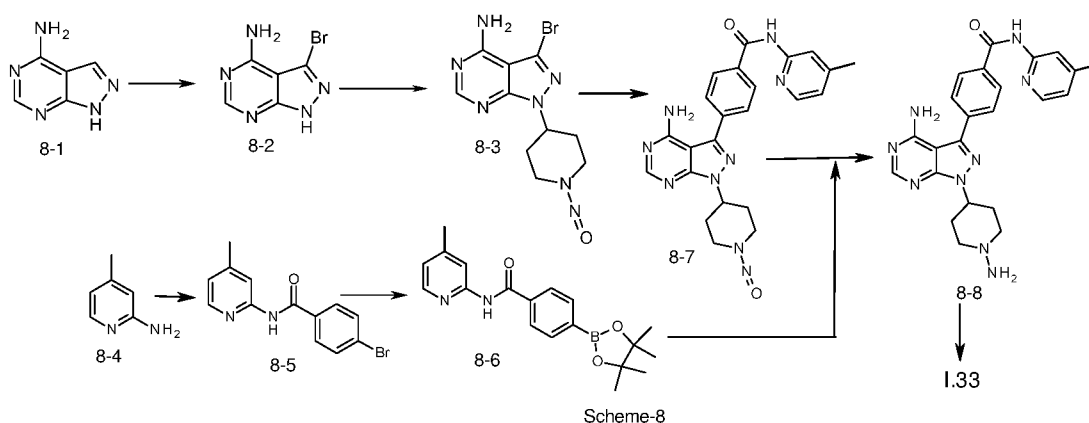
A stirred solution of *tert*-butyl *N*-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidyl]carbamate (1.7 g) in 1,4-dioxane (20 ml) was treated with concentrated hydrochloric acid (conc. HCl) (4.0 ml) at ambient condition for 16 h and solution was concentrated, basified with triethylamine and extracted with dichloromethane. The organic layer was washed with water, dried over anh. sodium sulfate and evaporated under reduced pressure to obtain the title compound as an off white solid.

Example 5: 1-Nitrosopiperidin-4-ol

To a cold (0-10 °C) and stirred solution of 4-hydroxypiperidine (50 g, 0.49 mole) in a mixture of 300 ml water and acetic acid (45 g, 0.741 mole), sodium nitrite (68.2 g, 0.99 mole) was added and the mixture was stirred for 1-2 h at ambient temperature. The reaction mixture was quenched with sodium carbonate extracted with ethyl acetate and the organic layer was concentrated to obtain title compound as off white solid.

Example 6: (1-Nitroso-4-piperidyl) methanesulfonate

To a cold (0-5 °C) solution of 1-nitrosopiperidin-4-ol (33 g, 0.25 mol) in dichloromethane (300 ml) triethylamine (88 ml, 0.6337 mol) was added. Methanesulfonyl chloride (30 ml, 0.38 mol) was added drop-wise into the mixture. The reaction mixture was stirred for 1 h at ambient temperature. The reaction mixture was quenched into water and separated the organic phase was concentrated to obtain the title compound as an off white solid.



Example 7: 4-Bromo-N-(4-methyl-2-pyridyl)benzamide (8-5)

To a stirred solution of 4-bromobenzoic acid (10 g) in toluene (40 ml), thionyl chloride (7.2 mL) was added drop-wise at 25 °C. The reaction mass was heated to reflux for 3 h and concentrated to remove the volatiles under reduced pressure and the residue was dissolved in dichloromethane (50 mL). A solution of 2-amino-4-methylpyridine (8-4; 6 g) in a mixture of dichloromethane (30 mL) and pyridine (8 mL) previously cooled in ice-bath under nitrogen was drop-wise added into the reaction mass. The reaction mass was stirred at ambient condition for 6 h. The reaction mass was quenched with water and the organic phase was separated, dried (over anh. sodium sulfate), filtered, concentrated and purified by column chromatography to obtain title compound as a white solid.

Example 8: *N*-(4-Methyl-pyridin-2-yl)-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-benzamide (8-6)

To a stirred solution of 4-bromo-*N*-(4-methyl-2-pyridyl)-benzamide (8-5; 3.0 g) in 1,4-dioxane (10 mL), *bis*(pinacolato)diboron (3.15 g), potassium acetate (3 g) and [1,1'-
5 *bis*(diphenylphosphino)ferrocene]-dichloropalladium(II) complex (0.24 g) were added. The contents of the flask were refluxed for 3 to 4 h, cooled and filtered over Hyflo[®]. The filtrate was concentrated and purified by column chromatography to obtain the title compound (2.8 g) as a pale yellow solid.

10 **Example 9: 3-Bromo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine (8-2)**

To a stirred suspension of 1*H*-pyrazolo-[3,4-*d*]pyrimidin-4-ylamine (8-1; 50 g) in DMF (500 mL) *N*-bromosuccinimide (66 g) was added and the reaction mass was heated for 5 h at 70 °C. The solvent was removed under reduced pressure. Water was added to the residue and stirred for 30 minutes. The reaction mass was filtered and the solid was washed with diethyl
15 ether. The product was dried under reduced pressure overnight to obtain the title compound as a brown solid.

Example 10: 3-Bromo-1-(1-nitroso-piperidin-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine (8-3)

20 To a stirred suspension of 3-bromo-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-ylamine (8-2; 11 g) in DMF (150 mL) methanesulfonic acid 1-nitrosopiperidin-4-yl ester (17.1 g) and potassium carbonate (18 g) were added. The reaction mixture was heated under nitrogen atmosphere for 12 h at 85 °C. After completion of reaction, the reaction mass was filtered and concentrated under reduced pressure to obtain red oil, which was purified by column chromatography to
25 obtain the title compound as light brown solid.

Example 11: 4-[4-Amino-1-(1-nitroso-piperidin-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-*N*-(4-methyl-pyridin-2-yl)benzamide (8-7)

To a stirred solution of 3-bromo-1-(1-nitroso-piperidin-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-
30 4-ylamine (8-3; 2.16 g) and *N*-(5-methyl-pyrimidin-2-yl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzamide (8-6) (2.8 g) in 1,4-dioxane (20 mL) aq. potassium carbonate (2N, 5.66 g) and [1,1'-*Bis*(diphenylphosphino)ferrocene]dichloropalladium(II) complex (0.3 g) were added. The reaction mass was refluxed for 4 h, cooled and filtered over

Hyflo[®]. The filtrate was concentrated and purified by column chromatography to obtain compound title compound as pale yellow solid.

Example 12: 4-[4-Amino-1-(1-amino-piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-N-(4-methyl-pyridin-2-yl)benzamide (8-8)

To a stirred and cooled (0-5 °C) suspension of 4-[4-amino-1-(1-nitrosopiperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-N-(4-methyl-pyridin-2-yl)benzamide (8-7; 1.5 g) in acetic acid (10.5 mL) and water (4.5 mL) was added zinc dust (0.85 g) in small portions. The reaction mass was stirred for one hour at 25 °C and excess zinc was filtered off, basified with aq. sodium hydroxide and extracted with ethyl acetate. The combined organic phase was concentrated to obtain the title compound as a brown solid.

On similar lines several other A ring scaffold containing compounds were prepared by the methods published or known in the art and converted to compounds of Formula I.

Example 13: Cyclopropanecarboxylic acid {4-[4-amino-3-(4-phenoxy-phenyl)-pyrazolo[3,4-d]pyrimidin-1-yl]-piperidin-1-yl}amide I.1:

To a stirred solution of 1-(1-aminopiperidin-4-yl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine (0.5 g) in dichloromethane (10 mL) triethylamine (0.5 mL) was added and the reaction mass was cooled to 0-5 °C and treated with neat cyclopropane carbonyl chloride (0.11 mL) for 30 minutes. The reaction mass was quenched into cold water, the organic phase was separated and dried over anh. sodium sulfate. The crude mass was subjected to column chromatography on silica gel (elution with hexane:acetone) to obtain compound I.1 as an off-white solid.

Example 14: 3-[4-[4-Amino-3-(4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-ylamino]-cyclopent-2-enone I.6:

To a stirred suspension of 1-(1-aminopiperidin-4-yl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine (0.3 g) and molecular sieves in dichloroethane (12 mL) under nitrogen atmosphere, was added 1,3-cyclopentadione (0.22 g) and the mixture was refluxed overnight. The reaction mass was cooled, methanol was added, filtered and evaporated to dryness under reduced pressure. The residue was subjected to column chromatography on silica gel to obtain I.6 as an off-white solid.

Example 15: 1-Cyano-cyclopropanecarboxylic acid {4-[4-amino-3-(4-phenoxy-phenyl)-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidine-1-yl}-amide I.11:

To a stirred solution of 1-(1-aminopiperidin-4-yl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine (0.3 g) in DMF (10 mL) diisopropylethyl amine (0.26 mL), 1-cyano-cyclopropane carboxylic acid (0.1g) were added and treated with HATU (0.34 g) for 120 minutes at ambient condition. The solvent was removed under reduced pressure. Dichloromethane was added to the residue and washed with water. The organic phase was separated, dried (over anh. sodium sulfate), concentrated and subjected to column chromatography to obtain **1.11** as an off-white solid.

Example 16: 1-[1-(2-Chloro-5-fluoropyrimidin-4-ylamino)piperidin-4-yl]-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine I.14:

To a stirred and cold (0-5 °C) solution of 1-(1-aminopiperidin-4-yl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine (2 g, 0.005 mol) in THF (40 mL) DIPEA (1.4 mL, 0.0075 mol) was added. Into the reaction mass 2,4-dichloro-5-fluoropyrimidine (1 g) was added portion-wise. The reaction mass was stirred at 25 °C for 1 h. The reaction mass was concentrated under reduced pressure and subjected to column chromatography (eluted with dichloromethane / methanol as mobile phase) to obtain **I. 14** as a white solid.

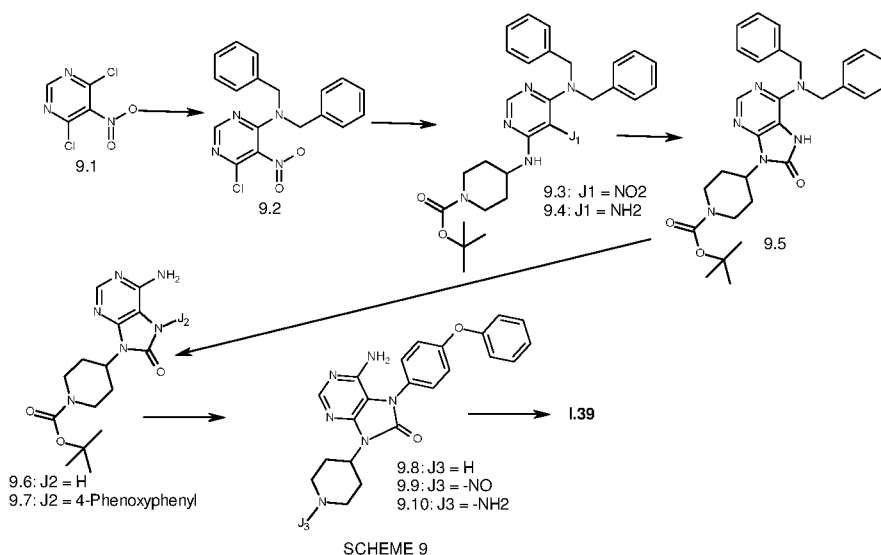
Example 17: 1-[1-[(*E*)-But-2-en-(*Z*)-ylidene]amino]-piperidin-4-yl]-3-(4-phenoxy-phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine I.17:

To a stirred suspension of 1-(1-aminopiperidin-4-yl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine (0.5 g) and molecular sieves in dichloroethane (20 mL), crotonaldehyde (0.26 g) was added under nitrogen atmosphere and the reaction mass was heated at reflux for about 5-6 h. The reaction mass was cooled and methanol was added. The mixture was filtered and evaporated to dryness under reduced pressure. The crude was subjected to column chromatography on silica gel to obtain **I.17** as a yellow solid.

Example 18: 4-[1-(1-Acryloylamino-piperidine-4-yl)-4-amino-1*H*-pyrazolo-[3,4-*d*]pyrimidine-3-yl]-*N*-(5-methyl-pyridin-2-yl)-benzamide I.33

To a cold (-55 °C to -65 °C) and stirred solution of 4-[4-amino-1-(1-amino-piperidin-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-*N*-(5-methyl-pyridin-2-yl)benzamide (8-8) (0.5 g) in dichloromethane (10 mL) was added triethylamine (0.23 mL). A solution of acryloyl chloride (0.1 mL) in dichloromethane (5mL) was then added drop-wise into it and temperature of

reaction mass was raised to 25 °C. The reaction mass was quenched with water and organic layer was separated dried and subjected to column chromatography to obtain **1.33** as a white solid.



5 Examples 19: *N, N*-Dibenzyl-6-chloro-5-nitro-pyrimidin-4-amine (9.2)

A solution of dibenzylamine (26.17g) in dichloromethane (60 mL) was added drop-wise into a solution of 4,6-dichloro-5-nitropyrimidine (20.0 g) in dichloromethane (140 mL) over an ice bath. Triethylamine (18.3 mL) was added, and the mixture was stirred for 1 hour. Water was added to the reaction mixture, the organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain the title compound (32.1 g) as a pale yellow solid.

Example 20: *tert*-Butyl 4-[[6-(dibenzylamino)-5-nitro-pyrimidin-4-yl]amino]piperidine-1-carboxylate (9.3)

N,N-Dibenzyl-6-chloro-5-nitro-pyrimidin-4-amine (18g) and *tert*-butyl 4-aminopiperidine-1-carboxylate (15.15 g) were dissolved in dioxane (90.0 mL). Triethylamine (10.5 mL) was added and the mixture was stirred for 16 hours at 60 °C. The reaction mixture was cooled to room temperature and the solvent was distilled off. Residue was extracted with ethyl acetate and the organic layer was washed with water, saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off after filtration and the residue was subjected to silica gel column chromatography to obtain the title compound (22.0 g) as an off-white solid.

Example 21: *tert*-Butyl 4-[[5-amino-6-(dibenzylamino)pyrimidin-4-yl]amino]piperidine-1-carboxylate (9.4)

An ethyl acetate (400 mL) solution of compound (9.3) (20.0 g) was added drop-wise into a suspension of zinc (26.2 g) and 3.0 M aqueous ammonium solution (12.3 g) over an ice bath.

- 5 The temperature was immediately raised to room temperature. After stirring for 16 hour, the reaction mixture was filtered through CeliteTM and the solvent was distilled off. The residue was subjected to silica gel column chromatography to obtain the title compound (12.0 g) as an off-white solid.

10 **Example 22: *tert*-Butyl 4-[6-(dibenzylamino)-8-oxo-7H-purin-9-yl]piperidine-1-carboxylate (9.5)**

Compound 9.4 (12.0 g) and 1,1'-carbonyl diimidazole (7.96 g) were dissolved in tetrahydrofuran (240 mL) and the solution was stirred for 16 hours at 65 °C. The solvent was distilled off from the reaction mixture, water was added and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered and the solvent was distilled off. The residue was subjected to silica gel column chromatography to obtain the title compound (11.0 g) as an off-white solid.

20 **Example 23: *tert*-Butyl 4-(6-amino-8-oxo-7H-purin-9-yl)piperidine-1-carboxylate (9.6)**

- The compound 9.7 (9.0 g) was dissolved in acetic acid (90 mL), 5 % wet Pd on Carbon (10.0 g) was added, hydrogen gas replacement was carried out and stirring was performed for 16 hours at 60 °C. The reaction mixture was filtered through CeliteTM. The solvent was distilled off from the reaction mixture, water was added, and the extraction with ethyl acetate was performed. The organic layer was washed with saturated aqueous sodium chloride solution then dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography to obtain the title compound (4.2 g) as an off-white solid.

30 **Example 24: *tert*-Butyl 4-[6-amino-8-oxo-7-(4-phenoxyphenyl)purin-9-yl]piperidine-1-carboxylate (9.7)**

At room temperature, *p*-phenoxy phenyl boronic acid (7.63 g), copper(II) acetate (4.73 g), molecular sieve 4A (8.0 g), pyridine (4.8 mL) and triethylamine (8.2 mL) were added to a suspension of compound 9.6 (4.0 g) in dichloromethane (200 mL) and stirred for 72 hours.

The reaction mixture was filtered through Celite™ and the residue was purified by silica gel column chromatography to obtain the title compound (4.0 g) as an off-white solid.

Example 25: 6-Amino-7-(4-phenoxyphenyl)-9-(4-piperidyl)purin-8-one (9.8)

5 At room temperature, 4 N HCl in dioxane (44 mL) was added to a suspension of compound 9.7 (4.0 g) in methanol (40 mL) and the mixture was stirred for 4.0 hours. The solvent was then distilled off to obtain the title compound (2.0 g) as an off-white solid.

Example 26: 6-Amino-9-(1-nitroso-4-piperidyl)-7-(4-phenoxyphenyl)purin-8-one (9.9)

10 A solution of sodium nitrite (0.42 g) in water (10 mL) was added drop-wise into a solution of compound 9.8 (1.0 g) in acetic acid (15.0 mL) at low temperature (-5 to 0 °C) and stirred at room temperature for 6 hours. The solvent was distilled off from the reaction mixture, water was added, and the extraction with ethyl acetate was performed. The organic layer was washed with saturated aqueous sodium chloride solution then dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography to obtain the title compound (0.8 g) as an off-white solid.

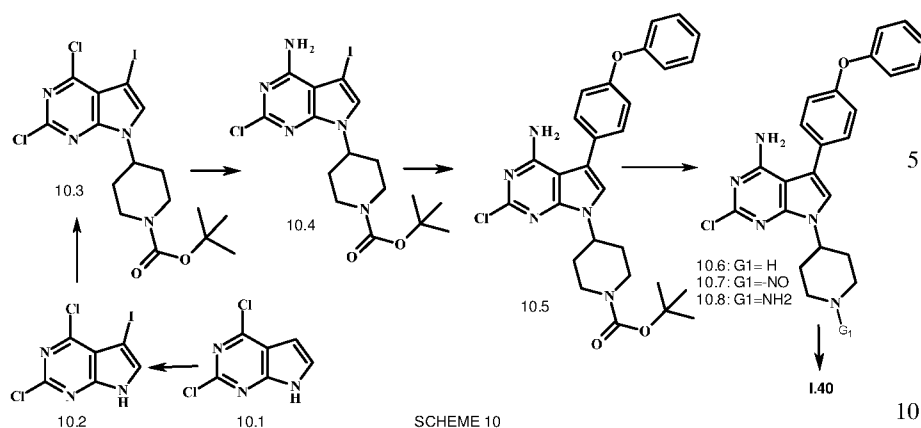
Example 27: 6-Amino-9-(1-amino-4-piperidyl)-7-(4-phenoxyphenyl)purin-8-one (9.10)

20 An Ethyl acetate (30 mL) solution compound 9.9 (0.80 g) was dripped into a mixture of zinc (1.2 g) and 3.0 M aqueous ammonium solution (0.57 g) on an ice bath, followed by stirring at room temperature for 6 hours. The reaction mixture was filtered through Celite™. The organic layer was washed with saturated aqueous sodium chloride solution then dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography to obtain the title compound (0.5 g) as an off-white solid

25

Example 28: N-[4-[6-Amino-8-oxo-7-(4-phenoxyphenyl)purin-9-yl]-1-piperidyl]-3-(2,5-dioxopyrrol-1-yl)propanamide (I.39)

30 To stirred solution of compound 9.10 (0.2 g) in MDC (10.0 mL) and triethylamine (0.13 mL), solid 3-(2,5-dioxopyrrol-1-yl) propanoic acid (0.16 g) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.15 g) was added, followed by stirring for 16 hours. The reaction mass was quenched with water, the organic phase was separated, dried over anhydrous sodium sulphate and filtered. Evaporated the filtrate and the crude mass was subjected to column chromatography to obtain the title compound (34 mg) as an off-white solid.



Example 29: 2,4-Dichloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (10.2)

To a stirred solution of 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (25 g) in DMF (100 mL) was charged *N*-Iodosuccinamide (31.41g). The reaction mixture was stirred for 3-4 h at ambient temperature and poured into water. Precipitates were filtered and washed with water (500 mL). Filtered solid was suck dried and extracted into ethylacetate (800 mL) and washed with water (300 mL). Organic layer was dried over anhydrous sodium sulphate and concentrated under vacuum. Trituration of the solid with hexanes (125 mL) followed by filtration and drying afforded an off-white solid (30 g).

20

Example 30: *tert*-Butyl 4-(2,4-dichloro-5-iodo-pyrrolo[2,3-d]pyrimidin-7-yl)piperidine-1-carboxylate (10.3)

To a stirred solution of compound 10.2 (10 g) in THF (200 mL) was charged, triphenylphosphine (16.68 g) and maintained at ambient temperature. The reaction flask was flushed with nitrogen and charged DEAD (8.28 mL) and maintained at ambient temperature for 16 h. The reaction mass subjected to silica gel column chromatography to obtain the title compound (12 g) as an off-white solid,

25

Example 31: *tert*-Butyl 4-(4-amino-2-chloro-5-iodo-pyrrolo[2,3-d]pyrimidin-7-yl)piperidine-1-carboxylate (10.4)

To a stirred solution of compound 10.3 (12 g) in 1,4-dioxan (120 mL) was added aq. ammonia solution (25 %, 60 mL). The contents were transferred into an autoclave and heated at 80-85 °C for 16 h. Concentrated the reaction mass, suspended the residue in water (25 mL), filtered and dried to obtain the title compound (10 g) as an off-white solid.

30

Example 32: *tert*-Butyl 4-[4-amino-2-chloro-5-(4-phenoxyphenyl)pyrrolo[2,3-*d*]pyrimidin-7-yl]piperidine-1-carboxylate (10.5)

To a stirred solution of compound 10.4 (11 g) in 1,4-dioxan (155 mL) were charged 4-phenoxyphenylboronic acid (6.4 g) and aq. sodium carbonate (7.3 g in 30 mL). The reaction mass was flushed with nitrogen and *bis*-(triphenylphosphine)palladium (II) dichloride (1.61 g). The contents were stirred at 80-85 °C for 2 h and concentrated. The residues were partitioned between ethyl acetate and water. Organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure after filtration. The residues were purified by column chromatography to afford the title compound (8.5 g) an off-white solid.

Example 33: 2-Chloro-5-(4-phenoxyphenyl)-7-(4-piperidyl)pyrrolo[2,3-*d*]pyrimidin-4-amine (10.6)

To a cooled (0 °C) and stirred solution of compound 10.5 (8 g) in dichloromethane (80 mL) was added trifluoroacetic acid (40 mL). The reaction mass was allowed to warm to ambient temperature and stirred for 4-5 h. The reaction mixture was concentrated and residues were partitioned between dichloromethane (100 mL) and 5 % aq. sodium carbonate solution. Removal of solvents afforded the title compound (5 g) as an off-white solid.

Example 34: 2-chloro-7-(1-nitroso-4-piperidyl)-5-(4-phenoxyphenyl)pyrrolo[2,3-*d*]pyrimidin-4-amine (10.7)

To a stirred solution of compound 10.6 (5 g) in THF (200 mL) was added isoamyl nitrite (1.33 g) and refluxed for 24 h. At the end the reaction mixture was concentrated and residues were subjected to column chromatography to give the title compound (4.5 g) as a golden yellow solid.

Example 35: 7-(1-amino-4-piperidyl)-2-chloro-5-(4-phenoxyphenyl)pyrrolo[2,3-*d*]pyrimidin-4-amine (10.8)

To a solution of compound 10.7 (4.5 g) in glacial acetic acid (31 mL) was added water (13.5 mL) and cooled to 0-5 °C in ice-salt bath. Activated zinc (2.61 g) was added during period of 10-20 minutes and allowed to warm to room temperature. The contents were filtered over Celite™ and mother liquor was poured into excess aq. 20 % sodium carbonate solution and extracted with mixture of ethyl acetate: THF. Organics were dried over anhydrous sodium sulphate and concentrated to yield the title compound (2.5 g) as a slight pinkish solid.

Example 36: *N*-[4-[4-amino-2-chloro-5-(4-phenoxyphenyl)pyrrolo[2,3-*d*]pyrimidin-7-yl]-1-piperidyl]prop-2-enamide (I.40)

To a cooled (-10 °C) and stirred solution of compound 10.8 (0.8 g) in dichloromethane (10 mL) was added triethylamine (0.38 mL) and flushed with nitrogen. Acryloyl chloride (0.2 mL) was added during 4-5 minutes and maintained for 30 minutes. The reaction was quenched with water (10 mL) and layers were separated. Organics layer was dried and concentrated and subjected to chromatographic separation with mixture of ethyl acetate and hexanes to afford the title compound (0.1 g) as an off-white solid.

Biological Data:

Radioligand binding assay:

BTK (b) was incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 μM KVEKIGEGTYGVVYK (Cdc2 peptide), 10 mM MgAcetate and [γ-33P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction was initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction was stopped by the addition of 3 % phosphoric acid solution. 10 μL of the reaction was then spotted onto a P30 filtermat and washed three times for 5 minutes with 75 mM phosphoric acid and once with methanol prior to drying and scintillation counting.

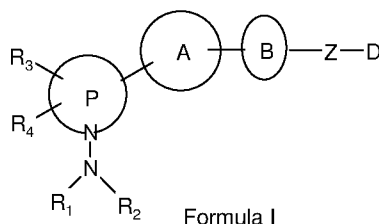
The compounds of present invention showed more than 50 % inhibition of BTK at 100 nM. Table 2 provides percentage inhibition at 10 nM and 100 nM for few representative compounds in radioligand binding assay.

Table 2

Compd	% inhibition		Compd	% inhibition		Compd	% inhibition	
	10 nM	100 nM		10 nM	100 nM		10 nM	100 nM
I.1	45	83	I.11	87	99	I.22	29	79
I.2	60	97	I.12	64	94	I.23	14.5	45
I.3	52	89	I.13	61	94	I.24	53.7	84.12
I.4	31	81	I.14	78	99	I.25	-18.71	9.43
I.5	67	95	I.16	71	93	I.26	14.4	47.7
I.6	61	95	I.17	72	94	I.27	34.2	64.2
I.7	61	96	I.18	57	92	I.28	30	87
I.8	31	81	I.19	65	93	I.29	29.1	84
I.9	65	96	I.20	23	73	I.30	26.8	42.8
I.10	72	96	I.21	45	88	I.31	21	20.5

CLAIMS

1. A compound of Formula I and pharmaceutically acceptable salts thereof



5 wherein, R_1 is selected from a group consisting of hydrogen, $-C_{1-4}$ alkyl, $-C_{3-4}$ alkenyl, $-C_{3-4}$ alkynyl, $-C_{1-4}$ haloalkyl, $-C_{2-4}$ haloalkenyl, $-C_{3-4}$ haloalkylalkynyl, $-C_{1-4}$ cyanoalkyl, $-C_{2-4}$ cyanoalkenyl, $-C_{2-4}$ cyanoalkynyl, $-C_{2-5}$ O-alkyl, $-C_{2-5}$ O-haloalkyl, $-C_{3-6}$ cycloalkyl, $-C_{4-6}$ heterocycloalkyl containing 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with $-C_{1-4}$ alkyl or $-CO-C_{1-4}$ alkyl group; and when R_1 is alkenyl or alkynyl, the double and triple bond, respectively, is not on the carbon directly attached to the nitrogen atom;

R_2 is selected from hydrogen, $-C_{1-4}$ alkyl, $-C_{3-4}$ alkenyl, $-C_{3-4}$ alkynyl, $-C_{1-4}$ haloalkyl, $-C_{2-4}$ haloalkenyl, $-C_{3-4}$ haloalkylalkynyl, $-C_{1-4}$ cyanoalkyl, $-C_{2-4}$ cyanoalkenyl, $-C_{2-4}$ cyanoalkynyl, $-C_{2-5}$ O-alkyl, $-C_{2-5}$ O-haloalkyl, $-C_{3-6}$ cycloalkyl, $-CN$, $-C(O)R_5$, $-C(S)R_5$, $-SO_2R_5$, $-SOR_5$, $-CONHSO_2R_5$, $-CSNHSO_2R_5$, $-CONHCOR_5$, $-CSNHCOR_5$, $-CON(C_{1-4} \text{ alkyl})COR_5$, $-C(S)N(C_{1-4} \text{ alkyl})COR_5$, $-CON(C_{1-4} \text{ alkyl})SO_2R_5$, $-CSN(C_{1-4} \text{ alkyl})SO_2R_5$, $-C(=NR_6)R_5$, $-C(=NR_6)N(R_6)C(O)R_5$, $-C_{4-6}$ heterocycloalkyl containing 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with $-C_{1-4}$ alkyl and $-CO-C_{1-4}$ alkyl group, and when R_2 is alkenyl or alkynyl, the double and triple bond, respectively, is not on the carbon directly attached to the nitrogen atom;

wherein R_5 is selected from a group comprising R_5' , hydrogen, $-NH_2$, $-NHOH$, $-NR_1(C_{1-4} \text{ alkyl})$ -, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-6}$ cycloalkenyl, $-C_{1-3}$ heterocycloalkenylalkyl, $-C_{3-6}$ heterocycloalkyl, $-NH$ C_{6-10} aryl, C_{5-10} heteroaryl containing 1-3 heteroatoms selected from oxygen, nitrogen or sulfur; wherein alkyl, cycloalkenyl, cycloalkyl are optionally further substituted with CN group; and aryl, heteroaryl and heterocycloalkenylalkyl are optionally substituted with one or more halogen; and R_5' is selected from a group consisting of $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ alkenylaryl, $-C_{3-6}$

alkenylheteroaryl, $-C_{3-6}$ alkynylaryl, $-C_{3-6}$ alkynylheteroaryl, $-\text{CH}=\text{CH}-(\text{CH}_2)_n-\text{COOR}_6$, $-\text{C}(\text{=CH}_2)\text{CH}_2\text{COOR}_6$, $-\text{C}\equiv\text{C}-(\text{CH}_2)_n-\text{COOR}_6$, $-\text{CH}=\text{CH}-(\text{CH}_2)_n-\text{CN}$, $-\text{C}\equiv\text{C}-(\text{CH}_2)_n-\text{CN}$, $-\text{CH}=\text{CH}-(\text{CH}_2)_n-\text{OR}_6$, $-\text{C}\equiv\text{C}-(\text{CH}_2)_n-\text{OR}_6$, $-\text{CH}=\text{CH}-(\text{CH}_2)_n-\text{NR}_6\text{R}_7$ and $-\text{C}\equiv\text{C}-(\text{CH}_2)_n-\text{NR}_6\text{R}_7$;

5 n is an integer and at each occurrence is selected from 0 to 3; m is an integer and at each occurrence is selected from 1 to 3; R_6 and R_7 at each occurrence are independently selected from hydrogen, $-C_{1-3}$ alkyl and $-C_{4-6}$ cycloalkyl or R_6 and R_7 together forms a 4-6 membered ring optionally containing one additional heteroatom selected from oxygen, nitrogen, or sulfur;

10

or R_2 is an aryl group substituted with at least one halogen atom and at least one group at *ortho* or *para* position with respect to halogen atom selected from $-\text{CN}$, $-\text{COOH}$, $-\text{COO}-C_{1-3}$ alkyl, $-\text{CON}(-C_{1-3}$ alkyl), $-\text{NO}_2$, $-\text{SO}_2C_{1-3}$ alkyl, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NH}-C_{1-3}$ alkyl, $-\text{SO}_2\text{N}(C_{1-3}$ alkyl)₂, $-\text{CO}-C_{1-3}$ alkyl, $-\text{CONH}_2$, $-\text{CONH}(C_{1-3}$ alkyl), $-\text{CON}(C_{1-3}$ alkyl)₂;

15

or R_2 is a 6 membered heteroaryl ring containing 1-3 nitrogen atoms or 5 membered ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur wherein the 6 membered or 5 membered ring is substituted with at least one group selected from halogen, C_{3-6} alkenyl, C_{3-6} alkynyl, $-\text{COOH}$ and $-\text{SH}$ group; and optionally further substituted with one or more groups selected from $-\text{CN}$, $S-C_{2-4}$ alkenyl, $-\text{COOH}$, $-\text{OC}_{1-6}$ alkyl, $-\text{COO}-C_{1-3}$ alkyl, $-\text{CON}(-C_{1-3}$ alkyl), $-\text{NO}_2$, $-\text{SO}_2C_{1-3}$ alkyl, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NH}-C_{1-3}$ alkyl, $-\text{SO}_2\text{N}(C_{1-3}$ alkyl)₂, $-\text{CO}-C_{1-3}$ alkyl, $-\text{CONH}_2$, $-\text{CONH}(C_{1-3}$ alkyl), $-\text{CON}(C_{1-3}$ alkyl)₂;

20

or R_2 is a group selected from moieties provided in Figure 1

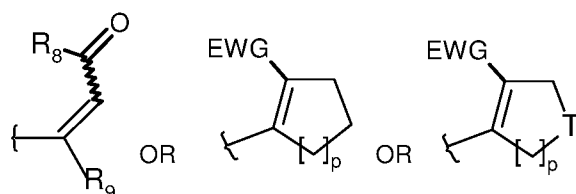


Figure 1

25

wherein, R_8 and R_9 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl or R_8 and R_9 together forms 4 to 10 membered mono or bicyclic carbocyclic ring optionally substituted with one or more C_{1-3} alkyl group or a 5 to 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from oxygen, nitrogen, or sulfur and when the

heteroatom is nitrogen it is optionally further substituted with $-C_{1-4}$ alkyl or $-CO-C_{1-4}$ alkyl group;

EWG is an electron withdrawing group selected from $-COOR_{10}$, $-CON(R_{10})_2$, $-CN$, $-NO_2$, $-SO_3H$, $-SO_2N(R_{10})_2$, $-SO_2R_{10}$ wherein R_{10} is selected from hydrogen, $-C_{1-3}$ alkyl and $-C_{4-6}$ cycloalkyl;

T is a heteroatom selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with $-C_{1-4}$ alkyl or $-CO-C_{1-4}$ alkyl group;

10

p is an integer selected from 1 and 2;

'{' is the point of attachment of R_2 with nitrogen atom;

or

15 R_1 and R_2 together forms a group selected from the groups provided in Figure 2

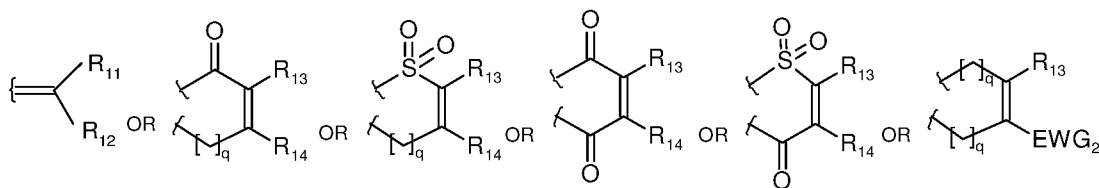


Figure 2

wherein, R_{11} and R_{12} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, $-COOR$, $-CON(R)_2$, $-CH=CHCOOR$, $-CH=CHCONRR'$, $-C_{4-6}$ heteroaryl containing 1-3 heteroatoms selected from oxygen, nitrogen or sulfur, the heteroaryl is optionally substituted with one or more halogen atoms; wherein R and R' are selected from hydrogen or C_{1-6} alkyl or R and R' together with the nitrogen to which they are attached forms a 5-6 membered saturated or unsaturated ring;

25 or R_{11} and R_{12} together forms 4 to 10 membered mono or bicyclic saturated or unsaturated carbocyclic ring or a 5 to 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from oxygen, nitrogen and sulfur and when the heteroatom is nitrogen it is optionally further substituted with $-C_{1-4}$ alkyl or $-CO-C_{1-4}$ alkyl group; the carbocyclic and the heterocyclic rings are optionally further substituted with one or more halogen atoms;

30

R₁₃ and R₁₄ are independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl or R₁₃ and R₁₄ together forms 4 to 10 membered mono or bicyclic carbocyclic ring or a 5 to 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from oxygen, nitrogen, or sulfur and when the heteroatom is nitrogen it is optionally further substituted with -C₁₋₄ alkyl or -CO-C₁₋₄ alkyl group;

EWG₂ is an electron withdrawing group selected from -COOR₁₅, -CON(R₁₅)₂, -CN, -NO₂, -SO₃H, -SO₂N(R₁₅)₂, -SO₂R₁₅ wherein R₁₅ at each occurrence is independently selected from hydrogen, -C₁₋₃ alkyl and -C₄₋₆ cycloalkyl;

q is an integer selected from 1 and 2;

'{ ' is the point of attachment of R₁ and R₂ with nitrogen atom;

R₃ and R₄ are independently selected from hydrogen, halogen, C₁₋₆ alkyl and C₃₋₆ cycloalkyl;

ring P is 4 to 13 membered saturated or unsaturated monocyclic, bicyclic or tricyclic ring optionally containing one additional heteroatom selected from oxygen, nitrogen and sulfur;

ring A is a heterocycle selected from moieties provided in Figure 3

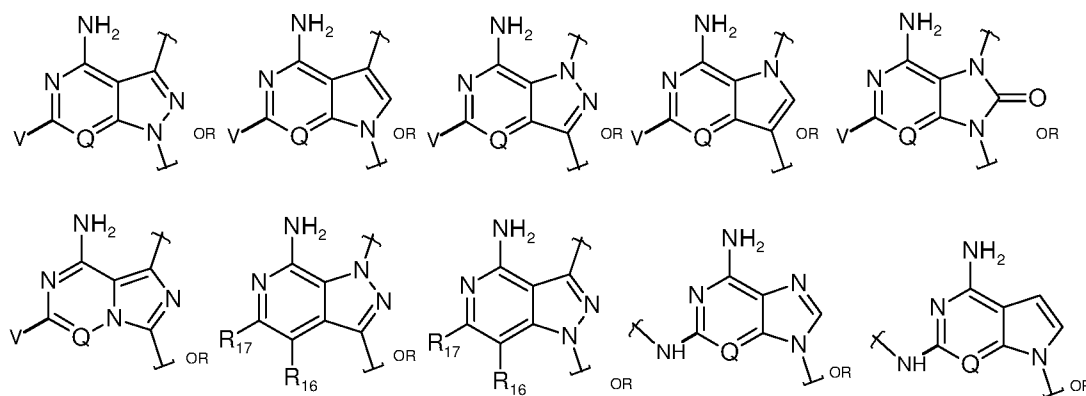


Figure 3

wherein Q is selected from CH or nitrogen;

R₁₆ and R₁₇ together forms a phenyl ring optionally substituted with halogen, -O-C₁₋₃ alkyl, -COOH, -COOC₁₋₃ alkyl, -C₁₋₃ alkyl, -OH;

or R₁₆ and R₁₇ together forms a 5 to 6 membered heterocyclic ring containing 1 to 2
5 heteroatoms selected from oxygen, nitrogen and sulfur;

V independently selected from R₁₈, halogen, -C₁₋₄ haloalkyl, -C₂₋₄ alkenyl, -C₂₋₄ alkynyl, -SR₁₈, -OR₁₈, -SOR₁₈, -SO₂R₁₈, -N(R₁₈)₂, -NHCHO, -NHCOCH₃, -C₄₋₆ hetrocycloalkyl, -C₄₋₆ cycloalkenyl, -CO-R₁₈, -CN and -CHO wherein R₁₈ at each occurrence is independently
10 selected from hydrogen, -C₁₋₄ alkyl and -C₃₋₆ cycloalkyl;

'{' represents the attachment to ring B;

'[' represents the attachment to ring P;

15

ring B is selected from moieties provided in Figure 4

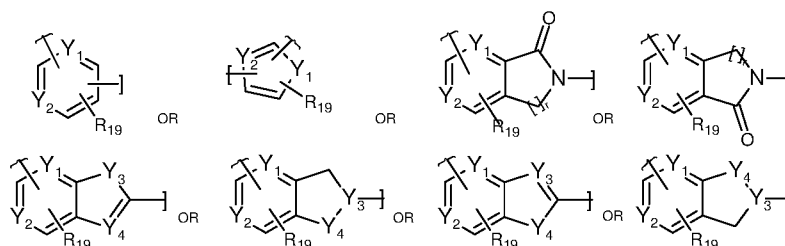


Figure 4

wherein, R₁₉ is selected from hydrogen, halogen, hydroxyl, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), -C₁₋₆ haloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ alkyl, -O C₃₋₆ alkenyl, -O C₃₋₆ alkynyl, -S-
20 C₁₋₆ alkyl, -CN, -CO-C₁₋₄ alkyl, -CO—C₃₋₆ cycloalkyl, -COOH, -CONH₂, -CON(C₁₋₆ alkyl)₂, -CONH(C₁₋₆ alkyl), -NHC(O) -C₁₋₄ alkyl, -N(C₁₋₄ alkyl)C(O) C₁₋₄ alkyl and when R₁₉ is -OC₃₋₆ alkenyl or -O C₃₋₆ alkynyl the double and triple bond, respectively, is not on the carbon directly attached to the oxygen atom;

25 Y₁, Y₂, Y₃ and Y₄ are independently and appropriately selected from CH, NR₂₀, O, or S; wherein, R₂₀ is selected from hydrogen, -C₁₋₃ alkyl and -C₄₋₆ cycloalkyl;

r is an integer selected from 1 to 3;

'{' represents the position of attachment to ring A;

'[' represents the position of attachment to Z;

Z is a bond or is selected from -O-, -S-, -NH-, -N(C₁₋₄ alkyl)-, -N(C₁₋₆ alkyl)CO-, -C(O)NH-, -C(C₁₋₂ alkyl)₂-, -C(O)-, -S(O)-, -S(O)₂-, -CH₂O-, -OCH₂-, -CH=CH-, -CH₂-, -N(CH₂CN)- and -NHC(O)-;

- 5 D is a ring containing 5 to 13 membered aryl, fused aryl, heteroaryl, fused heteroaryl, saturated or unsaturated monocyclic, bicyclic or tricyclic carbocyclic ring containing 0-3 heteroatoms selected from nitrogen, oxygen and sulfur; optionally substituted with C₁₋₃ alkyl;

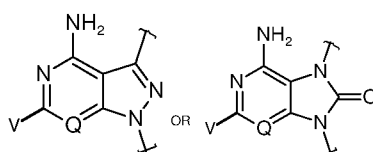
- or D is selected from -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₄ alkyl-O-C₂₋₄ alkyl, -C₃₋₆ cycloalkyl-O-C₂₋₄ alkyl, -C₁₋₄ alkyl-O-C₃₋₆ cycloalkyl, -C₁₋₄ haloalkyl-O-C₂₋₄ alkyl, -C₁₋₄ haloalkyl-S-C₂₋₄ alkyl and -C₁₋₄ alkyl-S-C₂₋₄ alkyl;
- 10

with the proviso that when:

ring B and D are phenyl;

- 15 Z is selected from -O-, -S-, -NH-, -N(C₁₋₄ alkyl)- or -C(O)-;

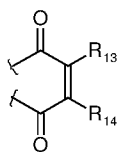
Ring A is selected from



and V is hydrogen then:

R₂ is not selected from -C(O)R₅, -C(S)R₅, -SO₂R₅, -SOR₅ wherein R₅ is R₅; and

- 20 R₁ and R₂ together does not form the following group



2. The compound of Formula I as in claim 1 wherein,

R₁ is hydrogen;

25

R₂ is selected from -CN, -C(O)R₅, -C(S)R₅, -SO₂R₅ wherein,

R_5 is selected from a group comprising R_5' , $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-3}$ heterocycloalkenylalkyl, NH C_{6-10} aryl, C_{5-10} heteroaryl containing 1-3 heteroatoms selected from oxygen, nitrogen or sulfur, wherein

alkyl and cycloalkyl are optionally further substituted with CN group; and aryl, heteroaryl and heterocycloalkenylalkyl are optionally substituted with one or more halogen;

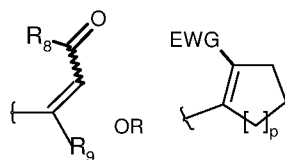
R_5' is selected from a group consisting of $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-CH=CH-(CH_2)_n-COOR_6$ and $-C(=CH_2)CH_2COOR_6$;

n is an integer and at each occurrence is selected from 0 to 3;

R_6 is selected from hydrogen, $-C_{1-3}$ alkyl;

or R_2 is a 6 membered heteroaryl ring substituted with at least one group selected from halogen, C_{3-6} alkenyl, C_{3-6} alkynyl and $-SH$ group; and optionally further substituted with one or more groups selected from $S-C_{2-4}$ alkenyl, $-COOH$, $-OC_{1-6}$ alkyl, $-CON(-C_{1-3}$ alkyl), $-NO_2$ and $-CONH_2$;

or R_2 is a group selected from following moieties

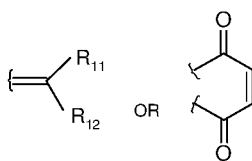


wherein, R_8 and R_9 are independently selected from hydrogen and C_{1-6} alkyl, or R_8 and R_9 together forms 4 to 10 membered mono-cyclic ring optionally substituted with one or more C_{1-3} alkyl group;

EWG is $-C(O)OC_{1-3}$ alkyl;

OR

R_1 and R_2 together forms a group selected from following groups



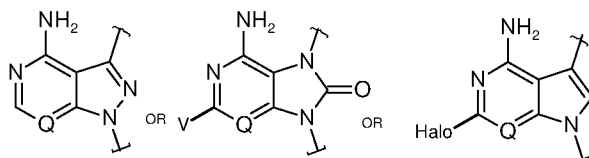
wherein, R_{11} and R_{12} are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, $-COOR$ and $-C_{4-6}$ heteroaryl containing 1-3 heteroatoms selected from oxygen, nitrogen or

sulfur; wherein R is hydrogen or C₁₋₆ alkyl and the heteroaryl is optionally substituted with one or more halogen atoms;

or R₁₁ and R₁₂ together forms substituted or unsubstituted 5 to 6 membered saturated or
 5 unsaturated mono carbocyclic ring or a 5 to 6 membered heterocyclic ring containing 1 to 2
 heteroatoms selected from oxygen and nitrogen; and the carbocyclic and the heterocyclic
 rings are optionally further substituted with one or more halogen atoms;

ring P is 4 to 6 membered saturated monocyclic, ring containing one additional heteroatom
 selected from nitrogen;

10 ring A is a heterocycle selected from following moieties



wherein Q is selected from CH or nitrogen;

ring B is phenyl;

Z is selected from -O-, -C(O)NH- and -NHC(O)-;

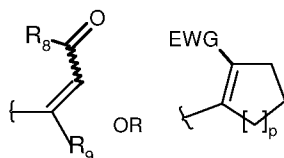
15 D is phenyl or pyridine ring unsubstituted or substituted with C₁₋₃ alkyl.

3. The compound of Formula I as in claims 1 and 2, wherein

R₁ is hydrogen; R₂ is -C(O)R₅ or a 6 membered heteroaryl ring substituted with one or more
 halogen radical;

20

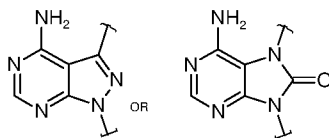
or R₂ is a group selected from following moieties



wherein, R₈ and R₉ are independently selected from hydrogen and C₁₋₆ alkyl, or R₈ and R₉
 together forms 4 to 10 membered mono-cyclic ring optionally substituted with one or more
 25 C₁₋₃ alkyl group;

EWG is -C(O)OC₁₋₃ alkyl;

ring A is a heterocycle selected from following moieties.



Z is -O-; and D is a phenyl ring.