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(54) Benævnelse: **PURINDERIVATER, DER ER ANVENDELIGE SOM HSP90-INHIBITORER**

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WO-A1-2008/115719
WO-A1-2009/007399
WO-A1-2009/065035
WO-A2-03/037860
WO-A2-2006/084030
WO-A2-2007/134298
WO-A2-2008/005937
HE H ET AL: "Identification of potent water soluble purine-scaffold inhibitors of the heat shock protein 90", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 49, no. 1, 12 January 2006 (2006-01-12), pages 381-390, XP002462212, ISSN: 0022-2623, DOI: 10.1021/JM0508078

DESCRIPTION

Statement of Related Cases

[0001] This application is related to US Patent Application No. 12/307,063 filed 12/30/2008, and US Patent Application No. 11/814,506, filed July 23, 2007.

Background of the Invention

[0002] This application relates to compounds that inhibit heat shock protein 90 (Hsp90).

[0003] The Hsp90 family of proteins has four recognized members in mammalian cells: Hsp90 α and β, Grp94 and Trap-1. Hsp90 α and β exist in the cytosol and the nucleus in association with a number of other proteins. Hsp90 in its various forms is the most abundant cellular chaperone, and has been shown in experimental systems to be required for ATP-dependent refolding of denatured or "unfolded" proteins. It has therefore been proposed to function as part of the cellular defense against stress. When cells are exposed to heat or other environmental stresses, the aggregation of unfolded proteins is prevented by pathways that catalyze their refolding or degradation. This process depends on the association of the unfolded protein in an ordered fashion with multiple chaperones (Hsp 60, 90 and 70 and p23), forming a "refoldosome" and ultimately the ATP-dependent release of the chaperones from the refolded protein.

[0004] Hsp90 may also play a role in maintaining the stability and function of mutated proteins. It seems to be required for expression of mutated p53 and v-src to a much greater extent than for their wild-type counterparts. It has been suggested that this occurs as a result of Hsp90-mediated suppression of the phenotypes of mutations that lead to protein unfolding.

[0005] Hsp90 is also necessary to the conformational maturation of several key proteins involved in the growth response of the cell to extracellular factors. These include the steroid receptors as well as certain transmembrane kinases (i.e., Raf serine kinase, v-src and Her2). The mechanism whereby Hsp90 affects these proteins is not fully understood, but appears to be similar to its role in protein refolding. In the case of the progesterone receptor, it has been shown that binding and release of Hsp90 from the receptor occurs in a cyclic fashion in concert with release of other chaperones and immunophilins and is required for high affinity binding of the steroid to the receptor. Thus, Hsp90 could function as a physiologic regulator of signaling pathways, even in the absence of stress.

[0006] Hsp90 has been shown to be overexpressed in multiple tumor types and as a function of oncogenic transformation. Whether it plays a necessary role in maintaining transformation is unknown, but it could have at least three functions in this regard. Cancer cells grow in an environment of hypoxia, low pH and low nutrient concentration. They also rapidly adapt to or are selected to become resistant to radiation and cytotoxic chemotherapeutic agents. Thus, the general role of Hsp90 in maintaining the stability of proteins under stress may be necessary for cell viability under these conditions. Secondly, cancer cells harbor mutated oncogenic proteins. Some of these are gain-of-function mutations which are necessary for the transformed phenotype. Hsp90 may be required for maintaining the folded, functionally-active conformation of these proteins. Thirdly, activation of signaling pathways mediated by steroid receptors, Raf and other Hsp90 targets is necessary for the growth and survival of many tumors which thus probably also require functional Hsp90.

[0007] Hsp90 has been recognized as a viable target for therapeutic agents. Hsp90 family members possess a unique pocket in their N-terminal region that is specific to and conserved among all Hsp90s from bacteria to mammals, but which is not present in other molecular chaperones. The endogenous ligand for this pocket is not known, but it binds ATP and ADP with low affinity and has weak ATPase activity. The ansamycin antibiotics geldanamycin (GM) and herbimycin (HA) have been shown to bind to this conserved pocket, and this binding affinity has been shown for all members of the Hsp90 family. International Patent Publication No. WO98/51702 discloses the use of ansamycin antibiotics coupled to a targeting moiety to provide targeted delivery of the ansamycin leading to the degradation of proteins in and death of the targeted cells. International Patent Publication No. WO00/61578 relates to bifunctional molecules having two moieties which interact with the chaperone protein Hsp90, including in particular homo- and heterodimers of ansamycin antibiotics. These bifunctional molecules act to promote degradation and/or inhibition of HER-family tyrosine kinases and are effective for treatment of cancers which overexpress Her-kinases.

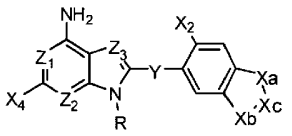
[0008] Exemplary small molecule therapeutics that bind to the same binding pocket of Hsp90 as ATP and the ansamycin antibiotics are disclosed in PCT Publication Nos. WO02/36075, WO09/042646 and WO09/065035, and US Patent Publications

2005/0113339, 2005/0004026, 2005/0049263, 2005/0256183, 2005/0119292, 2005/0113340, 2005/0107343, 2008/0096903, 2008/0234297, 2008/0234314 and 2008/0253965.

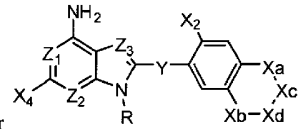
Further patent publications particularly include:

[0009] WO 2008/005937 A2 of Sloan-Kettering Institute for Cancer Research entitled "Treatment of Neurodegenerative Diseases through Inhibition of HSP90" discloses substituted 9H-purin-6-amine compounds and their use for the treatment of neurodegenerative diseases through inhibition of HSP90.
The publication of He et al. entitled "Identification of Potent Water Soluble Purine-Scaffold Inhibitors of the Heat Shock Protein 90". J. Med. Chem. 49:381-390 (2006) discloses water soluble substituted 9H-purin-6-amine compounds and their use for the inhibition of HSP90. WO 2009/065035 A1 of Myriad Genetics, Inc. entitled "Therapeutic Compounds and Their Use in Treating Diseases and Disorders" discloses substituted 8-((2.3-dihydrobenzo[b][1.4]dioxin-6-yl)thio)-9H-purin-6-amine compounds to treat diseases and disorders such as cancers.
WO 2007/134298 A2 of Myriad Genetics, Inc. entitled "Therapeutic Compounds and Their Use in Cancer" discloses substituted 5H-purin-6(9H)-one, 3H-purin-6-amine, and 9H-purin-6-amine compounds and their use for the treatment of cancer.
WO 2008/115719 A1 of Curis, Inc. entitled "Fused Amino Pyridine as HSP90 Inhibitors" discloses substituted 3a,4-dihydro-1 H-pyrrolo[3,2-c]pyridine and 3a,4-dihydro-1H-imidazo[4,5-c]pyridine compounds and their use as HSP90 inhibitors.
WO 2006/084030 A2 of Sloan-Kettering Institute for Cancer Research entitled "Small-Molecule HSP90 Inhibitors" discloses substituted 9H-purin-6-amine compounds and their use in cancer therapy through inhibition of HSP90.

[0010] Many of the small molecule therapeutics that bind to the same binding pocket of Hsp90 as ATP and the ansamycin antibiotics are based on a scaffold of the type disclosed by Chiosis et al in PCT Publication No. WO02/36075, with variations in substituents. In some cases, the compositions can be described by one of the following two general formulas:

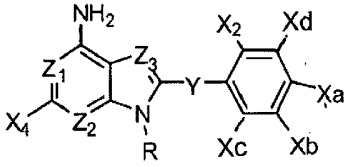


(1A) or



(1B)

wherein Z1, Z2, Z3 are selected from C and N in which numerous options are disclosed for each variable substituent, resulting in an astronomical number of combinations and permutations. In other cases, the compositions can be described by a structural formula in which Xa, Xb, Xc and Xd are not connected to one another but are simply substituents on the benzene ring. These structures have the general formula:



(1C)

wherein Z1, Z2, Z3 are selected from C and N. While these compounds are generally active as inhibitors of Hsp90, the level of activity is extremely variable with measured values for EC_{50} and IC_{50} being reported in both micromolar and nanomolar ranges.

Summary of the Invention

[0011] The present application provides compounds useful in the inhibition of Hsp90, and hence in the treatment of disease.

Brief Description of the Figures

[0012]

Fig. 1 shows examples of unsubstituted aryl groups, including some heterocyclic aryl groups.

Fig. 2 shows examples of unsubstituted heterocyclic groups.

Fig. 3 shows average tumor volume in mice treated with compound 1B-1-HCl or with vehicle.

Detailed Desciption of the Invention

[0013] The present invention provides compounds within the scope of Formula 1A, with particular combinations of substituents that are effective to inhibit Hsp90. Inhibitors of Hsp90 are recognized as effective in treatments of cancer, and also can be used in the treatment of neurodegenerative diseases as described in PCT Patent Publication WO2008/005397. WO 2007/14360 discloses the use of Hsp90 inhibitors in treatment of neurofibromatosis Thus, the compounds of the invention can be used in therapeutic methods in the same manner as used other known Hsp90 inhibitors, by administering a therapeutically effective amount of a compound of the invention to an individual, including a human, in need of treatment for cancer, neurodegenerative disease or other condition for which Hsp90 inhibition is relevant.

[0014] As used in this application, the term "treatment" refers to delaying the onset of symptoms, reducing the severity or delaying the symptomatic progression of cancer, neurodegenerative disease or other condition in the individual. A cure of the disease is not required to fall within the scope of treatment. Further, it will be appreciated that the specific results of these treatment goals will vary from individual to individual, and that some individuals may obtain greater or lesser benefits than the statistical average for a representative population. Thus, treatment refers to administration of composition to an individual in need, with the expectation that they will obtain a therapeutic benefit.

[0015] The term "administering" refers to the act of introducing into the individual the therapeutic compound. In general, any route of administration can be used. Thus, administration by oral, intrathecal, intravenous, intramuscular or parenteral injection is appropriate depending on the nature of the condition to be treated. Administration may also be done to the brain by inhalation because there is a compartment at the upper side of the nose that connects with the brain without having the BBB capillaries. Compounds that cross the blood brain barrier are preferred for this mode of administration, although this characteristic is not strictly required.

[0016] The term "therapeutically effective amount" encompasses both the amount of the compound administered and the schedule of administration that on a statistical basis obtains the result of preventing, reducing the severity or delaying the progression of the disease in the individual. As will be appreciated, preferred amounts will vary from compound to compound in order to balance toxicity/tolerance with therapeutic efficacy and the mode of administration. Determination of maximum tolerated dose and of the treatment regime in terms of number and frequency of dosing is a routine part of early clinical evaluation of a compound.

[0017] In all of the compounds of the present invention, the compound may be as depicted, or as a pharmaceutically acceptable salt or ester thereof.

[0018] In naming options for X_2, X_4 and R, the name refers to the type of group that is directly attached to the central structure, which group may include additional functionality.
Thus, *"alkyl"* group refers to a saturated hydrocarbon which is a linear or a branched hydrocarbon and *"cyclo alkyl"* group refers to a cyclic saturated hydrocarbon, for example a hydrocarbon having from 1 to 10 carbon atoms, in which the atom directly attached to the central structure is a carbon atom.
Such an alkyl or cycloalkyl group may include substituents other than hydrogen, for example an oxygen-containing group including without limitation hydroxyl and alkoxy; a halogen group; a nitrogen-containing group including without limitation amino, amido and alkylamino; an aryl group; a sulfur-containing group including without limitation thioalkyl; and/or a non-aromatic cyclic group including heterocycles and carbocycles. Carbon atoms in these substituents may increase the total number of carbon atoms in the alkyl group to above 10 without departing from the invention. All references to alkyl groups or cycloalkyl groups in the specification and claims hereof encompass both substituted and unsubstituted alkyl or cycloalkyl groups unless the context is clearly to the contrary.

[0019] *"Alkenyl"* group refers to a linear, or a branched hydrocarbon, and *"cyclo alkenyl"* group refers to a cyclic hydrocarbon for example a hydrocarbon having from 1 to 10 carbon atoms, and at least one double bond, in which the atom directly attached to the central structure is a carbon atom. The alkenyl or cycloalkenyl group may include any of the substituents mentioned above for an alkyl group or cycloalkyl group. All references to alkenyl or cycloalkenyl groups in the specification and claims hereof encompass both substituted and unsubstituted alkenyl groups unless the context is clearly to the contrary.

[0020] *"Alkynyl"* group refers to a linear, or a branched hydrocarbon, for example a hydrocarbon having from 1 to 10 carbon atoms, and at least one triple bond, in which the atom directly attached to the central structure is a carbon atom. The alkynyl group may include any of the substituents mentioned above for an alkyl or alkenyl group. All references to alkynyl groups in the specification and claims hereof encompass both substituted and unsubstituted alkynyl groups unless the context is clearly to the contrary.

[0021] *"Aryl"* group refers to any group derived from a simple aromatic ring. Aryl group includes heteroaryl.(See Fig. 1) Aryl groups may be substituted or unsubstituted. When X_2, X_4 and R is identified as an aryl group, an atom of the aryl ring is bound directly to an atom of the central structure. An aryloxy substituent is an aryl group connected to the central structure through an oxygen atom. The aryl group may include any of the substituents mentioned above for an alkyl group, and in addition an aryl group may include an alkyl, alkenyl or alkynyl group. All references to aryl groups in the specification and claims hereof encompass both substituted and unsubstituted aryl groups unless the context is clearly to the contrary.

[0022] *"Amino"* group refers to any group which consists of a nitrogen attached by single bonds to carbon or hydrogen atoms. In certain instances, the nitrogen of the amino group is directly bound to the central structure. In other instances, an amino group may be a subtituent on or within a group, with the nitrogen of the amino group being attached to the central structure through one or more intervening atoms. Examples of amino groups include NH_2, alkylamino, alkenylamino groups and N-containing non-aromatic heterocyclic moiety (i.e., cyclic amines). Amino groups may be substituted or unsubstituted. All references to amino groups in the specification and claims hereof encompass substituted and unsubstituted amino groups unless the context is clearly to the contrary.

[0023] *"Halogen" group* refers to fluorine, chlorine, bromine or iodine.

[0024] *"Heterocyclic"* group refers to a moiety containing at least one atom of carbon, and at least one atom of an element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure. These heterocyclic groups may be either aromatic rings or saturated and unsaturated non-aromatic rings. Some examples are given in Fig. 2. Heterocylic groups may be substituted or unsubstituted. All references to heterocyclic groups in the specification and claims encompass substituted and unsubstituted heterocyclic groups unless the context is clearly to the contrary.

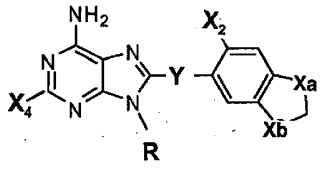
[0025] In the compounds of the invention, all of the atoms have sufficient hydrogen or non-hydrogen substituents to satisfy valence, or the compound includes a pharmaceutically acceptable counterion, for example in the case of a quaternary amine.

[0026] In the structures set forth below examples are provided in which all of Z1, Z2 and Z3 are nitrogen. These examples are intended as exemplary, and are not intended to exclude options in which one or more of Z1, Z2 and Z3 is carbon. In particular, corresponding compositions in which Z2 or Z3 is carbon are considered to be within the scope of this disclosure.

[0027] X_2 and R are in combinations as discussed below.

G. Structures of formula 1A in which Xa and Xb are both O

[0028] In accordance with the invention, the compounds have general formula 1A, in which Xa and Xb are O and Xc is CH_2. Thus, the compounds of this embodiment may be represented by the general formula



(2)

wherein:

in which Xa and Xb are O,

Y is $-CH_2-$ or -S-,

X_4 is hydrogen or halogen; and

X_2 and R are a combination selected from:

(i) X_2 is a substituted or non-substituted, linear, branched or cyclic cyano-alkyl and R is a substituted or non-substituted, linear, in which Xa and Xb are O, branched primary amino-alkyl, secondary alkyl-amino-alkyl, tertiary alkyl-amino-alkyl, or trialkylammonioalkyl group; or

(ii) X_2 is an aryl, an alkynyl, a cycloalkyl, or a cycloalkenyl group and R is:

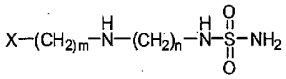
1. (a) hydrogen; or
2. (b) a straight-chain- or branched- Cl to C_{10} alkyl, C_2 to C_6 alkenyl, or C_2 to C_6 alkynyl, which is unsubstituted or substituted; or
3. (c) amino-alkyl, secondary or tertiary alkyl-amino-alkyl, or trialkylammonioalkyl;

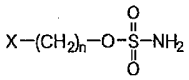
[0029] **G-I**. In some embodiments of the invention, X_2 is an aryl group. In these embodiments, R may be any of the groups disclosed as a substituent at the 9-position nitrogen in this application.

[0030] In some embodiments within this group, R includes a heteroatom, such as nitrogen, oxygen or sulfur.

[0031] In some embodiments, the heteroatom is nitrogen. In some of these embodiments, R is suitably a primary amino-alkyl, a secondary or tertiary alkyl-amino-alkyl. Specific R groups include without limitation 2-(methyl, t-butyl- amino) ethyl, 2-(methyl, isopropyl amino) ethyl, 3-(neopentyl amino) propyl, 2-(isobutyl-amino) ethyl, 2-(ethyl, isopropyl amino) ethyl, 3-(isopropyl amino) propyl, 3-(t-butyl- amino) propyl, 2-(isopropyl amino) ethyl, 2-(hydroxyethyl, isopropyl amino) ethyl, 3-(ethylamino) propyl, 3-(ethyl, methyl amino) propyl, 2-(neopentyl amino) ethyl, 3-(methyl, isopropyl amino) propyl, 3-(ethyl, isopropyl amino) propyl, 3-(hydroxyethyl, isopropyl amino) propyl, 3-(methyl, propargyl amine) propyl, 2-(methyl, propargyl amine) ethyl, 3-(allyl, methyl amino) propyl, and 2-(methyl, isobutyl amino) ethyl.

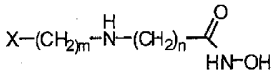
[0032] In embodiments of the invention within this group, R has the formula
site of 9*N*-attachment





where m= 2-3 and n= 1-6.

[0033] In embodiments within this group, R has the formula
site of 9*N*-attachment



where m= 2-3 and n= 1-6.

[0034] In specific embodiments, X_2 is a heterocycle.

[0035] In specific embodiments, X_2 is phenyl, furan, thiophene, pyrazole, imidazole, thiazole, oxazole or pyrrole.

[0036] In specific embodiments of the X_2 is phenyl, furan, methylfuran, thiophene, pyrazole, thiazole, oxazole or imidazole.

[0037] In particular embodiments of formula (2), Y is S, X_4 is H, X_2 is 2-, 3-furan or 5-methyl-2-furanyl.

[0038] In particular embodiments of formula (2), Y is CH_2, X_4 is Cl, X_2 is 2-, 3- furan or 5-methyl-2-furanyl.

[0039] In particular embodiments of formula (2), Y is CH_2, X_4 is F, X_2 is 2-, 3-furan or 5-methyl-2-furanyl.

[0040] In particular embodiments of formula (2), Y is S, X_4 is F, X_2 is 2-, 3-furan or 5-methyl-2-furanyl.

[0041] In particular embodiments of formula (2), Y is S, X_4 is H, X_2 is 2- or 3-thiophene.

[0042] In particular embodiments of formula (2), Y is CH_2, X_4 is Cl, X_2 is 2- or 3- thiophene.

[0043] In particular embodiments of formula (2), Y is CH_2, X_4 is F, X_2 is 2- or 3-thiophene.

[0044] In particular embodiments of formula (2), Y is S, X_4 is F, X_2 is 2- or 3-thiophene.

[0045] In particular embodiments of formula (2), Y is S, X_4 is H, X_2 is 2- or 3-pyrazole.

[0046] In particular embodiments of formula (2), Y is CH_2, X_4 is Cl, X_2 is 2- or 3- pyrazole.

[0047] In particular embodiments of formula (2), Y is CH_2, X_4 is F, X_2 is 2- or 3-pyrazole.

[0048] In particular embodiments of formula (2), Y is S, X_4 is F, X_2 is 2- or 3-pyrazole.

[0049] In particular embodiments of formula (2), Y is S, X_4 is H, X_2 is 2-thiazolyl, 5-methyl-2-thiazolyl, 2-oxazolyl or 5-methyl-2-oxazolyl.

[0050] In particular embodiments of formula (2), Y is CH_2, X_4 is Cl, X_2 is 2-thiazolyl, 5-methyl-2-thiazolyl, 2-oxazolyl or 5-methyl-2-oxazolyl.

[0051] In particular embodiments of formula (2), Y is CH_2, X_4 is F, X_2 is 2-thiazolyl, 5-methyl-2-thiazolyl, 2-oxazolyl or 5-methyl-2-oxazolyl.

[0052] In particular embodiments of formula (2), Y is S, X_4 is F, X_2 is 2-thiazolyl, 5-methyl-2-thiazolyl, 2-oxazolyl or 5-methyl-2-oxazolyl.

[0053] In particular embodiments of formula (2), Y is S, X_4 is H, X_2 is optionally substituted phenyl.

[0054] In particular embodiments of formula (2), Y is CH_2, X_4 is Cl, X_2 is optionally substituted phenyl.

[0055] In particular embodiments of formula (2), Y is CH_2, X_4 is F, X_2 is optionally substituted phenyl.

[0056] In particular embodiments of formula (2), Y is S, X_4 is F, X2 is optionally substituted phenyl.

[0057] In particular embodiments of formula (2), Y is S, X_4 is H, X_2 is optionally substituted pyridine.

[0058] In particular embodiments of formula (2), Y is CH_2, X_4 is Cl, X_2 is optionally substituted pyridine.

[0059] In particular embodiments of formula (2), Y is CH_2, X_4 is F, X_2 is optionally substituted pyridine.

[0060] In particular embodiments of formula (2), Y is S, X_4 is F, X_2 is optionally substituted pyridine.

[0061] In particular embodiments of formula (2), Y is S, X_4 is H, X_2 is optionally substituted isooxazole.

[0062] In particular embodiments of formula (2), Y is CH_2, X_4 is Cl, X_2 is optionally substituted isooxazole.

[0063] In particular embodiments of formula (2), Y is CH_2, X_4 is F, X_2 is optionally substituted isooxazole.

[0064] In particular embodiments of formula (2), Y is S, X_4 is F, X_2 is optionally substituted isooxazole.

[0065] In particular embodiments of formula (2), Y is S, X_4 is H, X_2 is optionally substituted imidazole.

[0066] In particular embodiments of formula (2), Y is CH_2, X_4 is Cl, X_2 is optionally substituted imidazole.

[0067] In particular embodiments of formula (2), Y is CH_2, X_4 is F, X_2 is optionally substituted imidazole.

[0068] In particular embodiments of formula (2), Y is S, X_4 is F, X_2 is optionally substituted imidazole.

[0069] In these particular embodiments, R may be any one of the types of groups described above.

[0070] Specific examples of compounds in accordance with this embodiment of the invention are listed in Tables 4A, 4C, 4D, and 4F. As shown, in preferred embodiments of formula (2) in which X2 is an aryl group, X_4 is H, chlorine or fluorine.

[0071] Table 2G shows measured values for EC_{50} in JNPL3 brain cell lysates and in SKBr3 cell lysate for compounds 4A-1 to 4A-8, 4Cl to 4C-11, 4C14, 4C-16, 4C-38 to 4C-41, 4D-1 to 4D-3, 4D-16, 4D-17, 4F-1, 4G-1 to 4G-7, 4G-9, 4H-1 to 4H-7 in accordance with this embodiment of the invention which incorporates a hydrogen as X_4 and in which Y is S or a fluorine as X_4 and in which Y is $-CH_2-$. Desirably low values of EC_{50} were observed for several examples.

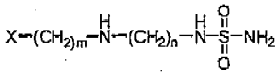
[0072] **G-II.** In some embodiments of the invention, X_2 is an alkynyl group. In these embodiments, R maybe any of the groups disclosed as a substituent at the 9-position nitrogen in this application.

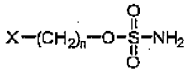
[0073] In some embodiments when X_2 is alkynyl, R includes a nitrogen heteroatom.

[0074] In a further embodiment, when X_2 is alkynyl, R is suitably an amino alkyl, a secondary or tertiary alkyl-amino-alkyl, or a trialkylammonioalkyl group.

[0075] Specific R groups include without limitation 2-(methyl, t-butyl- amino) ethyl, 2-(methyl, isopropyl amino) ethyl, 3-(neopentyl amino) propyl, 2-(isobutyl-amino) ethyl, 2-(ethyl, isopropyl amino) ethyl, 3-(isopropyl- amino) propyl, 3-(t-butyl- amino) propyl, 2-(isopropyl amino) ethyl, 2-(hydroxyethyl, isopropyl amino) ethyl, 3-(ethylamino)propyl, 3-(ethyl, methyl amino) propyl, 2-(neopentyl amino) ethyl, 3-(methyl, isopropyl amino) propyl, 3-(ethyl, isopropyl amino) propyl, 3-(hydroxyethyl, isopropyl amino) propyl, 3-(methyl, propargyl amine) propyl, 2-(methyl, propargyl amine) ethyl, 3-(allyl, methyl amino) propyl, 3-(propyl, propane) and 2-(methyl, isobutyl amino) ethyl.

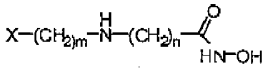
[0076] In embodiments of the invention when X_2 is alkynyl, R has the formula site of 9*N*-attachment





where m= 2-3 and n= 1-6.

[0077] In embodiments when X_2 is alkynyl, R has the formula
site of 9*N*-attachment



where m= 2-3 and n= 1-6.

[0078] In specific embodiments, X_2 is acetylene.

[0079] In particular embodiments of formula (2), Y is S, X_4 is H, X_2 is acetylene.

[0080] In particular embodiments of formula (2), Y is CH_2, X_4 is Cl, X_2 is acetylene.

[0081] In particular embodiments of formula (2), Y is CH_2, X_4 is F, X_2 is acetylene.

[0082] In particular embodiments of formula (2), Y is S, X_4 is F, X_2 is acetylene.

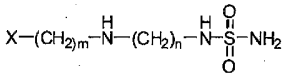
[0083] In these particular embodiments, R may be any one of the types of groups described above.

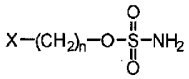
[0084] Specific examples of compounds in accordance with this embodiment of the invention are listed in Tables 4B. As shown, in preferred embodiments of formula (2) in which X_2 is an alkynyl group, X_4 is H, chlorine or fluorine.

[0085] Table 2H shows measured values for EC_{50} in JNPL3 brain cell lysates and in SKBr3 cell lysate for compounds 4B-1 to 4B-4, 4B13 and 4B-14 in accordance with this embodiment of the invention which incorporates a hydrogen as X_4 and in which Y is S, or a fluorine as X_4 and in which Y is $-CH_2-$. Desirably low values of EC_{50} were observed.

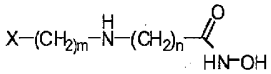
[0086] **G-III.** In some embodiments of the invention, X_2 is a cyano or cyanoalkyl group. In these embodiments, R is suitably an amino alkyl, a secondary or tertiary alkyl-amino-alkyl, or a trialkylammonioalkyl group. Specific R groups include without limitation 2-(methyl, t-butyl- amino) ethyl, 2-(methyl, isopropyl amino) ethyl, 3-(neopentyl amino) propyl, 2-(isobutyl-amino) ethyl, 2-(ethyl, isopropyl amino) ethyl, 3-(isopropyl amino) propyl, 3-(t-butyl- amino) propyl, 2-(isopropyl amino) ethyl, 2-(hydroxyethyl, isopropyl amino) ethyl, 3-(cyclopentyl, methyl amino) propyl, 3-(ethylamino) propyl, 3-(ethyl, methyl amino) propyl, 2-(neopentyl amino) ethyl, 3-(methyl, isopropyl amino) propyl, 3-(ethyl, isopropyl amino) propyl, 3-(hydroxyethyl, isopropyl amino) propyl, 3-(methyl, propargyl amine) propyl, 2-(methyl, propargyl amine) ethyl, 3-(allyl, methyl amino) propyl, and 2-(methyl, isobutyl amino) ethyl.

[0087] In other embodiments in which X_2 is cyanoalkyl group, R is site of 9*N*-attachment





where m= 2-3 and n= 1-6, or
site of 9*N*-attachment



where m= 2-3 and n= 1-6.

[0088] A specific example of a compound in accordance with this embodiment of the invention is listed in Table 4E.

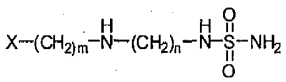
[0089] Table 21 shows measured values for EC_{50} in JNPL3 brain cell lysates and in SKBr3 cell lysate for compounds (4E-1 to 4E-4) in accordance with this embodiment of the invention which incorporates a hydrogen as X_4 and in which Y is S or a fluorine as X_4 and in which Y is $-CH_2-$. Desirably low values of EC_{50} were observed for several examples.

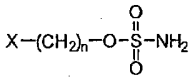
[0090] **G-IV.** In some embodiments of the invention, X_2 is a cycloalkyl (saturated carbocyclic) or cycloalkenyl. In these embodiments, R may be any of the groups disclosed as a substituent at the 9-position nitrogen in this application.

[0091] In some embodiments within this group, R includes a nitrogen heteroatom.

[0092] In a further embodiment within this group, R is suitably an amino alkyl, a secondary or tertiary alkyl-amino-alkyl, or a trialkylammonioalkyl group. Specific R groups include without limitation 2-(methyl, t-butyl- amino) ethyl, 2-(methyl, isopropyl amino) ethyl, 3-(neopentyl amino) propyl, 2-(isobutyl-amino) ethyl, 2-(ethyl, isopropyl amino) ethyl, 3-(isopropyl amino) propyl, 3-(t-butyl-amino) propyl, 2-(isopropyl amino) ethyl, 2-(hydroxyethyl, isopropyl amino) ethyl, 3-(ethylamino)propyl, 3-(ethyl, methyl amino) propyl, 2-(neopentyl amino) ethyl, 3-(methyl, isopropyl amino) propyl, 3-(ethyl, isopropyl amino) propyl, 3-(hydroxyethyl, isopropyl amino) propyl, 3-(methyl, propargyl amine) propyl, 2-(methyl, propargyl amine) ethyl, 3-(allyl, methyl amino) propyl, propyl, 2-(methyl, isobutyl amino) ethyl,

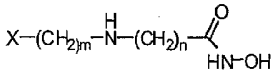
[0093] In embodiments of the invention within this group, R has the formula
site of 9*N*-attachment





where m= 2-3 and n= 1-6.

[0094] In embodiments when X_2 is aryl, R has the formula
site of 9*N*-attachment



where m= 2-3 and n= 1-6.

[0095] In specific embodiments, X_2 is a cycloalkyl with one ring.

[0096] In specific embodiments, X_2 is a cyclopropane, cyclobutane or cyclopentane.

[0097] In particular embodiments of formula (2), Y is S, X_4 is H, X_2 is cyclopentyl.

[0098] In particular embodiments of formula (2), Y is CH_2, X_4 is F, X_2 is cyclopentyl.

[0099] In particular embodiments of formula (2), Y is S, X_4 is F, X_2 is cyclopentyl.

[0100] In particular embodiments of formula (2), Y is CH_2, X_4 is Cl, X_2 is cyclopentyl.

[0101] In these particular embodiments, R may be any one of the types of groups described above.

[0102] Specific examples of compounds of this type are shown in Table 4I.

[0103] Table 2J shows measured values for EC_{50} in JNPL3 brain cell lysates and in SKBr3 cell lysate for compound 4I-12 in accordance with this embodiment of the invention which incorporates a hydrogen as X_4 and in which Y is S. Desirably low values of EC_{50} were observed for several examples.

[0104] Table 2G shows results for EC_{50} measured in SKBr3 breast cancer cells and JNPL3 brain cell lysates for compounds listed in Table 4A. As shown, compounds of this type are generally more active with respect to brain cancer cells. As shown, the greatest activity was observed for compound 4A-1, in which there is no substituent on the X_2 phenyl group, and the least activity is seen for compounds 4A-3 and 4A-4 in which electron withdrawing CF_3 substituents are at the meta positions.

[0105] An embodiment of the invention therefore has the structure (2) shown above, in which Y is S, X_4 is hydrogen, X_2 is phenyl, optionally substituted at the para position, and R includes a nitrogen heteroatom, and therefore is an alkylamino, an (alkylamino) alkyl or (dialkylamino) alkyl. Preferred R groups of this type are as listed above.

[0106] Examples of compounds within this seventh embodiment of the invention, in which X_2 is alkynyl are shown in Table 4B. Table 2H shows results for EC_{50} for Hsp90 binding in JNPL3 brain cell lysates. As shown, all of the compounds tested were active, however, those with an acetylene substituent, such as 4B-1, 4B-4, 4B-13 and 4B-14, were most active.

[0107] Examples of compounds within this seventh embodiment of the invention, in which X_2 is an aryl group containing an oxygen atom are shown in Table 4C. Specific suitable substituent groups are 2-furanyl, 3-furanyl and 5-methyl-2-furanyl.

[0108] Table 2G shows results for EC_{50} for Hsp90 binding in SKBr3 breast cancer cells and JNPL3 brain cell lysates for some of the compounds shown in Table 4C. All of the compounds show good activity in both experimental systems. In Table 4C, compound 4-C11 has X_2= isoxazole, whereas 4C-11, 4C-38 and 4C-39 have X_2= oxazolyl, including both a nitrogen and an oxygen. Compounds with X_2 = 2-oxazolyl (4C-38 and 4C-39) were more active than those with X_2 = iso-oxazolyl (4C-11).

[0109] Examples of compounds within this seventh embodiment of the invention, in which X_2 is an aryl group containing a sulfur atom in the aryl ring are shown in Table 4D. Table 2G shows results for EC_{50} for Hsp90 binding in SKBr3 breast cancer cells and JNPL3 brain cell lystates for some of the compounds shown in Table 4D. All of the compounds show good activity in both

experimental systems. In Table 4D, compounds 4D-16 and 4D-17 have X_2= 2-thiazolyl, including both a nitrogen and an oxygen.

[0110] Examples of compounds within this seventh embodiment of the invention, in which X_2 is -CN or cyanoalkyl are shown in Table 4E. Table 2I shows results for EC $_{50}$ for Hsp90 binding in JNPL3 brain cell lystates for the two -CN compounds shown in Table 4E. Both of the compounds show good activity in both experimental systems.

[0111] An example of a compound within this seventh embodiment of the invention, in which X_2 is a 6-membered aryl ring containing a nitrogen atom in the aryl ring, with the proviso that there is not also an oxygen in the ring, is shown in Table 2 (labeled as 4F-1). In Compound 4F-1, X_2 is 4-pyridinyl. X_2 could also be 2-pyridinyl, 3-pyridinyl, or pyrazinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl or 4-pyridazinyl.

[0112] EC_{50} for Hsp90 binding in SKBr3 breast cancer cells and JNPL3 brain cells were determined for compound 4F-1 to be 9,620 nM and 4,120 nM, respectively.

[0113] Examples of compounds within this seventh embodiment of the invention, in which X_2 is a 5-membered aryl rings containing 2 nitrogens in the ring are shown in Table 4G. The specific X_2 groups shown are 3-, 4- and 5-pyrazolyl. Other examples of X_2 groups in this category are 4- or 5-imidazolyl.

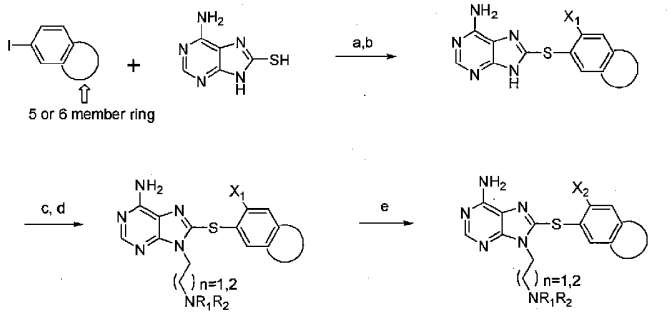
[0114] EC_{50} for Hsp90 binding in SKBr3 breast cancer cells and JNPL3 brain cell lysates were determined for some of the compounds listed in Table 4G. The results are summarized in Table 2K. Particularly good results were observed for compounds 4G-3, 4G-6 and 4G-9 in which the substituent is a 3-pyrazolyl.

[0115] Examples of compounds of the invention, include the compounds in which X_2 is a pyrrolyl group. In some of the ambodiments, the X_2 groups are 2 or 3-pyrrolyl.

[0116] EC_{50} for Hsp90 binding in SKBr3 breast cancer cells and JNPL3 brain cell lysates were determined for some of the compounds and the results are summarized in Table 2L.

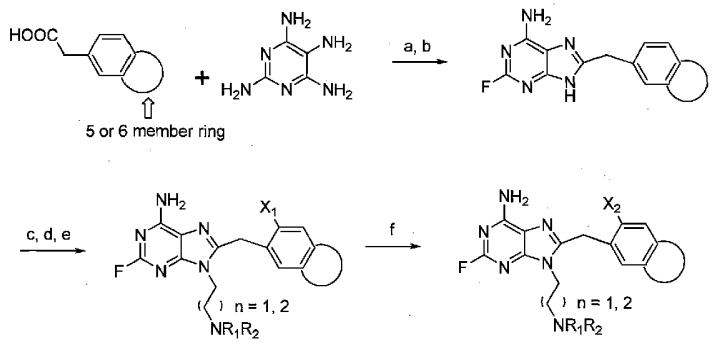
Synthetic Methods

[0117] Compounds in accordance with formulas (1A) and (1B) can be made through the application of the following methodologies.



(a) CuI, neocuproine, NaOt-Bu, DMF, 110 °C; (b) NIS, acetonitrile, RT; (c) Cs_2CO_3, 1,2-dibromoethane or 1,3-dibromopropane; (d) HNR_1R_2, DMF, rt; (e) X_2M, Pd (cat.), DMF, 50-100 °C.

Scheme 1.

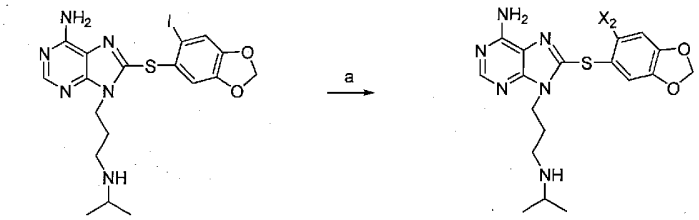


(a) triphenyl phosphite, pyridine, microwave; (b) HF-pyridine, $NaNO_2$; (c) NIS, acetonitrile, rt; (d) Cs_2CO_3, 1,2-dibromoethane or 1,3-dibromopropane; (e) HNR_1R_2, DMF, rt; (f) X_2M, Pd (cat.), DMF, 50-100 °C.

Scheme 2.

[0118] General Methods: ^1H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz instrument. Chemical shifts are reported in δ values in ppm downfield from TMS as the internal standard. ^1H data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), integration. ^{13}C chemical shifts are reported in δ values in ppm downfield from TMS as the internal standard. High resolution mass spectra were recorded on a Waters LCT Premier system. Low resolution mass spectra were obtained on a Waters Acquity Ultra Performance LC with electrospray ionization and SQ detector. High-performance liquid chromatography analyses were performed on a Waters Autopurification system with PDA, MicroMass ZQ, and ELSD detector, and a reversed phase column (Waters X-Bridge C18, 4.6 x 150 mm, 5 µm) using a gradient of; method A (a) H_2O + 0.1% TFA and (b) CH_3CN + 0.1% TFA, 5 to 95% b over 10 minutes at 1.2 mL/min; method B (a) H_2O + 0.1% TFA and (b) CH_3CN + 0.1 % TFA, 20 to 90% b over 16 minutes at 1.0 mL/min. Column chromatography was performed using 230-400 mesh silica gel (EMD).

[0119] Specific compounds were synthesized as follows;



PU-H71

Reagents and conditions: (a) $RB(OH)_2$, $PdCl_2(PPh_3)_2$, $NaHCO_3$, H_2O, DMF, 90°C.

Scheme 3. Suzuki coupling of PU-H71.

[0120] 9-(3-(isopropylamino)propyl)-8-(6-phenylbenzo[d] [1,3]dioxol-5-ylthio)-9H-purin-6-amine [DZ2-388]. Phenylboronic acid (10.7 mg, 0.0876 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (0.5 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 10:1) to give 19.8 mg (73%) of **DZ2-388.** ^1H NMR (500 MHz, MeOH-d_4) δ 8.14 (s, 1H), 7.28-7.34 (m, 3H), 7.17-7.21 (m, 2H), 7.12 (s, 1H), 6.90 (s, 1H), 6.09 (s, 2H), 4.03 (t, *J*= 6.4 Hz, 2H), 3.27 (septet, *J* = 6.6 Hz, 1H), 2.72 (t, *J* = 6.6 Hz, 2H), 2.13 (m, 2H), 1.40 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 156.0, 153.4, 152.1, 151.1, 150.3, 149.4, 142.3, 141.8, 130.4, 129.1, 128.7, 120.3, 119.8, 115.7, 112.2, 103.8, 52.2, 43.2, 41.1, 27.6, 19.3; HRMS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{27}N_6O_2S$, 463.1916; found 463.1905; HPLC: method A R_t = 6.50,

method B R_t = 7.40.

[0121] 8-(6-(4-*tert*-butylphenyl)benzo[d] [1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ2-390]. 4-*tert*-Butylphenylboronic acid (15.6 mg, 0.0876 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (0.5 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 3 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:5:2:1) to give 25.0 mg (83%) of **DZ2-390**. ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.11 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.14 (s, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.86 (s, 1H), 6.06 (s, 2H), 3.93 (t, *J*= 6.9 Hz, 2H), 2.92 (septet, *J* = 6.5 Hz, 1H), 2.61 (t, *J* = 7.3 Hz, 2H), 1.86 (m, 2H), 1.28 (s, 9H), 1.12 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 155.9, 153.3, 151.9, 151.8, 150.9, 150.2, 149.2, 141.9, 138.8, 130.0, 125.9, 120.4, 120.3, 115.4, 112.3, 103.6, 50.6, 44.0, 41.8, 35.4, 31.8, 29.3, 21.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{28}H_{35}N_6O_2S$, 519.2542; found 519.2545; HPLC: method A R_t = 7.43, method B R_t = 9.45.

[0122] 8-(6-(3,5-bis(trifluoromethyl)phenyl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ2-391]. 3,5-Bis(trifluoromethyl)phenylboronic acid (22.6 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (0.5 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 3 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:5:2:1) to give 24.4 mg (70%) of **DZ2-391**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.79 (s, 3H), 7.12 (s, 1H), 6.86 (s, 1H), 6.09 (s, 2H), 5.71 (br s, 2H), 4.07 (t, *J*= 6.6 Hz, 2H), 2.82 (septet, *J* = 6.2 Hz, 1H), 2.49 (t, *J* = 6.5 Hz, 2H), 1.95 (m, 2H), 1.12 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 152.3, 151.5, 149.6, 148.6, 147.5, 142.1, 137.2, 131.2 (q, *J* = 33 Hz), 129.6, 123.1 (q, *J* = 270 Hz), 121.3, 119.6, 119.4, 114.9, 110.8, 102.4, 49.5, 42.8, 40.6, 28.8, 21.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{26}H_{25}F_6N_6O_2S$, 599.1664; found 599.1653; HPLC: method A R_t = 7.45, method B R_t = 9.38.

[0123] 8-(6-(4-dimethylamino)phenyl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ2-392]. 4-(Dimethylamino)phenylboronic acid (14.5 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 3 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:5:2:1) to give 25.3 mg (85%) of **DZ2-392.** ^{1}H NMR (500 MHz), $CDCl_3$) δ 8.24 (s, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.93 (s, 1H), 6.83 (s, 1H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.01 (br s, 2H), 5.98 (s, 2H), 4.02 (t, *J* = 6.7 Hz, 2H), 2.97 (s, 6H), 2.78 (septet, *J* = 6.3 Hz, 1H), 2.44 (t, *J* = 6.7 Hz, 2H), 1.87 (m, 2H), 1.10 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 152.4, 151.5, 149.9, 148.5, 148.0, 147.1, 139.6, 130.0, 127.8, 120.5, 119.7, 112.8, 111.7, 111.0, 101.7, 49.3, 43.1, 40.9, 40.4, 28.9, 21.9; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{26}H_{32}N_7O_2S$, 506.2338; found 506.2330; HPLC: method A R_t = 5.72, method B R_t = 5.12.

[0124] 9-(3-(isopropylamino)propyl)-8-(6-(thiophen-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine [DZ2-395]. 2-Thienylboronic acid (11.2 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 5 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 12.5:1) to give 12.4 mg (45%) of **DZ2-395.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.17 (s, 1H), 7.33 (dd, *J*= 1.4, 4.9 Hz, 1H), 7.07 (s, 1H), 7.04 (s, 1H), 7.00-7.02 (m, 2H), 6.09 (s, 2H), 4.12 (t, *J* = 6.6 Hz, 2H), 2.95 (septet, *J* = 6.6 Hz, 1H), 2.62 (t, *J* = 6.8 Hz, 2H), 2.00 (m, 2H), 1.19 (d, *J*= 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.2, 152.0, 151.1, 149.4, 148.8, 148.4, 140.5, 132.9, 127.8, 126.9, 126.3, 119.2, 119.0, 114.6, 111.8, 102.3, 49.6, 42.5, 40.6, 27.8, 20.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_6O_2S_2$, 469.1480; found 469.1461; HPLC: method A R_t = 6.38, method B R_t = 7.18.

[0125] **8-(6-(furan-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-**amine [**DZ3-4**]. 2-Furanylboronic acid (9.8 mg, 0.0877 mmol) was added to PU-H71 (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 3.5 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 12.5:1) to give 19.1 mg (72%) of **DZ3-4.** ^1H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.18 (s, 1H), 7.49 (d, *J* = 1.8 Hz, 1 H), 7.25 (s, 1H), 6.96 (s, 1H), 6.71 (d, *J* = 3.3 Hz, 1H), 6.47 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.06 (s, 2H), 4.20 (t, *J* = 7.0 Hz, 2H), 2.87 (m, 1H), 2.61 (t, *J* = 6.9 Hz, 2H), 2.00 (m, 2H), 1.14 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.3, 152.2, 151.2, 150.9, 149.5, 148.14, 148.08, 142.4, 129.0, 119.2, 117.5, 114.5, 111.5, 110.0, 109.0, 102.3, 42.8, 41.0, 28.5, 21.2; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_6O_3S$, 453.1709; found 453.1705; HPLC: method A R_t = 6.23, method B R_t = 6.82.

[0126] **9-(3-(isopropylamino)propyl)-8-(6-(4-methoxyphenyl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine [DZ3-3].** 4-Methoxyphenylboronic acid (13.3 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 12.5:1) to give 20.5 mg (71%) of **DZ3-3.** ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.19 (d, *J*= 8.7 Hz, 2H), 6.95 (s, 1H), 6.86 (d, *J*= 8.7 Hz, 2H), 6.82 (s, 1H), 6.00 (s, 2H), 5.92 (br s, 2H), 4.01 (t, *J*= 6.7 Hz, 2H), 3.82 (s, 3H), 2.75 (septet, *J* = 6.3 Hz, 1H), 2.43 (t, *J* = 6.7 Hz, 2H), 1.85 (m, 2H), 1.07 (d, *J*= 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 154.3, 152.5, 151.5, 148.6, 147.8, 147.5, 139.0, 132.5, 130.4, 120.6, 119.8, 113.5, 113.0, 111.0, 101.8, 55.3, 49.1, 43.2, 40.9; 29.2, 22.2; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{25}H_{29}N_6O_3S$, 493.2022; found 493.2010; HPLC: method A R_t = 6.57, method B R_t = 7.55.

[0127] **9-(3-(isopropylamino)propyl)-8-(6-(pyridin-4-yl)benzo[d][1,31]dioxol-5-ylthio)-9H-purin-6-amine [DZ3-5].** 4-Pyridinylboronic acid (10.8 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 3.5 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 12.5:1) to give 14.8 mg (55%) of **DZ3-5.** ^1H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.53 (dd, *J* = 1.6, 4.8 Hz, 2H), 8.19 (s, 1H), 7.25 (dd, *J* = 1.6,4.5 Hz, 2H), 7.11 (s, 1H), 6.89 (s, 1H), 6.11 (s, 2H), 4.07 (t, *J* = 6.8 Hz, 2H), 2.82 (m, 1H), 2.51 (t, *J* = 6.8 Hz, 2H), 1.91 (m, 2H), 1.13 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.1, 152.0, 151.2, 150.0, 148.90, 148.85, 148.69, 137.9 124.5, 119.1, 117.7, 115.3, 110.6, 102.5, 49.2, 42.8, 40.7, 28.4, 21.2; HRMS (ESI) *m/z* $[M+H:]^+$ calcd. for $C_{23}H_{26}N_7O_2S$, 464.1869; found 464.1848; HPLC: method A R_t = 5.13, method B R_t = 2.57.

[0128] **8-(6-(4-bromophenyl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ3-6].** 4-Bromophenylboronic acid (17.6 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:5:2:1) to give 13.9 mg (44%) of **DZ3-6.** ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J*= 8.2 Hz, 2H), 7.01 (s, 1H), 6.81 (s, 1H), 6.05 (s, 2H), 5.69 (br s, 2H), 4.08 (t, *J* = 6.0 Hz, 2H), 2.91 (m, 1H), 2.50 (t, *J* = 5.9 Hz, 2H), 1.98 (m, 2H), 1.20 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.2, 152.0, 151.2, 149.8, 149.1, 148.2, 139.8, 139.1, 131.2, 131.0, 122.0, 119.0, 117.9, 115.0, 111.1, 102.4, 50.1, 42.1, 40.2, 27.3, 20.2; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{24}H_{26}BrN_6O_2S$, 541.1021/543.1001; found 541.1016/543.1004; HPLC: method A R_t = 6.93, method B R_t = 8.30.

[0129] **8-(6-(furan-3-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ3-27].** 3-Furanylboronic acid (9.8 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then

nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Ch_2:MeOH-NH_3 (7N), 20:1) to give 23.9 mg (90%) of **DZ3-27.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.17 (s, 1H), 7.51 (s, 1H), 7.44 (s, 1H), 7.07 (s, 1H), 6.97 (s, 1H), 6.49 (s, 1H), 6.08 (s, 2H), 4.17 (t, *J* = 6.9 Hz, 2H), 2.93 (septet, *J* = 6.4 Hz, 1H), 2.64 (t, *J* = 7.1 Hz, 2H), 2.02 (m, 2H), 1.17 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.1, 151.8, 151.0, 149.7, 149.0, 147.8, 142.6, 140.4, 131.7, 124.2, 118.9, 117.8, 114.8, 111.5, 110.7, 102.1, 49.2, 42.6, 40.6, 28.0, 20.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_6O_3S$, 453.1709; found 453.1711; HPLC: method A R_t = 6.18, method B R_t = 6.67.

[0130] 5-(6-(6-amino-9-(3-(isopropylamino)propyl)-9H-purin-8-ylthio)benzo[d][1,3]dioxol-5-yl)furan-2-carbaldehyde [DZ3-33]. 2-Formyl-5-furanylboronic acid (12.3 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 9.5 mg (34%) of **DZ3-33.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 9.57 (s, 1H), 8.18 (s, 1H), 7.36 (d, *J* =3.8 Hz, 1H), 7.32 (s, 1H), 7.07 (s, 1H), 6.98 (d, *J*= 3.8 Hz, 1H), 6.12 (s, 2H), 4.32 (t, *J*= 6.7 Hz, 2H), 3.31 (septet, *J* = 6.6 Hz, 1H), 2.93 (t, *J* = 6.8 Hz, 2H), 2.30 (m, 2H), 1.42 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 177.5, 156.8, 154.5, 152.2, 151.9, 151.4, 150.1, 149.7, 148.1, 127.5, 124.3, 119.2, 118.7, 115.7, 112.7, 109.9, 102.9, 51.3, 41.8, 40.4, 26.4, 19.2; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{25}N_6O_4S$, 481.1658; found 481.1657; HPLC: method A R_t = 5.87, method B R_t = 5.93.

[0131] 8-(6-(1H-pyrrol-2-yl)benzo[d][1,3] dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ3-29]. 1-N-Boc-pyrrole-2-boronic acid (18.5 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. DMF was removed under reduced pressure and to the resulting residue was added CH_2Cl_2 (1.5 mL) and TFA (0.3 mL). The mixture was stirred for 5 h at rt, then solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:9:2:1) to give 5.8 mg (22%) of **DZ3-29.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.17 (s, 1H), 7.04 (s, 1H), 7.01 (s, 1H), 6.88 (m, 1H), 6.27 (m, 1H), 6.21 (m, 1H), 6.03 (s, 2H), 4.17 (t, *J* = 6.8 Hz, 2H), 3.29 (septet, *J* = 6.6 Hz, 1H), 2.80 (t, *J* = 6.7 Hz, 2H), 2.15 (m, 2H), 1.41 (d, *J* = 6.6 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{26}N_7O_2S$, 452.1869; found 452.1872; HPLC: method A R_t = 6.13, method B R_t = 6.43.

[0132] 8-(6-(1H-pyrazol-4-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ3-30]. 1-Boc-pyrazole-4-boronic acid pinacol ester (25.8 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 13.7 mg (53%) of **DZ3-30.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.17 (s, 1H), 7.58 (s, 2H), 7.10 (s, 1H), 6.95 (s, 1H), 6.06 (s, 2H), 4.08 (t, *J* = 6.9 Hz, 2H), 2.89 (septet, *J* = 6.4 Hz, 1H), 2.57 (t, *J* = 7.2 Hz, 2H), 1.91 (m, 2H), 1.14 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.0, 152.1, 151.2, 149.7, 148.9, 147.5, 133.6, 132.0, 119.8, 119.1, 117.9, 115.3, 110.9, 102.1, 49.2, 42.9, 40.8, 28.3, 21.3; HRMS (ESI) *m/z* $[M+H:]^+$ calcd. for $C_{21}H_{25}N_{25}O_2S$, 453.1821; found 453.1819; HPLC: method A R_t = 5.60, method B R_t = 4.87.

[0133] 9-(3-(isopropylamino)propyl)-8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine [DZ3-35]. 4,4,5,5-Tetramethyl-2-(5-methyl-furan-2-yl)-(1,3,2)dioxaborolane (21.9 mg, 0.1053 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC

(hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:9:2:1) to give 11.5 mg (42%) of **DZ3-35.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.19 (s, 1H), 6.84 (s, 1H), 6.63 (d, *J* = 3.1 Hz, 1H), 6.07 (d, *J* = 2.5 Hz, 1H), 5.98 (s, 2H), 5.93 (br s, 2H), 4.22 (t, *J* = 6.6 Hz, 2H), 2.94 (m, 1H), 2.59 (t, *J* = 6.6 Hz, 2H), 2.34 (s, 3H), 2.05 (m, 2H), 1.20 (d, *J* = 6.3 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}N_6O_3S$, 467.1865; found 467.1869; HPLC: method A R_t = 6.49, method B R_t = 7.53.

[0134] 2-(6-(6-amino-9-(3-(isopropylamino)propyl)-9H-purin-8-ylthio)benzo[d][1,3]dioxol-5-yl)acetonitrile [DZ3-39]. 4-Isoxazoleboronic acid pinacol ester (20.5 mg, 0.1053 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 10.3 mg (%) of **DZ3-39.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.17 (s, 1H), 7.14 (s, 1H), 7.12 (s, 1H), 6.10 (s, 2H), 4.35 (t, *J* = 6.9 Hz, 2H), 3.99 (s, 2H), 3.08 (septet, *J*= 6.5 Hz, 1H), 2.82 (t, *J* = 7.0 Hz, 2H), 2.25 (m, 2H), 1.27 (d, *J*= 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.2, 152.1, 152.0, 151.5, 150.8, 148.6, 147.7, 129.5, 119.2, 117.6, 116.2, 110.3, 102.7, 49.8, 42.5, 40.7, 27.7, 22.9, 20.4; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{20}H_{24}N_7O_2S$, 426.1712; found 426.1712; HPLC: method A R_t = 5.69, method B R_t = 4.57.

[0135] 8-(6-(1H-pyrrol-3-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ3-41]. 1-Boc-pyrrole-3-boronic acid pinacol ester (30.9 mg, 0.1053 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 7.9 mg (30%) of **DZ3-41.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.16 (s, 1H), 7.02 (s, 1H), 6.99 (s, 1H), 6.86 (m, 1H), 6.76 (m, 1H), 6.21 (m, 1H), 6.02 (s, 2H), 4.07 (t, *J* = 6.9 Hz, 2H), 2.95 (septet, *J* = 6.4 Hz, 1H), 2.59 (t, *J* = 7.1 Hz, 2H), 1.96 (m, 2H), 1.19 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.4, 152.1, 152.0, 151.0, 149.4, 146.7, 135.9, 131.6, 122.1, 119.1, 117.8, 117.5, 114.6, 111.0, 109.2, 101.9, 53.6, 42.6, 40.6, 27.8, 20.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{26}N_7O_2S$, 452.1869; found 452.1862; HPLC: method A R_t = 6.02, method B R_t = 6.27.

[0136] 9-(3-(isopropylamino)propyl)-8-(6-(1-methyl-1H-pyrazol-5-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine [DZ3-44]. 1-Methyl-1-H-pyrazole-5-boronic acid pinacol ester (18.2 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHO_3$ (14.7 mg, 0.1755 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 2 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 20.1 mg (74%) of **DZ3-44.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.40 (d, *J* = 1.8 Hz, 1H), 7.05 (s, 1H), 6.80 (s, 1H), 6.08 (s, 2H), 6.06 (d, *J*= 1.8 Hz, 1H), 5.91 (br s, 2H), 4.10 (t, *J* = 6.7 Hz, 2H), 3.67 (s, 3H), 2.85 (septet, *J*= 6.3 Hz, 1H), 2.53 (t, *J*= 6.7 Hz, 2H), 1.97 (m, 2H), 1.13 (d, *J*= 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 152.7, 151.7, 149.3, 149.0, 147.0, 140.6, 138.5, 127.7, 123.3, 120.0, 113.8, 111.7, 107.4, 102.5, 49.6, 43.2, 41.1, 37.1, 29.1, 22.0; HRMS (ESI) *m/z* $[M+H:]^+$ calcd. for $C_{22}H_{27}N_8O_2S$, 467.1978; found 467.1985; HPLC: method A R_t = 5.74, method B R_t = 5.20.

[0137] 8-(6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ3-46]. 1H-pyrazole-3-boronic acid (33 mg, 0.293 mmol) was added to **PU-H71** (50 mg, 0.0975 mmol) and $NaHCO_3$ (24.6 mg, 0.293 mmol). DMF (2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.2 mL) and $Pd(PPh_3)_2Cl_2$ (7 mg, 0.0098 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 3.7 mg (8%) of **DZ3-46.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.17 (s, 1H), 7.59 (d, *J* = 2.0 Hz, 1 H), 7.10 (s, 1H), 7.07 (s, 1H), 6.38 (d, *J*= 2.0 Hz, 1H), 6.08 (s, 2H), 4.19 (t, *J*= 6.8 Hz, 2H), 3.31 (septet, *J*= 6.6 Hz, 1H), 2.89 (t, *J*= 7.2 Hz, 2H), 2.10 (m, 2H), 1.39 (d, *J*= 6.6 Hz,

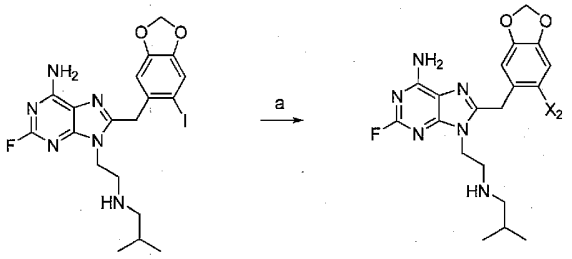
6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.5, 152.2, 152.1, 150.7, 149.5, 148.5, 148.3, 119.3, 119.1, 114.6, 114.5, 111.0, 110.9, 106.1, 102.3, 51.1, 41.7, 40.3, 26.0, 18.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{21}H_{25}N_8O_2S$, 453.1821; found 453.1826; HPLC: method A R_t = 5.65, method B R_t = 4.83.

[0138] 9-(3-(isopropylamino)propyl)-8-(6-(isoxazol-4-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine [DZ3-49]. 4-Isoxazoleboronic acid pinacol ester (20.5 mg, 0.1053 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 60°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was attempted to be purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:7:2:1) to give 7.4 mg (28%) of an inseparable mixture of **DZ3-49** and **DZ3-39** in a ratio of approximately 71:29, respectively, as determined by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.66 (s, 1H), 8.45 (s, 1H), 8.17 (s, 1H), 7.18 (s, 1H), 7.01 (s, 1H), 6.13 (s, 2H), 4.37 (t, *J*= 7.0 Hz, 2H), 3.27 (septet, *J*= 7.1 Hz, 1H), 2.89 (t, *J* = 7.1 Hz, 2H), 2.22 (m, 2H), 1.38 (d, *J* = 6.5 Hz, 6H); MS (ESI) *m/z* $[M+H]^+$ 454.1; HPLC: method A R_t = 5.67 (**DZ3-39,** 29%) and 5.87 (**DZ3-49,** 71%); method B R_t = 4.58 (DZ3-39, 34%) and 5.57 (DZ3-49, 66%).

[0139] 4-(6-(6-amino-9-(3-(isopropylamino)propyl)-9H-purin-8-ylthio)benzo[d][1,3]dioxol-5-yl)benzaldehyde [DZ3-50]. 4-Formylphenylboronic acid (13 mg, 0.0877 mmol) was added to **PU-H71** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 18.8 mg (66%) of **DZ3-50.** ^{1}H NMR (500 MHz, MeOH-d_4) δ 10.01 (s, 1H), 8.15 (s, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.14 (s, 1H), 6.93 (s, 1H), 6.13 (s, 2H), 4.05 (t, *J*= 6.8 Hz, 2H), 2.99 (septet, *J* = 6.4 Hz, 1H), 2.62 (t, *J* = 6.9 Hz, 2H), 1.99 (m, 2H), 1.24 (d, *J*= 6.4 Hz, 6H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 192.3, 154.1, 151.9, 151.0, 149.8, 148.8, 148.5, 146.4, 139.5, 135.3, 130.0, 129.4, 119.0, 117.7, 115.0, 110.8, 102.4, 49.9, 42.2, 40.3, 27.4, 20.2; HRMS (ESI) m/z [M+H:] $^+$ calcd. for $C_{25}H_{27}N_6O_3S$, 491.1865; found 491.1877; HPLC: method A R_t = 6.23, method B R_t = 6.83.

[0140] *tert*-Butyl 6-(3-(6-amino-8-(6-(3,5-bis(trifluoromethyl)phenyl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)propylamino)hexylcarbamate [TT-V-43A].
Bis(trifluoromethyl)phenylboronic acid (22.7 mg, 0.0878 mmol) was added to PU-H71-C6-linker (39.2 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 3 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:MeOH-NH_3 (7N), 10:1) to give 27.7 mg (63%) of **TT-V-43A.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.78 (s, 3H), 7.14 (s, 1H), 6.89 (s, 1H), 6.12 (s, 2H), 5.80 (br s, 2H), 4.68 (br s, 1H), 4.16 (t, *J* = 6.3 Hz, 2H), 3.10 (m, 2H), 2.81 (t, *J* = 7.7 Hz, 2H), 2.67 (t, *J*= 6.2 Hz, 2H), 2.21 (m, 2H), 1.81 (m, 2H), 1.30-1.53 (m, 15H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{34}H_{40}F_6N_7O_4S$, 756.2767; found 756.2753; HPLC: method A R_t = 8.17, method B R_t = 11.00.

[0141] N^1-(3-(6-amino-8-(6-(3,5-bis(trifluoromethyl)phenyl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)propyl)hexane-1,6-diamine [TT-V-47B]. TT-V-43A (26 mg, 0.0344 mmol) was dissolved in CH_2Cl_2 (1.2 mL) and TFA (0.3 mL) was added and stirred at rt for 45 min. Then solvent was removed under reduced pressure and residue dried under high vacuum for 2 h to give TT-V-47B. Purified by preparatory TLC (hexane:CH_2Cl_2:MeOH-NH_3 (7N), 7:1) to give mg (%) of **TT-V-47B.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.04 (s, 1H), 7.67 (s, 1H), 7.64 (s, 2H), 7.12 (s, 1H), 6.84 (s, 1H), 6.04 (s, 2H), 3.97 (t, *J*= 6.7 Hz, 2H), 2.85 (t, *J*= 7.0 Hz, 2H), 2.84 (t, *J*= 6.9 Hz, 2H), 2.77 (t, *J*= 7.0 Hz, 2H), 2.06 (m, 2H), 1.71 (m, 2H), 1.63 (m, 2H), 1.28 (m, 4H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{29}H_{32}F_6N_7O_2S$, 656.2242; found 656.2242; HPLC: method A R_t = 6.98, method B R_t = 8.38.



PU-DZ13

Reagents and conditions: (a) $RB(OH)_2$, $PdCl_2(PPh_3)_2$, $NaHCO_3$, H_2O, DMF, 90°C.

Scheme 4. Suzuki coupling of PU-DZ13.

[0142] 2-fluoro-8-((6-(furan-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine [DZ3-25]. 2-Furanylboronic acid (9.8 mg, 0.0877 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 19.1 mg (72%) of **DZ3-25.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 7.46 (d, *J* = 1.4 Hz, 1H), 7.08 (s, 1H), 6.64 (s, 1H), 6.46 (dd, *J* = 1.4, 3.2 Hz, 1H), 6.34 (d, *J* = 3.2 Hz, 1H), 6.00 (s, 2H), 4.34 (s, 2H), 4.08 (t, *J* = 6.3 Hz, 2H), 2.85 (t, *J* = 6.3 Hz, 2H), 2.38 (d, *J*= 6.8 Hz, 2H), 1.70 (m, 1H), 0.88 *(d, J*= 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 158.9 (d, *J* = 208.5 Hz), 156.2 (d, *J* = 20.2 Hz), 152.6, 152.3 (d, *J* = 18.3 Hz), 151.9, 147.9, 147.1, 142.1, 126.1, 124.3, 115.8, 111.3, 110.0, 108.7, 108.2, 101.6, 57.0, 48.1, 42.3, 32.0, 27.7, 20.2; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{26}FN_6O_3$, 453.2050; found 453.2041; HPLC: method A R_t = 7.10, method B R_t = 8.52.

[0143] 2-fluoro-8-((6-(furan-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine [DZ3-26]. 3-Furanylboronic acid (9.8 mg, 0.0877 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 23.4 mg (88%) of **DZ3-26.** ^{1}H NMR (500 MHz), $CDCl_3$) δ 7.49 (m, 1H), 7.46 (m, 1H), 6.82 (s, 1H), 6.63 (s, 1H), 6.46 (m, 1H), 5.96 (s, 2H), 5.70 (br s, 2H), 4.22 (s, 2H), 3.91 (t, *J* = 6.1 Hz, 2H), 2.75 (t, *J* = 6.1 Hz, 2H), 2.29 (d, *J* = 6.5 Hz, 2H), 1.70 (m, 1H), 0.83 (d, *J*= 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9 (d, *J*= 208.5 Hz), 156.2 (d, *J* = 20.3 Hz), 152.7 (d, *J* = 18.2 Hz), 152.2, 147.5, 146.9, 143.1, 140.1, 127.0, 125.7, 124.7, 116.6, 111.8, 110.2, 109.4, 101.4, 57.5, 48.5, 43.0, 31.9, 28.1, 20.4; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{26}FN_6O_3$, 453.2050; found 453.2044; HPLC: method A R_t = 7.10, method B R_t = 8.50.

[0144] 8-((6-(1H-pyrrol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine [DZ3-31]. 1-N-Boc-pyrrole-2-boronic acid (18.5 mg, 0.0877 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. DMF was removed under reduced pressure and to the resulting residue was added CH_2Cl_2 (1.5 mL) and TFA (0.3 mL). The mixture was stirred for 5 h at rt, then solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:15:2:1) to give 5.2 mg (20%) of **DZ3-31.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 6.91 (s, 1H), 6.84 (dd, *J* = 1.4, 2.5 Hz, 1H), 6.65 (s, 1H), 6.22 (m, 1H), 6.08 (dd, *J* = 1.4, 3.3 Hz, 1H), 5.97 (s, 2H), 4.26 (s, 2H), 4.06 (t, *J* = 6.7 Hz, 2H), 2.80 (t, *J* = 6.7 Hz, 2H), 2.55 *(d, J*= 7.0 Hz, 2H), 1.88 (m, 1H), 0.96 *(d, J*= 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 158.8 (d, *J*= 208.1 Hz), 156.4 (d, *J* = 20.0 Hz), 152.9, 152.3 (d, *J* = 21.2 Hz), 147.4, 129.8, 127.9, 126.7, 118.5, 110.5, 109.3, 108.7, 108.6, 101.5, 56.6, 47.4, 41.1, 31.6, 27.1, 20.2; HRMS (ESI) *m/z* $[M+H:]^+$ calcd. for $C_{23}H_{27}FN_7O2$,

452.2210; found 452.2212; HPLC: method A R_t = 7.02, method B R_t = 8.30.

[0145] 5-(6-((6-amino-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-8-yl)methyl)benzo[d][1,3]dioxol-5-yl)furan-2-carbaldehyde [DZ3-34]. 2-Formyl-5-furanylboronic acid (12.3 mg, 0.0877 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 2.0 mg (7%) of **DZ3-34.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 9.47 (s, 1H), 7.27 (d, *J*= 3.7 Hz, 1H), 7.20 (s, 1H), 6.77 (s, 1H), 6.63 (d, *J* = 3.7 Hz, 1H), 6.06 (s, 2H), 4.45 (s, 2H), 4.32 (t, *J*= 6.3 Hz, 2H), 2.83 (t, *J*= 6.3 Hz, 2H), 2.54 (d, *J* = 6.8 Hz, 2H), 1.83 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{24}H_{26}FN_6O_4$, 481.2000; found 481.1984; HPLC: method A R_t = 6.61, method B R_t = 7.62.

[0146] 8-((6-(1H-pyrazol-4-yl)benzol[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine [DZ3-32]. 1-Boc-pyrazole-4-boronic acid pinacol ester (25.8 mg, 0.0877 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHO_3$ (14.7 mg, 0.1755 mmol). DMF (1.5 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.15 mL) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00584 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 5 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 10.6 mg (40%) of **DZ3-32.** ^{1}H NMR (500 MHz), $CDCl_3$/MeOH-d_4) δ 7.50 (s, 2H), 6.83 (s, 1H), 6.69 (s, 1H), 5.98 (s, 2H), 4.18 (s, 2H), 4.01 (t, *J*= 6.6 Hz, 2H), 2.78 (t, *J* = 6.6 Hz, 2H), 2.40 (d, *J*= 7.0 Hz, 2H), 1.71 (m, 1H), 0.88 (d, *J*= 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 158.6 (d, *J*= 208.3 Hz), 156.3 (d, *J*= 19.6 Hz), 152.3, 152.1 (d, *J*= 21.2 Hz), 147.3, 147.1, 126.4, 126.2, 120.1, 115.8, 110.7, 109.9, 101.4, 56.3, 47.3, 40.8, 31.9, 27.0, 20.0; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{26}FN_8O_2$, 453.2163; found 453.2162; HPLC: method A R_t = 6.23, method B R_t = 6.55.

[0147] 2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine [DZ3-36]. 4,4,5,5-Tetramethyl-2-(5-methyl-furan-2-yl)-(1,3,2)dioxaborolane (21.9 mg, 0.1053 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:15:2:1) to give 15.6 mg (57%) of **DZ3-36.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.53 (s, 1H), 6.26 (d, *J* = 3.1 Hz, 1H), 6.21 (br s, 2H), 6.05 (d, *J*= 3.1 Hz, 1H), 5.94 (s, 2H), 4.37 (s, 2H), 3.98 (t, *J*= 6.3 Hz, 2H), 2.80 (t, *J* = 6.2 Hz, 2H), 2.34 (s, 3H), 2.31 (d, *J* = 6.8 Hz, 2H), 1.64 (m, 1H), 0.83 (d, *J* = 6.7 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{24}H_{28}FN_6O_3$, 467.2207; found 467.2200; HPLC: method A R_t = 7.29, method B R_t = 9.13.

[0148] 8-((6-(1H-pyrrol-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine [DZ3-38]. 1-Boc-pyrrole-3-boronic acid pinacol ester (30.9 mg, 0.1053 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.2 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h, then at 120°C for 6.5 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:7:2:1) to give 20.9 mg (79%) of **DZ3-38.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (br s, 1H), 6.85 (s, 1H), 6.83 (m, 1H), 6.76 (m, 1H), 6.62 (s, 1H), 6.34 (br s, 2H), 6.23 (m, 1H), 5.91 (s, 2H), 4.29 (s, 2H), 3.84 (t, *J*= 6.3 Hz, 2H), 2.67 (t, *J* = 6.3 Hz, 2H), 2.28 (d, *J*= 6.8 Hz, 2H), 1.60 (m, 1H), 0.82 (d, *J*= 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8 (d, *J* = 208.0 Hz), 156.4 (d, *J*= 19.8 Hz), 153.0, 152.9 (d, *J* = 21.3 Hz), 146.82, 146.76, 130.0, 126.5, 123.3, 118.4, 116.9, 116.6, 110.6, 109.8, 109.3, 101.3, 57.6, 48.7, 43.0, 32.0, 28.3, 20.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}FN_7O_2$, 452.2210; found 452.2204; HPLC: method A R_t = 6.77, method B R_t = 7.93.

[0149] 2-(6-((6-amino-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-8-yl)methyl)benzo[d][1,3]dioxol-5-yl)acetonitrile [DZ3-40]. 4-Isoxazoleboronic acid pinacol ester (20.5 mg, 0.1053 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHC0_3$ (14.7 mg, 0.1755 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen.

This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:7:2:1) to give 8.3 mg (%) of **DZ3-40.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 6.94 (s, 1H), 6.70 (s, 1H), 6.00 (s, 2H), 4.39 (t, *J*= 6.7 Hz, 2H), 4.31 (s, 2H), 3.84 (s, 2H), 3.18 (t, *J*= 6.6 Hz, 2H), 2.65 (d, *J* = 7.1 Hz, 2H), 1.94 (m, 1H), 0.99 (d, *J*= 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/ MeOH-d_4) δ 158.7 (d, *J*= 210.4 Hz), 156.6 (d, *J*= 20.1 Hz), 152.1 (d, *J*= 18.2 Hz), 150.5, 148.1, 147.7, 126.7, 122.4, 117.9, 116.1, 110.6, 109.9, 101.8, 56.5, 47.4, 41.2, 31.3, 27.1, 21.5, 20.0; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{21}H_{25}FN_7O_2$, 426.2054; found 426.2048; HPLC: method A R_t = 6.48, method B R_t = 7.10.

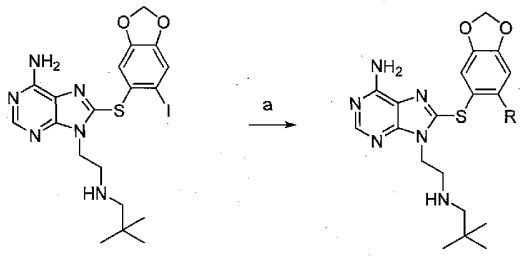
[0150] 8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine [DZ3-43]. 1H-pyrazole-3-boronic acid (11.8 mg, 0.1053 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4.5 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 3.5 mg (13%) of **DZ3-43.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 7.63 (d, *J* = 2.15 Hz, 1H), 6.95 (s, 1H), 6.82 (s, 1H), 6.34 (d, *J*= 2.15 Hz, 1H), 6.01 (s, 2H), 4.35 (t, *J*= 6.8 Hz, 2H), 4.29 (s, 2H), 2.98 (t, *J*= 6.9 Hz, 2H), 2.64 *(d, J*= 7.0 Hz, 2H), 1.96 (m, 1H), 0.99 (d, *J*= 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/ MeOH-d_4) δ 158.8 (d, *J* = 208.7 Hz), 156.6 (d, *J*= 19.3 Hz), 152.4,152.2 (d, *J* = 18.7 Hz), 148.3, 147.3, 127.1, 115.94, 115.93, 110.3, 110.1, 105.6, 101.8, 56.3, 47.4, 40.5, 31.5, 27.0, 20.2; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{26}FN_8O_2$, 453.2163; found 453.2149; HPLC: method A R_t = 6.37, method B R_t = 6.93.

[0151] 2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(1-methyl-1H-pyrazol-5-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine [DZ3-45]. 1-Methyl-1-H-pyrazole-5-boronic acid pinacol ester (18.2 mg, 0.0877 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 2 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 4:7:2:1) to give 26.5 mg (97%) of **DZ3-45.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 1.5 Hz, 1H), 6.76 (s, 1H), 6.74 (s, 1H), 6.28 (br s, 2H), 6.17 (d, *J* = 1.5 Hz, 1H), 6.01 (s, 2H), 3.99 (s, 2H), 3.90 (t, *J*= 6.3 Hz, 2H), 3.66 (s, 3H), 2.76 (t, *J* = 6.3 Hz, 2H), 2.31 (d, *J*= 6.8 Hz, 2H), 1.72 (m, 1H), 0.84 *(d, J*= 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0 (d, *J* = 208.7 Hz), 156.4 (d, *J* = 20.0 Hz), 152.8 (d, *J*= 18.5 Hz), 151.5, 149.0, 147.1, 141.3, 138.8, 129.4, 123.4, 116.6, 110.7, 109.9, 106.9, 101.9, 57.8, 48.7, 43.1, 36.9, 31.8, 28.3, 20.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $G_{23}H_{29}FN_8O_2$, 467.2319; found 467.2323; HPLC: method A R_t = 6.37, method B R_t = 6.90.

[0152] 2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(thiophen-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine [DZ3-48]. 2-Thienylboronic acid (11.2 mg, 0.0877 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 2 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 18.3 mg (67%) of **DZ3-48.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 7.31 (d, *J* = 5.0 Hz, 1H), 7.03 (dd, *J* = 3.1, 5.0 Hz, 1H), 6.92 (s, 1H), 6.87 (d, *J*= 3.0 Hz, 1H), 6.74 (s, 1H), 6.01 (s, 2H), 4.19 (s, 2H), 3.99 (t, *J*= 6.5 Hz, 2H), 2.78 (t, *J*= 6.5 Hz, 2H), 2.37 (d, *J*= 6.9 Hz, 2H), 1.70 (m, 1H), 0.88 (d, *J*= 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 158.7 (d, *J*= 209.4 Hz), 156.4 (d, *J*= 19.6 Hz), 152.21 (d, *J* = 18.4 Hz), 152.20, 148.1, 147.0, 141.5, 127.7, 127.3, 127.0, 126.0, 125.8, 115.9, 111.3, 110.0, 101.6, 57.1, 48.1, 42.2, 32.0, 27.8, 20.3; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{26}FN_6O_2S$, 469.1822; found 469.1830; HPLC: method A R_t = 7.21, method B R_t = 8.93.

[0153] 2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(isoxazol-4-yl)benzo[d][1,3] dioxol-5-yl)methyl)-9H-purin-6-amine [DZ3-51]. 4-Isoxazoleboronic acid pinacol ester (20.5 mg, 0.1053 mmol) was added to **PU-DZ13** (30 mg, 0.0585 mmol) and $NaHCO_3$ (14.7 mg, 0.1755 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen.

This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 60°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 2:2:1:0.5) to give 7.8 mg (29%) of an inseparable mixture of **DZ3-51** and **DZ3-40** in a ratio of approximately 44:56, respectively, as determined by HPLC. MS (ESI) *m/z* $[M+H:]^+$ 454.4; HPLC: method A R_t = 6.46 (**DZ3-40,** 56%) and 6.65 (**DZ3-51,** 44%); method B R_t = 7.08 (**DZ3-40,** 65%) and 7.52 (**DZ3-51,** 35%).



PU-HZ151

Reagents and conditions: (a) $RB(OH)_2$, $PdCl_2(PPh_3)_2$, $NaHCO_3$, H_2O, DMF, 90°C.

Scheme 5. Suzuki coupling of PU-HZ151.

[0154] 8-(6-(furan-2-yl)benzo[d][1,3] dioxol-5-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine [**TT5-53A**]. 2-Furanylboronic acid (42.4 mg, 0.379 mmol) was added to **PU-HZ151** (66.4 mg, 0.126 mmol) and $NaHCO_3$ (63.6 mg, 0.756 mmol). DMF (2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.4 mL) and $Pd(PPh_3)_2Cl_2$ (17.6 mg, 0.025 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 3.5 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 25.2 mg (43%) of **TT5-53A**. ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.49 (d, *J* = 1.3 Hz, 1H), 7.17 (s, 1H), 6.84 (s, 1H), 6.75 (d, *J* = 3.3 Hz, 1H), 6.48 (dd, *J* = 1.8, 3.3 Hz, 1H), 5.97 (s, 2H), 5.89 (br s, 2H), 4.18 (t, *J*= 6.5 Hz, 2H), 2.86 (t, *J*= 6.5 Hz, 2H), 2.25 (s, 2H), 0.83 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 153.0, 151.7, 151.1, 148.4, 147.9, 146.8, 142.2, 127.2, 120.8, 120.0, 112.8, 111.5, 110.0, 108.7, 101.9, 61.9, 49.6, 43.9, 31.5, 27.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}N_6O_3S$, 467.1865; found 467.1870; HPLC: method A R_t = 6.78, method B R_t = 7.83.

[0155] 8-(6-(5-methylfuran-2-yl)benzo[d][1,3] dioxol-5-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine [DZ3-56]. 4,4,5,5-Tetramethyl-2-(5-methyl-furan-2-yl)-(1,3,2)dioxaborolane (17.7 mg, 0.0853 mmol) was added to **PU-HZ151** (30 mg, 0.0569 mmol) and $NaHCO_3$ (14.3 mg, 0.1707 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0113 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4.5 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 15:1) to give 9.3 mg (34%) of **DZ3-56.** ^1H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.19 (s, 1H), 7.24 (s, 1H), 6.89 (s, 1H), 6.62 (d, *J* = 3.2 Hz, 1H), 6.05 (d, *J* = 3.2 Hz, 1H), 6.03 (s, 2H), 4.36 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 6.0 Hz, 2H), 2.47 (s, 2H), 2.33 (s, 3H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.5, 152.4, 152.3, 151.2, 149.4, 149.2, 148.5, 147.7, 129.1, 119.4, 117.4, 114.3, 111.2, 108.6, 107.8, 102.2, 61.4, 49.3, 43.2, 31.4, 27.7, 13.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{24}H_{29}N_6O_3S$, 481.2022; found 481.2002; HPLC: method A R_t = 6.89, method B R_t = 7.58.

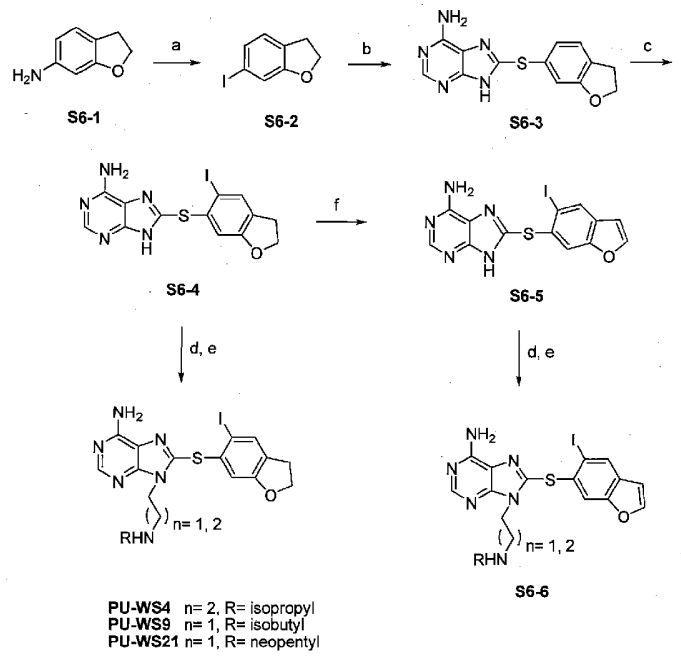
[0156] 9-(2-(neopentylamino)ethyl)-8-(6-(thiophen-2-yl)benzo[d][1,3] dioxol-5-ylthio)-9H-purin-6-amine [DZ3-58]. 2-Thiopheneboronic acid (10.9 mg, 0.0853 mmol) was added to PU-**HZ151** (30 mg, 0.0569 mmol) and $NaHCO_3$ (14.3 mg, 0.1707 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0113 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 16.0 mg (58%) of

DZ3-58. ^{1}H NMR (500 MHz), $CDCl_3$/MeOH-d_4) δ 8.18 (s, 1H), 7.32 (dd, *J* = 1.6, 4.7 Hz, 1H), 6.98-7.03 (m, 4H), 6.07 (s, 2H), 4.29 (t, *J*= 5.4 Hz, 2H), 3.03 (t, *J* = 5.4 Hz, 2H), 2.48 (s, 2H), 0.97 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.3, 152.0, 150.8, 149.2, 148.9, 148.3, 140.5, 132.5, 127.8, 127.0, 126.3, 120.1, 119.2, 114.4, 111.8, 102.2, 61.1, 49.0, 42.9, 31.2, 27.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}N_6O_2S_2$, 483.1637; found 483.1621; HPLC: method A R_t = 7.14, method B R_t = 7.73.

[0157] 8-(6-(1H-pyrrol-3-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine [DZ3-59]. 1-Boc-pyrrole-3-boronic acid pinacol ester (25 mg, 0.0853 mmol) was added to **PU-HZ151** (30 mg, 0.0569 mmol) and $NaHCO_3$ (14.3 mg, 0.1707 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0113 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 10.1 mg (38%) of **DZ3-59.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.15 (s, 1H), 7.03 (s, 1H), 6.95 (s, 1H), 6.85 (m, 1H), 6.76 (m, 1H), 6.20 (dd, *J* = 1.7, 2.4 Hz, 1H), 6.01 (s, 2H), 4.24 (t, *J* = 5.7 Hz, 2H), 2.98 (t, *J* = 5.7 Hz, 2H), 2.50 (s, 2H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.3, 152.1, 149.6, 149.3, 146.8, 135.7, 122.3, 119.3, 118.6, 117.9, 117.4, 114.5, 111.1, 109.4, 101.9, 61.0, 49.3, 42.7, 31.2, 27.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{2s}N_7O_2S$, 466.2025; found 466.2016; HPLC: method A R_t = 6.86, method B R_t = 7.20.

[0158] 8-(6-(furan-3-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine [DZ3-60]. 3-Furanylboronic acid (9.5 mg, 0.0853 mmol) was added to **PU-HZ151** (30 mg, 0.0569 mmol) and $NaHCO_3$ (14.3 mg, 0.1707 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0113 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 13.8 mg (52%) of **DZ3-60.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.17 (s, 1H), 7.50 (s, 1H), 7.43 (d, *J*= 1.5 Hz, 1H), 7.02 (s, 1H), 6.94 (s, 1H), 6.49 (d, *J* = 1.5 Hz, 1H), 6.06 (s, 2H), 4.29 (t, *J* = 5.9 Hz, 2H), 3.02 (t, *J*= 5.8 Hz, 2H), 2.46 (s, 2H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.3, 152.0, 151.1, 149.6, 149.3, 147.9, 142.8, 140.6, 131.5, 124.3, 119.3, 118.8, 114.7, 111.7, 110.9, 102.2, 61.4, 49.1, 43.0, 31.3, 27.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}N_6O_3S$, 467.1865; found 467.1845; HPLC: method A R_t = 6.65, method B R_t = 7.09.

[0159] 8-(6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine [DZ3-61]. 1H-Pyrazole-3-boronic acid (19 mg, 0.1707 mmol) was added to **PU-HZ151** (30 mg, 0.0569 mmol) and $NaHCO_3$ (14.3 mg, 0.1707 mmol). DMF (1.2 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0113 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 4 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 15:1) to give 6.5 mg (25%) of **DZ3-61.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.18 (s, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.05 (s, 2H), 6.40 (d, *J*= 2.0 Hz, 1H), 6.06 (s, 2H), 4.36 (t, *J* = 6.0 Hz, 2H), 3.01 (t, *J* = 6.0 Hz, 2H), 2.51 (s, 2H), 0.97 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.6, 152.3, 150.8, 149.4, 148.6, 148.5, 120.1, 119.2, 114.5, 110.9, 106.0, 102.3, 61.2, 49.1, 42.5, 31.1, 27.5; HRMS (ESI) *m/z* $[M+H:]^+$ calcd. for $C_{22}H_{27}N_8O_2S$, 467.1978; found 467.1972; HPLC: method A R_t = 6.50, method B R_t = 6.61.



Reagents and conditions: (a) $NaNO_2$, KI, AcOH/TFA, 0°C; (b) 8-mercaptoadenine, Cs_2CO_3, $PdCl_2(dppf)$, DMF, 80°C, 48h; (c) NIS, TFA, CH_3CN, rt, 2h ;(d) 1,3-dibromopropane or 1,2-dibromoethane, Cs_2CO_3, DMF, rt; (e) isopropylamine or isobutylamine or neopentylamine, DMF, rt; (f) DDQ, dioxane, 100°C.

Scheme 6. Synthesis of PU-WS4, PU-WS9 and PU-WS21.

[0160] 6-iodo-2,3-dihydrobenzofuran (S6-2). A solution of 2,3-dihydrobenzofuran-6-amine (**S6-1;** 0.74 g, 5.5 mmol) in acetic acid (25 mL) and TFA (2 mL) was cooled in an ice bath for 5 minutes. $NaNO_2$ (0.454g, 6.6 mmol) was added in 3 portions followed by KI (2.73 g, 16.4 mmol). The resulting mixture was stirred at 0°C for 15 minutes and quenched with H_2O (20 mL). The mixture was extracted with EtOAc (3 x 150 mL) and the organic layer was washed with NaS_2O_3, brine, dried over $MgSO_4$ and filtered. The filtrate was condensed under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc, 90:10 to 40:60) to yield **S6-2** (0.82 g, 61 %) as a pale-yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.6 Hz, 1H), 7.11 (s, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 4.54 (t, *J* = 8.7 Hz, 2H), 3.14 (t, *J* = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 129.4, 127.1, 126.4, 118.7, 91.7, 71.6, 29.4.

[0161] 8-(2,3-dihydrobenzofuran-6-ylthio)-9*H*-purin-6-amine (S6-3). To a solution of **S6-2** (50 mg, 0.2 mmol) in DMF (2 mL) was added 8-mercaptoadenine (34 mg, 0.2 mmol), Cs_2CO_3 (99.4 mg, 0.3 mmol) and $PdCl_2(dppf)$ (33 mg, 0.02 mmol). The mixture was degassed for 5 minutes with argon and stirred at 80 °C under argon protection for 48 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2:MeOH, 100:0 to 90:10) to yield S6-3 (25 mg, 44%) as a yellow solid. ^1H NMR (500 MHz, CD_3OD) δ 8.14 (s, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 6.97 (s, 1H), 4.62 (t, *J*= 8.7 Hz, 2H), 3.25 (t, *J*= 8.7 Hz, 2H); MS (ESI) *m/z* 285.8 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{13}H_{12}N_5OS$; 286.0763; found 286.0768.

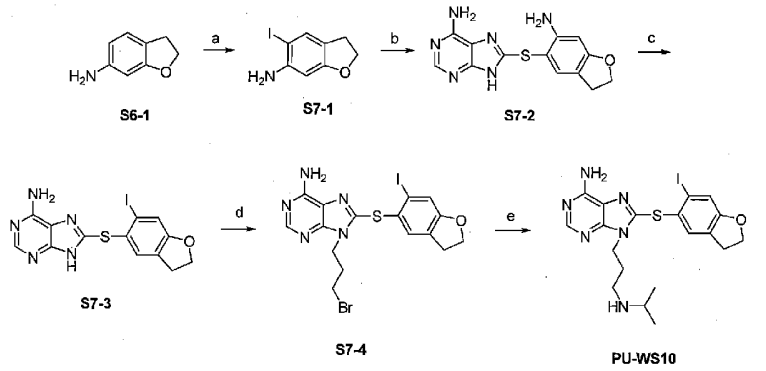
[0162] 8-(5-iodo-2,3-dihydrobenzofuran-6-ylthio)-9*H*-purin-6-amine (S6-4) To a solution of **S6-**3 (40 mg, 0.14 mmol) in 6 mL of acetonitrile was added TFA (40 µL) and NIS (63 mg, 0.28 mmol). The resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2:MeOH, 100:0 to 90:10) to afford **S6-4** (48 mg, 53%) as a yellow gum. ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.79 (s, 1H), 7.12 (s, 1H), 4.65 (t, *J* = 8.8 Hz, 2H), 3.28 (t, *J*= 8.7 Hz, 2H); MS (ESI) *m/z* 412.0 $(M+H)^+$.

[0163] 8-(5-iodo-2,3-dihydro-benzofuran-6-ylsulfanyl)-9-(3-isopropylamino-propyl)-9*H*-purin-6-ylamine (PU-WS4). A mixture of **S6-4** (54 mg, 0.13 mmol), Cs_2CO_3 (127 mg, 0.39 mmol) and 1,3-dibromopropane (202 mg, 0.65 mmol) in anhydrous

DMF (2 mL) was stirred at rt for 2 h. Solvent was removed under reduced pressure and the residue purified by chromatography (CH_2Cl_2:MeOH:AcOH). The resulting solid was dissolved in DMF (2 mL) and isopropylamine (0.347 g, 0.5 mL, 5.9 mmol) was added and the solution stirred overnight at rt. The reaction afforded **PU-WS4** (13 mg, 20%; over two-steps) as a yellow solid after purification. ^{1}H NMR (500 MHz, $CDCl_3/CD_3OD$) δ 8.26 (s, 1H), 7.77 (s, 1H), 7.07 (s, 1H), 4.65 (t, *J*= 8.7 Hz, 2H), 4.47 (t, *J*= 6.9 Hz, 2H), 3.20-3.33 (m, 3H), 3.01 (t, *J*= 7.5 Hz, 2H), 2.33 (m, 2H), 1.34 (d, *J*= 6.5 Hz, 6H); MS (ESI) *m/z* 511.2 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{19}H_{24}IN_6OS$, 511.0777; found 511.0779.

[0164] 8-(5-iodo-2,3-dihydro-benzofuran-6-ylsulfanyl)-9-(2-isobutylamino-ethyl)-9*H*-purin-6-ylamine (PU-WS9). A mixture of **S6-4** (30 mg, 0.073 mmol), Cs_2CO_3 (71 mg, 0.22 mmol) and 1,2-dibromoethane (69 mg, 0.365 mmol) in anhydrous DMF (1 mL) was stirred at rt for 2 h. Solvent was removed under reduced pressure and the residue purified by chromatography (CH_2Cl_2:MeOH:AcOH). The resulting solid was dissolved in DMF (2 mL) and isobutylamine (0.241 g, 0.33 mL, 3.3 mmol) was added and the solution stirred overnight at rt. The reaction afforded **PU-WS9** (15 mg, 40%; over two-steps) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.63 (s, 1H), 6.56 (s, 1H), 6.27 (br s, 2H), 4.57 (t, *J*= 8.5 Hz, 2H), 4.50 (t, *J*= 5.5 Hz, 2H), 3.20 (t, *J*= 8.5 Hz, 2H), 3.12 (t, *J*= 5.5 Hz, 2H), 2.59 (d, *J*= 7 Hz, 2H), 1.99 (m, 1H), 0.97 (d, *J*= 7 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{19}H_{24}IN_6OS$, 511.0777; found 511.0790.

[0165] 8-((5-iodo-2,3-dihydrobenzofuran-6-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine (PU-WS21). Following the procedure to make **PU-WS9,** compound **PU-WS21** was obtained as a white solid. ^{1}HNMR (500 MHz, $CDCl_3$, δ): 7.56 (s, 1H), 6.60 (s, 1H), 4.47 (t, *J* = 8.7 Hz, 2H), 4.37 (m, 2H), 3.06-3.11 (m, 4H), 2.45 (s, 2H), 0.83 (s, 9H); HRMS *(m/z):* $[M+H]^+$ calcd for $C_{20}H_{26}IN_6OS$ 525.0933; found 525.0927.



Reagents and conditions: (a) NIS, CH_3CN, 0°C, 20 min.; (b) 8-mercaptoadenine, neocuproine, CuI, NaO*t*-Bu, DMF, 110°C; (c) $NaNO_2$, KI, AcOH/TFA, 0°C; (d) 1,3-dibromopropane, Cs_2CO_3, DMF, rt; (e) isopropylamine, DMF, rt.

Scheme 7. Synthesis of PU-WS10.

[0166] 5-iodo-2,3-dihydrobenzofuran-6-amine (S7-1). To a solution of 2,3-dihydrobenzofuran-6-amine (**S6-1;** 95 mg, 0.7 mmol) in acetonitrile (3 mL) cooled in an ice-bath was added NIS (158 mg, 0.7 mmol). After stirring at 0 °C for 20 min, the mixture was condensed and purified by flash chromatography (hexane:EtOAc, 90:10 to 20:80) to yield **S7-1** (180 mg, 98%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.26 (s, 1H), 4.53 (t, *J*= 8.5 Hz, 2H), 3.09 (t, *J*= 8.4 Hz, 2H); MS (ESI) *m/z* 261.9 $[M+H]^+$.

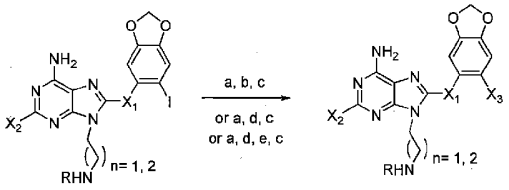
[0167] 8-(6-amino-2,3-dihydrobenzofuran-5-ylthio)-9*H*-purin-6-amine (S7-2). The mixture of **S7-1** (80 mg, 0.31 mmol), 8-mercaptoadenine (52 mg, 0.3 mmol), neocuproine (7 mg, 0.03 mmol), CuI (7 mg, 0.03 mmol) and sodium *t*-butoxide (100 mg, 1.04 mmol) was suspended in 10 mL of DMF and stirred at 110 °C overnight. The mixture was concentrated under reduced pressure and the residue purified by flash chromatography (hexane:EtOAc, 90:10 to 20:80) to yield **S7-2** (50 mg, 56%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.33 (s, 1H), 6.35 (s, 1H), 4.57 (t, *J*= 8.5 Hz, 2H), 3.14 (t, *J*= 8.4 Hz, 2H); MS (ESI) *m/z* 301.0 $[M+H]^+$.

[0168] 8-(6-iodo-2,3-dihydrobenzofuran-5-ylthio)-9*H*-purin-6-amine (S7-3). To a solution of **S7-2** (25 mg, 0.08 mmol) in

acetic acid/TFA (5 mL/1 mL) cooled in ice-bath was added $NaNO_2$ (7 mg, 0.1mmol) and KI (27 mg, 0.16 mmol). The mixture was stirred at 0°C for 10 minutes and condensed under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2:MeOH, 100:0 to 90:10) to yield **S7-3** (13 mg, 41%) as a yellow solid. ^1H NMR (500 MHz, CD_3OD) δ 8.13 (s, 1H), 7.57 (s, 1H), 7.44 (s, 1H), 4.66 (t, *J*= 8.5 Hz, 2H), 3.22 (t, *J*= 8.6 Hz, 2H); MS (ESI) *m/z* 411.9 $[M+H]^+$.

[0169] 9-(3-bromopropyl)- 8-(6-iodo-2,3-dihydrobenzofuran-5-ylthio)-9*H*-purin-6-amine (S7-4). To a solution of **S7-3** (13 mg, 0.03 mmol) in DMF (2 mL) was added 1,3-dibromopropane (16 µL, 0.16 mmol) and Cs_2CO_3 (20 mg, 0.06 mmol) and the resulting mixture was stirred at rt for 40 minutes. The mixture was condensed under reduced pressure and the residue was purified by flash chromatography to yield **S7-4** (6.2 mg, 34%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.37 (s, 2H), 6.00 (br s, 2H), 4.62 (t, *J*= 8.7 Hz, 2H), 4.36 (t, *J*= 6.7 Hz, 2H), 3.42 (t, *J*= 6.2 Hz, 2H), 3.18 (t, *J*= 8.9 Hz, 2H), 2.39 (m, 2H); MS (ESI) *m/z* 531.9/533.9 $[M+H]^+$.

[0170] 8-(6-iodo-2,3-dihydro-benzofuran-5-ylsulfanyl)-9-(3-isobutylamino-ethyl)-9*H*-purin-6-ylamine (PU-WS10). A solution of **S7-4** (6.2 mg, 0.012 mmol) and isopropylamine (0.2 mL) in DMF (1 mL) was stirred for 12 h. Solvent was removed under reduced pressure and the residue purified by preparative thin layer chromatography ($CHCl_3$:MeOH-NH_3 (7N), 20:1) to afford **PU-WS10** (4.0 mg, 60%) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.69 (s, 1H), 7.27 (s, 1H), 5.93 (br s, 2H), 4.66 (t, *J*= 8.8 Hz, 2H), 4.29 (t, *J*= 7 Hz, 2H), 3.33 (t, *J*= 8.7 Hz, 2H), 2.74 (septet, *J*= 6.2 Hz, 1H), 2.58 (t, *J*= 6.8 Hz, 2H), 1.98 (m, 2H), 1.05 (d, *J*= 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 154.4, 152.7, 151.9, 147.8, 141.7, 130.2, 128.6, 121.1, 120.0, 74.1, 71.7, 48.9, 44.0, 41.6, 30.9, 30.2; MS (ESI) *m/z* 511.1 $[M+H]^+$.



PU-DZ8 X_1=CH_2, X_2=F, n= 2, R= isopropyl
PU-H71 X_1=S, X_2=H, n= 2, R= isopropyl
PU-HZ150 X_1=S, X_2=H, n= 1, R= isobutyl
PU-HZ151 X_1=S, X_2=H, n= 1, R= neopentyl
PU-DZ13 X_1=CH_2, X_2=F, n= 1, R= isobutyl

PU-WS3 X_1=CH_2, X_2=F, X_3=CN, n=2, R= isopropyl
PU-WS5 X_1=S, X_2=H, X_3=CN, n= 2, R= isopropyl
PU-WS6 X_1=S, X_2=H, X_3=CC*t*-Bu, n= 2, R= isopropyl
PU-WS7 X_1=S, X_2=H, X_3=CCPh, n= 2 R= isopropyl
PU-WS8 X_1=S, X_2=H, X_3=CCH, n= 2, R= isopropyl
PU-WS16 X_1=S, X_2=H, X_3=CCH, n= 1, R= isobutyl
PU-WS19 X_1=S, X_2=H, X_3=CCH, n= 1, R= neopentyl
PU-WS20 X_1=CH_2, X_2=F, X_3=CCH, n= 1, R= isobutyl

Reagents and conditions: (a) Boc_2O, Et_3N, THF, rt, 12h; (b) $PdCl_2$(dppf), $Zn(CN)_2$, Zn, DMF, 130°C; (c) 10% TFA-CH_2Cl_2, rt, 2-5h; (d) CuI, $PdCl_2(PPh_3)_2$, *t*-butylacetylene or phenylacetylene or trimethylsilanylacetylene, Et_3N, DMF, 90°C, 24h; (e) KOH, MeOH, rt, 2h.

Scheme 8. Synthesis of PU-WS3, PU-WS5, PU-WS6, PU-WS7 and PU-WS8, PU-WS16, PU-WS19 and PU-WS20.

[0171] 6-[6-amino-2-fluoro-9-(3-isopropylamino-propyl)-9*H*-purin-8-ylmethyl]-benzo[1,3]dixole-5-carbonitrile (PU-WS3). A solution **of PU-DZ8** (118 mg, 0.231 mmol), $(Boc)_2O$ (55 mg, 0.254 mmol) and triethylamine (16 mg, 0.231 mmol) in THF (2 mL) was stirred at room temperature for 12 h. Following solvent removal, the residue was purified by preparative thin layer chromatography ($CHCl_3$:MeOH-NH_3 (7N), 20:1) to afford Boc-protected **PU-DZ8** (120 mg, 85%; MS (ESI) *m/z* 613.05 $[M+H]^+$). To a solution of Boc-protected **PU-DZ8** (26 mg, 0.04 mmol) in DMF (3 mL) was added $PdCl_2$(dppf) (17 mg, 0.02 mmol), $Zn(CN)_2$ (10 mg, 0.08 mmol) and Zn (3 mg, 0.04 mL) and the resulting mixture was stirred at 130°C overnight. The reaction mixture was condensed under reduced pressure and the residue was purified by flash chromatography ($CHCl_3$:MeOH-NH_3 (7N), 20:1) to yield Boc-protected **PU-WS3** as a white solid. To a solution of this in 2 mL ofCH_2Cl_2 was added 0.2 mL of TFA and the mixture was stirred at room temperature for 5 h. The reaction mixture was condensed under reduced pressure and the residue purified by flash chromatography ($CHCl_3$:MeOH-NH_3 (7N), 20:1) to yield **PU-WS3** as a white solid in quantitative yield (12 mg, 59% for three steps). ^1H NMR (500 MHz, CD_3OD) δ 7.13 (s, 1H), 6.96 (s, 1H), 6.03 (s, 2H), 4.31 (s, 2H), 4.25 (t, *J*= 7 Hz, 2H), 3.26 (m, 1H), 3.01 (t, *J*= 7.5 Hz, 2H), 2.14 (m, 2H), 1.23 (d, *J*= 6.5 Hz, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 160.4 (d, *J*= 208 Hz), 158.5 (d, *J*= 19 Hz), 153.8, 153.5 (d, *J*= 19 Hz), 151.7, 149.1, 137.2, 119.1, 117.4, 112.6, 112.4, 106.3, 104.4, 52.3, 43.4, 40.8, 33.2, 27.7, 19.3; MS

(ESI) *m/z* 412.3 $[M+H]^+$.

[0172] 6-[6-amino-9-(3-isopropylamino-propyl)-9*H*-purin-8-ylsulfanyl]benzo[1,3]dixole-5-carbonitrile (PU-WS5). The procedure for the preparation of **PU-WS3** was followed starting from **PU-H71.** The reaction afforded **PU-WS5** (6.5 mg, 32% for three steps) as a white solid. ^{1}HNMR (500 MHz, $CDCl_3/CD_3OD$) δ 8.21 (s, 1H), 7.22 (s, 1H), 7.19 (s, 1H), 6.19 (s, 2H), 4.40 (t, *J*= 7 Hz, 2H), 3.09 (septet, *J*=6.5 Hz, 1H), 2.83 (t, *J*= 7.5 Hz, 2H), 2.26 (m, 2H), 1.25 (d, *J*= 6.5 Hz, 6H); MS (ESI) *m/z* 412.2 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{19}H_{22}N_7O_2S$, 412.1556; found 412.1560.

[0173] 8-[6-(3,3-dimethyl-but-1-ynyl)-benzo[1,3]dioxol-5-ylsulfanyl]9-(3-isopropylamino-propyl)-9*H*-purin-6-ylamine (PU-WS6). A solution of **PU-H71** (70 mg, 0.137 mmol), $(Boc)_2O$ (35 mg, 0.161 mmol) and triethylamine (13 mg, 0.137 mmol) in THF (2 mL) was stirred at room temperature for 12 h. Following solvent removal, the residue was purified by preparative thin layer chromatography ($CHCl_3$:MeOH-NH_3 (7N), 20:1) to afford Boc-protected **PU-H71** (74 mg, 88%; MS (ESI) *m/z* 612.89 $[M+H]^+$). To a solution of Boc-protected **PU-H71** (0.24 g, 0.39 mmol) in DMF (2 mL) was added CuI (4 mg, 0.1 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), *t*-butylacetylene (72 µL, 0.59 mmol) and triethylamine (137 µL) and the mixture was stirred at 90 °C for 24 h. The reaction mixture was condensed under reduced pressure and purified by chromatography to afford a solid. To a solution of the solid in 15 mL of CH_2Cl_2 was added TFA (1.5 mL) and stirred at RT for 2 hrs. The mixture was condensed and purified by flash chromatography to afford **PU-WS6** (97 mg, 52 % for three steps) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3/CD_3OD$) δ 8.25 (s, 1H), 6.99 (s, 1H), 6.97 (s, 1H), 6.05 (s, 2H), 4.41 (t, *J*= 7 Hz, 2H), 3.29 (m, 1H), 2.98 (t, *J*= 7.5 Hz, 2H), 2.24 (m, 2H), 1.34 (d, *J*= 6.5 Hz, 6H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$) δ 50.5, 41.3, 40.2, 30.3, 27.8, 25.9, 18.5; MS (ESI) *m/z* 467.3 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{24}H_{31}N_6O_2S$, 467.2229; found 467.2233.

[0174] 9-(3-isopropylamino-propyl)-8-(6-phenylethynyl-benzo[1,3]dixool-5-ylsulfanyl)-9*H*-purin-6-ylamine (PU-WS7). The procedure for the preparation **of PU-WS6** was followed with phenylacetylene (65 µL, 0.59 mmol) to afford **PU-WS7** (46 mg, 34% in three steps) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3/CD_3OD$) δ 8.2 (s, 1H), 7.30-7.40 (m, 5H), 7.08 (s, 1H), 6.96 (s, 1H), 6.06 (s, 2H), 4.27 (m, 2H), 2.69 (m, 1H), 2.51 (m, 2H), 1.97 (m, 2H), 1.01 (d, *J*= 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$) δ 154.3, 152.3, 151.1, 148.8, 147.3, 131.3, 128.7, 128.3, 124.4, 122.4, 120.4, 119.3, 112.9, 112.4,102.3, 94.2, 86.6, 50.5, 43.1, 41.3, 29.2, 21.7; MS (ESI) *m/z* 487.2 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{26}H_{27}N_6O_2S$, 487.1903; found 487.1913.

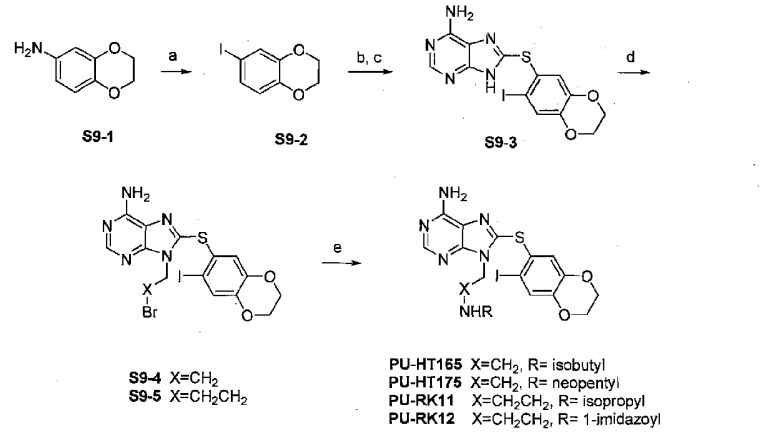
[0175] 8-(6-ethynyl-benzo[1,3]dioxol-5-ylsulfanyl)-9-(3-isopropylamino-propyl)-9*H*-purin-6-ylamine (PU-WS8). The procedure for the preparation of **PU-WS6** was followed with trimethylsilanylacetylene (82 µL, 0.59 mmol), and following coupling a white solid was obtained and used without further purification. To this was added MeOH (10 mL) and KOH (90 mg) and was stirred at rt for 2 hrs. The reaction mixture was concentrated under reduced pressure and to the resulting residue was added 2 mL of 10% TFA-CH_2Cl_2 and was stirred at rt for 2 hrs. The mixture was concentrated under reduced pressure and the residue chromatographed to afford **PU-WS8** (5.2 mg, 26% for four steps) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 6.99 (s, 1H), 6.84 (s, 1H), 6.00 (s, 2H), 5.61 (br s, 2H), 4.31 (t, *J* = 7 Hz, 2H), 3.31 (s, 1H), 2.71 (m, 1H), 2.56 (t, *J* = 7 Hz, 2H), 1.97 (m, 2H), 1.02 (d, *J*= 6.5 Hz, 6H); MS (ESI) *m/z* 411.2 $[M+H]^+$; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{20}H_{23}N_6O_2S$, 411.1603; found 411.1605.

[0176] 8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(isobutylamino)ethyl)-9*H*-purin-6-amine (PU-WS16). Following the procedure to make **PU-WS8, PU-WS16** was obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 6.91 (s, 1H), 6.77 (s, 1H), 6.01 (s, 2H), 5.78 (br s, 2H), 4.33 (t, *J*= 6.1 Hz, 2H), 3.24 (s, 1H), 2.92 (t, *J*= 6.1 Hz, 2H), 2.38 (d, *J* = 6.8 Hz, 2H), 1.63 (m, 1H), 0.77 (d, *J*= 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 153.5, 151.9, 149.6, 148.5, 147.0, 128.0, 124.1, 117.0, 114.8, 111.3, 102.6, 82.9, 81.4, 57.9, 49.3, 44.2, 28.8, 28.4, 20.9; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{20}H_{22}N_6O_2S$, 411.1603; found 411.1606.

[0177] 8-(6-ethynylbenzo[d][1,3] dioxol-5-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine (PU-WS19). Following the procedure to make **PU-WS8, PU-WS19** was obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 6.97 (s, 1H), 6.83 (s, 1H), 5.98 (s, 2H), 5.76 (br s, 2H), 4.35 (m, 2H), 3.06 (s, 1H), 2.97 (m, 2H), 2.33 (s, 2H), 0.82 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 152.9, 151.5, 149.1, 147.9, 146.5, 120.1, 117.7, 112.9, 111.9, 102.2, 82.3, 81.0, 61.9, 49.8, 43.9, 31.5, 27.7;

HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{21}H_{25}N_6O_2S$, 425.1760; found 425.1753.

[0178] 8-((6-ethynylbenzo [d] [1,3] dioxol-5yl)methyl)-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine (PU-WS20). Following the procedure to make **PU-WS8, PU-WS20** was obtained from **PU-DZ13** as a white solid. ^{1}H NMR (MeOH-d_4, 500 MHz) δ: 6.98 (s, 1H), 6.70 (s, 1H), 6.02 (s, 2H), 4.36 (s, 2H), 4.20 (t, J = 6.4 Hz, 2H), 2.92 (t, J = 6.4 Hz, 2H), 2.42 (d, J = 6.9 Hz, 2H), 2.03 (s, 1H), 1.69 (m, 1H), 0.87 (d, J = 6.8 Hz, 6H); ^{13}C NMR (MeOH-d_4, 125 MHz) δ: 159.8, 158.1, 152.6, 151.4, 149.8, 147.2, 134.3, 116.2, 114.2, 112.5, 109.8, 102.3, 80.9, 57.5, 43.0, 32.6, 29.8, 28.2, 20.5.



Reagents and conditions: (a) $NaNO_2$, 10% HCl, 0°C; KI, 0°C to rt; (b) 8-mercaptoadenine, neocuproine, CuI, NaO*t*-Bu, DMF, 110°C, 24 h; (c) NIS, TFA, CH_3CN, rt; (d) 1,2-dibromoethane or 1,3-dibromopropane, Cs_2CO_3, DMF, rt; (e) isobutylamine or neopentylamine or isopropylamine or imidazole, DMF, rt.

Scheme 9. Synthesis of PU-HT165, PU-HT175, PU-RK11, PU-RK12.

[0179] 6-Iodo-2,3-dihydrobenzo[b][1,4]dioxine (S9-2). 2,3-dihydrobenzo[b][1,4]dioxin-6-amine **(S9-1;** 5 g, 33 mmol) was dissolved in 10% HCl solution and cooled to 0°C. Then, 30 mL of a cold aqueous solution of $NaNO_2$ (4.6 g, 66 mmol) was added over a period of 15 min and the reaction mixture was stirred at 0°C for an additional 10 min, followed by the addition of urea (1.6 g, 27 mmol). After 15 min, 40 mL of a suspension of KI (16.5g, 100 mmol) in water/CH_2Cl_2 (1:1) was added. The reaction mixture was stirred overnight at room temperature then extracted with CH_2Cl_2, dried over $MgSO_4$. And condensed under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc, 100:0 to 90:10) to afford **S9-2** (7.4 g, 86%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 δ (s, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1 H), 4.27-4.24 (m, 4H).

[0180] 8-(7-Iodo-2,3-dihydrobenzo[b][1,4]dioxin-6-ylthio)-9*H*-purin-6-amine (S9-3). To a solution of **S9-2** (1.26 g, 4.8 mmol) in DMF (15 mL) was added 8-mercaptoadenine (0.400 g, 2.4 mmol), neocuproine (0.056 g, 0.24 mmol), CuI (0.044 g, 0.24 mmol) and Na*t*OBu (0.460 g, 4.8 mmol). The reaction mixture was stirred at 110 °C for 24h. Solids were filtered and the filtrate was condensed under reduced pressure. The residue was flash chromatographed ($CHCl_3$:MeOH:AcOH, 60:0.5:0.5 to 30:0.5:0.5) to yield 0.578 g (80%) of intermediate coupling product (MS (ESI) *m/z* 301.9 $[M+H]^+$). To 0.400 g (1.4 mmol) of this and NIS (0.945 g, 4.2 mmol) in acetonitrile (15 mL) was added TFA (540 µL, 0.800 g, 7 mmol) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by flash chromatography ($CHCl_3$:MeOH:AcOH, 60:0.5:0.5 to 30:0.5:0.5) to give **S9-3** (0.436 g, 73%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.37 (s, 1H), 8.03 (br s, 2H), 7.47 (s, 1H), 7.10 (s, 1H), 4.25-4.27 (m, 4H); MS (ESI) *m/z* 427.9 $[M+H]^+$.

[0181] 9-(2-Bromoethyl)-8-(7-iodo-2,3-dihydrobenzo[b][1,4]dioxin-6-ylthio)-9H-purin-6-amine (S9-4). A mixture of **S9-3** (0.213 g, 0.5 mmol), 1,2-dibromoethane (0.500 g, 2.5 mmol) and Cs_2CO_3 (0.184 g, 0.75 mmol) in anhydrous DMF (6 mL) was stirred at room temperature for 3h. Solids were filtered and the filtrate was condensed under reduced pressure to give a residue that was purified by preparative thin layer chromatography ($CHCl_3$:MeOH-NH_3 (7N), 20:1) to give **S9-4** (0.107 g, 40%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.29 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 6.23 (br s, 2H), 4.62 (t, *J*= 7.0 Hz, 2H), 4.16-4.24 (m, 4H), 3.69 (t, *J*= 7.0 Hz, 2H); MS (ESI) *m/z* 533.9/535.9 $[M+H]^+$.

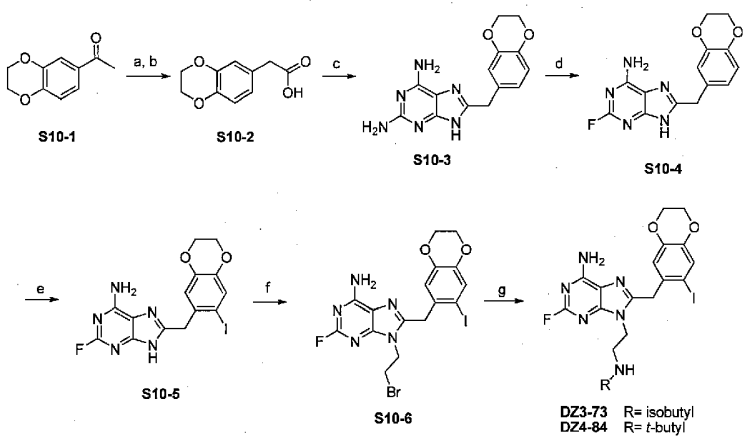
[0182] 9-(3-Bromopropyl)-8-(7-iodo-2,3-dihydrobenzo[b][1,4]dioxin-6-ylthio)-9*H*-purin-6-amine (S9-5). A mixture of **S9-3** (0.213 g, 0.5 mmol), 1,3-dibromopropane (0.512 g, 2.5 mmol) and Cs_2CO_3 (0.184 g, 0.75 mmol) in anhydrous DMF (6 mL) was stirred at room temperature for 3h. Solids were filtered and the filtrate was condensed under reduced pressure to give a residue that was purified by preparative thin layer chromatography ($CHCl_3$:MeOH-NH_3 (7N), 20:1) to give **S9-5** (0.104 g, 38 %). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.26 (s, 1H), 7.32 (s, 1H), 6.94 (s, 1H), 5.6 (br s, 2H), 4.27 (t, *J*= 7.0 Hz, 2H), 4.10-4.17 (m, 4H), 3.32 (t, *J*= 7.0 Hz, 2H), 2.26 (m, 2H); MS (ESI) *m/z* 547.9/549.8 $[M+H]^+$.

[0183] 8-(7-Iodo-2,3-dihydrobenzo[b][1,4]dioxin-6-ylthio)-9-(2-(isobutylamino)ethyl)-5,9-dihydro-4*H*-purin-6-amine (PU-HT165). S9-4 (0.052 g, 0.097 mmol) and isobutylamine (0.354 g, 4.9 mmol) in DMF (1 ml) was stirred overnight at rt. Solvent was removed under reduced pressure and the resulting residue was purified by chromatography (CH_2Cl_2:MeOH) to give 0.040 g, 78%) of **PU-HT165** as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.37 (s, 1H), 6.94 (s, 1H), 6.24 (br s, 2H), 4.44 (br s, 2H), 4.22-4.24 (m, 4H), 3.08 (m, 2H), 2.52 (d, *J*= 5.7 Hz, 2H), 1.92 (m, 1H), 0.92 (d, *J*= 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 152.8, 151.4, 147.7, 145.5, 145.2, 128.9, 127.5, 122.0, 120.5, 91.6, 64.9, 64.7, 57.3, 49.0, 43.9, 28.0, 21.0; MS (ESI) *m/z* 527.1 $[M+H]^+$.

[0184] 8-(7-Iodo-2,3-dihydrobenzo[b][1,4]dioxin-6-ylthio)-9-(2-(neopentylamino)ethyl)-5,9-dihydro-4*H*-purin-6-amine (PU-HT175). S9-4 (0.052, 0.097 mmol) and neopentylamine (0.426 g, 4.9 mmol) in DMF (1 mL) was stirred overnight at rt. Solvent was removed under reduced pressure and the resulting residue was purified by chromatography (CH_2Cl_2:MeOH) to give 0.038 g (73%) of **PU-HT175** as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.37 (s, 1H), 6.94 (s, 1H), 5.79 (br s, 2H), 4.33 (t, *J*= 6.5 Hz, 2H), 4.20-4.24 (m, 4H), 2.99 (t, *J*= 6.5 Hz, 2H), 2.34 (s, 2H), 0.84 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 152.9, 151.7, 147.0, 144.7, 144.6, 128.2, 127.8, 121.2, 120.2, 90.7, 64.3, 64.2, 62.0, 49.8, 44.0, 31.6, 27.7; MS *m/z* 541.1 $[M+H]^+$.

[0185] 8-(7-Iodo-2,3-dihydrobenzo[b][1,4]dioxin-6-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine (PU-RK11). S9-5 (0.045 g, 0.082 mmol) and isopropylamine (0.242 g, 4.1 mmol) in DMF (1 mL) was stirred overnight at rt. Solvent was removed under reduced pressure and the resulting residue was purified by chromatography (CH_2Cl_2:MeOH) to give 0.038 g (88%) of **PU-RK11.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.38 (s, 1H), 6.95 (s, 1H), 5.65 (br s, 2H), 4.32 (t, *J*= 6.9 Hz, 2H), 4.22-4.24 (m, 4H), 2.80 (septet, *J*= 6.7 Hz, 1H), 2.61 (t, *J*=6.7 Hz, 2H), 2.07 (m, 2H), 1.11 (d, *J*= 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 152.8, 151.7, 146.7, 144.8, 144.6, 128.3, 127.8, 121.3, 120.1, 91.0, 64.3, 64.2, 49.0, 43.6, 41.6, 29.8, 22.5; MS (ESI) *m/z* 527.1 $[M+H]^+$.

[0186] 9-(3-(1H-imidazol-1-yl)propyl)-8-(7-iodo-2,3-dihydrobenzo[b] [1,4] dioxin-6-ylthio)-9H-purin-6-amine (PU-RK12). S9-5 (0.045 g, 0.082 mmol) and imidazole (0.056 g, 0.82 mmol) in DMF (1 mL) was stirred overnight at rt. Solvent was removed under reduced pressure and the resulting residue was purified by chromatography (CH_2Cl_2:MeOH) to give 0.029 g (67%) of **PU-RK12.** NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.62 (s, 1H), 7.39 (s, 1H), 7.09 (s, 1H), 6.98 (s, 1H), 6.94 (s, 1H), 5.70 (br s, 2H), 4.19-4.28 (m, 6H), 4.00 (t, *J*= 7.5 Hz, 2H), 2.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 153.2, 151.8, 146.3, 145.0, 144.7, 137.1, 129.6, 128.3, 126.9, 121.3, 120.1, 118.7,90.9,64.3,64.2,44.3,41.0,31.8; MS (ESI) *m/z* 536.1 $[M+H]^+$.



Reagents and conditions: (a) sulfur, morpholine, 140°C, 14 h; (b) 10% KOH (aq.), reflux, 12 h; (c) 2,4,5,6-tetraaminopyrimidine, triphenyl phosphite, pyridine, microwave irradiation at 220°C, 75 min.; (d) HF/pyridine, $NaNO_2$, 0 °C to rt, 1 h; (e) NIS, TFA, CH_3CN, rt overnight; (f) Cs_2CO_3, 1,2-dibromoethane, DMF, rt, 3.5 h; (g) isobutylamine or *t*-butylamine, DMF, overnight, rt.

Scheme 10. Synthesis of DZ3-73 and DZ4-84.

[0187] 2-(2,3-dihydrobenzo[b] [1,4]dioxin-6-yl)acetic acid (S10-2). A mixture of 1,4-benzodioxan-6-yl methyl ketone (**S10-1;** 5.5 g, 30.9 mmol), sulfur (1.98 g, 61.8 mmol) and morpholine (6.73 g, 6.76 mL, 77.3 mmol) was refluxed at 140°C for 14 h. After cooling to rt, the reaction mixture was diluted with 150 mL of CH_2Cl_2, transferred to a seperatory funnel and washed with 25 mL of ice-cold brine. The aqueous layer was further extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, dried with Na_2SO_4, and filtered. Activated charcoal was added to the filtrate and after several minutes was filtered and concentrated to give 12.7 g of a brown oil. A mixture of this in 75 mL of 10% KOH (*aq.*) was refluxed for 12h. After cooling the reaction mixture was transferred to a seperatory funnel and washed with ether (30 mL), The aqueous layer was acidified with 6N HCl (~25 mL) to pH 2 and extracted with CH_2Cl_2 (4 x 100 mL). The organic layers were combined, washed with distilled water (100 ml), dried with Na_2SO_4 and filtered. This was treated with charcoal, filtered, and solvent removed under reduced pressure and the resulting residue was purified by chromatography (hexane:EtOAc, 90:10 to 70:30) to give 3.90 g (65%) of **S10-2.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80-6.82 (m, 2H), 6.74 (dd, *J*= 2.0, 8.2 Hz, 1H), 4.24 (s, 4H), 3.53 (s, 2H); MS (ESI) *m/z* 195.1 $[M+H]^+$.

[0188] 8-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-9H-purine-2,6-diamine (S10-3). A mixture of **S10-2** (1.00 g, 5.15 mmol), 2,4,5,6-tetraaminopyrimidine (0.868 g, 6.19 mmol), triphenyl phosphite (1.92 g, 1.63 mL, 6.19 mmol) in 15 mL ofpyridine was sonicated for several minutes. It was then subjected to microwave irradiation at 220°C for 75 minutes. The mixture was concentrated and the resulting residue was purified by chromatography (CH_2Cl_2:MeOH:MeOH-NH_3 (7N), 60:0.5:0.5 to 20:0.5:0.5) to give 1.12 g (73%) of **S10-3.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-*d4*) δ 6.75-6.84 (m, 3H), 4.24 (s, 4H), 3.98 (s, 2H); MS (ESI) *m/z* 299.3 $[M+H]^+$.

[0189] 8-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-2-fluoro-9H-purin-6-amine(S10-4). To a solution of **S10-3** (1.00 g, 3.35 mmol) in HF/pyridine (2.4 mL) at 0 °C, $NaNO_2$ (0.3 g, 4.36 mmol) was slowly added. The reaction was brought to room temperature and further stirred for 1 h. Following dilution with CH_2Cl_2 (20 mL), the excess HF was quenched by stirring for 1 h with $CaCO_3$ (1.19 g). The mixture was dried under reduced pressure and subsequently purified by chromatography (CH_2Cl_2:MeOH:AcOH, 90:1:0.5) to give 1.15 g (96%) of **S10-4.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-*d4*) δ 6.75-6.84 (m, 3H), 4.24 (s, 4H), 4.04 (s, 2H); MS (ESI) *m/z* 302.3 $[M+H]^+$.

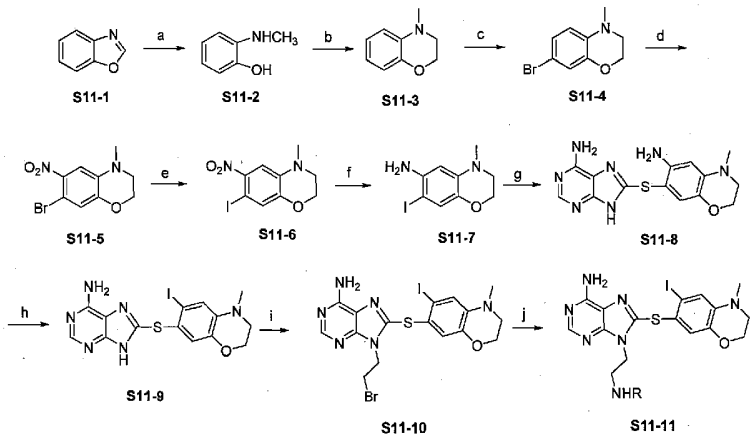
[0190] 2-fluoro-8-((7-iodo-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-9H-purin-6-amine (S10-5). S10-4 (0.310 g, 1.03 mmol), NIS (0.301 g, 1.34 mmol), CH_3CN (20 mL), TFA (2.34 g, 1.56 mL, 20.5 mmol) was stirred at rt overnight. The mixture was dried under reduced pressure and the residue chromatographed (CH_2Cl_2:MeOH:AcOH, 120:1:0.5 to 90:1:0.5) to give 0.340 g (77%) of a mixture of **S10-5** *(m/z* 428.2 $[M+H]^+$) along with diiodinated compound *(m/z* 554.1 $[M+H]^+$). LC-MS shows ratio of **S10-5** to diiodinated compound to be 83:17. This mixture was not separated but used further in the following step. ^{1}H NMR (500 MHz,

$CDCl_3$/MeOH-*d4*) δ 7.37 (s, 1H), 6.82 (s, 1H), 4.25 (s, 4H), 4.18 (s, 2H); MS (ESI) *m/z* 428.2 $[M+H]^+$.

[0191] 9-(2-bromoethyl)-2-fluoro-8-((7-iodo-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-9H-purin-6-amine (S10-6). S10-5 (0.340 g, 0.796 mmol), Cs_2CO_3 (0.337 g, 1.035 mmol), 1,2-dibromoethane (0.747 g, 0.343 mL, 3.99 mmol) in DMF (10 mL) was stirred at rt for 3.5 h. The mixture was dried under reduced pressure and the residue chromatographed (CH_2Cl_2:MeOH:AcOH, 200:1:0.5 to 120:1:0.5) to give 0.360 g (85%) of a mixture of **S10-6** (*m/z* 534.0/536.2 $[M+H]^+$) along with diiodinated compound (*m/z* 659.5/661.9 $[M+H]^+$). LC-MS shows ratio of titled compound to diiodinated compound to be 80:20. This mixture was not separated but used further in the following step.

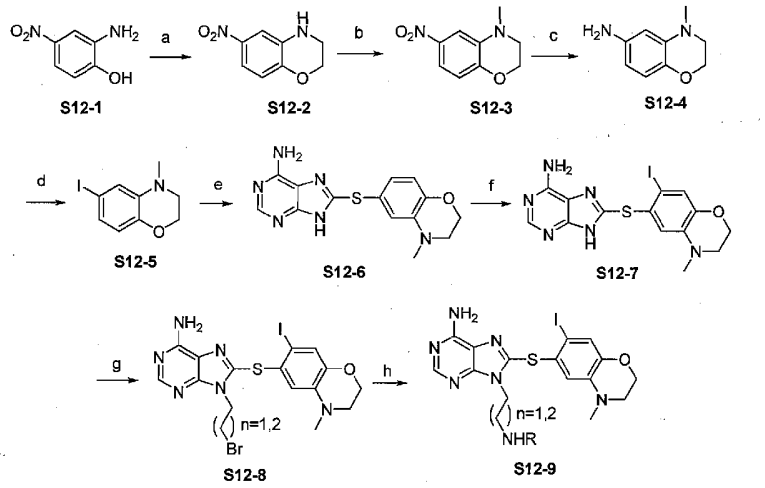
[0192] 2-fluoro-8-((7-iodo-2,3-dihydrobenzo[b] [1,4]dioxin-6-yl)methyl)-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine [DZ3-73]. S10-6 (0.360 g, 0.674 mmol) and isobutylamine (2.46 g, 3.38 ml) in DMF (8 mL) was stirred overnight at rt. Solvent was removed under reduced pressure and the resulting residue was chromatographed (CH_2Cl_2:MeOH:MeOH-NH_3 (7N), 120:0.5:0.5 to 60:0.5:0.5) to give 0.220 g of a mixture of **DZ3-73** along with the diiodinated compound. This mixture was separated by reverse phase HPLC ((a) H_2O + 0.1% TFA and (b) CH_3CN + 0.1% TFA, 10 to 75% b over 22 minutes at 16 mL/min) to give 0.196 g (58%) of **DZ3-73.** ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.57 (s, 1H), 6.37 (br s, 2H), 4.24 (s, 2H), 4.20 (s, 4H), 4.08 (t, *J*= 6.4 Hz, 2H), 2.91 (t, *J*= 6.4 Hz, 2H), 2.37 (d, *J*= 6.3 Hz, 2H), 1.64 (m, 1H), 0.85 (d, *J*= 6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8 (d, *J*= 208.1 Hz), 156.4 (d, *J*= 19.5 Hz), 152.8 *(d, J*= 18.8 Hz), 151.2, 144.2, 143.6, 131.5, 127.6, 117.9, 116.7, 88.3, 64.5, 57.8, 48.8, 43.5, 38.6, 28.4, 20.5; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{20}H_{25}FIN_6O_2$, 527.1068; found 527.1066; HPLC: method A R_t = 6.91, method B R_t = 8.48.

[0193] 9-(2-(tert-butylamino)ethyl)-2-fluoro-8-((7-iodo-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-9H-purin-6-amine [DZ4-84]. S10-6 (8 mg, 0.0149 mmol) and *tert*-butylamine (109 mg, 157 µl) in DMF (0.5 mL) was stirred overnight at rt. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAc:MeOH-NH_3 (7N), 7:2:1:0.5) to give 6 mg (77%) of **DZ4-84.** ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.55 (s, 1H), 5.86 (br s, 2H), 4.29 (s, 2H), 4.17-4.23 (m, 4H), 4.04 (t, *J*= 6.4 Hz, 2H), 2.85 (t, *J*= 6.4 Hz, 2H), 0.99 (s, 9H); MS (ESI) *m/z* 527.1 $[M+H]^+$.



Reagents and conditions: (a) $NaBH_4$, AcOH, THF, rt; (b) dibromoethane, acetone, H_2O, K_2CO_3, reflux; (c) NBS, DMF, 80°C; (d) KNO_3, H_2SO_4; (e) NaI, CuI, N,N'-dimethylethylenediamine, dioxane, 110°C; (f) Fe, NH_4Cl, isopropanol, reflux; (g) 8-mercaptoadenine, neocuproine, CuI, NaOtBu, DMF, 115°C; (h) $NaNO_2$, KI, AcOH, 0°C; (i) Cs_2CO_3, 1,2-dibromoethane or 1,3-dibromopropane, DMF, rt; (j) NH_2R, DMF, rt.

Scheme 11. Synthesis of Morpholine-type compounds S11-11.



Reagents and conditions: (a) 1,2-dibromoethane, K_2CO_3, DMF, 125°C; (b) MeI, DMF, 0°C then rt; (c) Pd/C, H_2, MeOH, rt; (d) $NaNO_2$, AcOH, KI, 0°C; (e) 8-mercaptoadenine, neocuproine, CuI, NaOtBu, DMF, 115°C; (f) NIS, CH_3CN, rt; (g) Cs_2CO_3, 1,3-dibromopropane or 1,2-dibromoethane, DMF, rt; (h) NH_2R, DMF, rt.

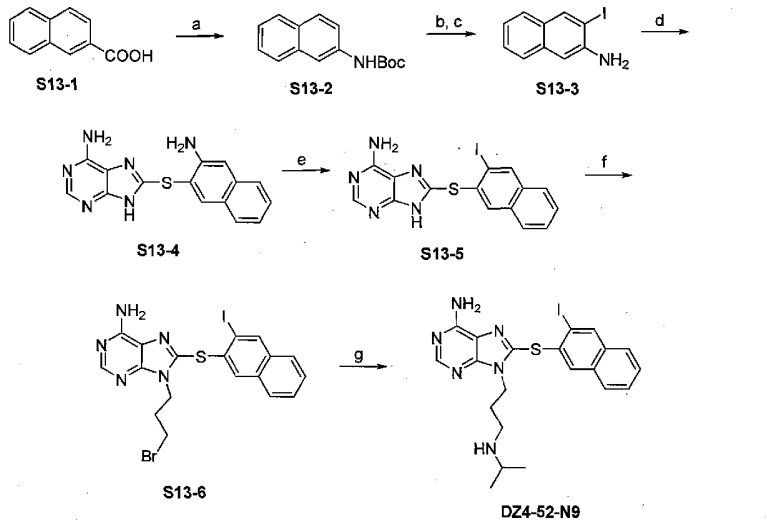
Scheme 12. Synthesis of Morpholine-type compounds S12-9.

[0194] 6-Nitro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine [S12-2]. To a solution of 2-amino-4-nitrophenol (**S12-1**; 1.5 g, 9.7 mmol) in 50 mL of DMF was added K_2CO_3 (4.04 g, 29.2 mmol) and 1,2-dibromoethane (1 mL, 11.7 mmol). The resulting mixture was stirred at 125 °C under argon overnight. The resulting mixture was concentrated under vacuum and purified by flash chromatography to give **S12-2** (1.2 g, 68%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55-7.58 (dd, *J*= 2.7, 8.9 Hz, 1H), 7.48 (d, *J*= 2.6 Hz, 1H), 6.81 (d, *J*= 8.9 Hz, 1H), 4.34 (m, 2H), 4.12 (br s, 1H), 3.47 (m, 2h); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.4, 141.8, 133.8, 115.0, 114.8, 110.2, 65.6, 40.0.

[0195] 4-Methyl-6-nitro-3,4-dihydro-2*H*-benzo[*b*]1,4]oxazine [S12-3]. To a solution of **S12-2** (0.66 g, 3.7 mmol) in 30 mL of DMF was added NaH (106 mg, 4.4 mmol) and stirred at 0 °C for 30 min. To the resulting mixture was added MeI (229 µL, 3.7 mmol) and kept stirring at rt for 2 h. The reaction mixture was concentrated in vacuum and purified by flash chromatography to give compound **S12-3** (564 mg, 79%) as yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, *J*= 8.8 Hz, 1H), 7.45 (s, 1H), 6.76 (d, *J*= 8.8 Hz, 1H), 4.36 (m, 2H), 3.32 (m, 2H), 2.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 149.7, 142.2, 136.5, 115.4, 114.5, 106.9, 65.3, 47.9, 38.6; MS (ESI) *m/z* 194.8 $(M+H)^+$.

[0196] 4- Methyl-3,4-dihydro-2*H*-benzo[*b*]][1,4]oxazin-6-amine [S12-4]. To a solution of **S12-3** (560 mg, 2.9 mmol) in 20 mL of methanol was added Pd/C powder (10%, 96 mg). The resulting suspension was stirred at rt under hydrogen overnight. The reaction mixture was filtered, concentrated in vacuum and purified by flash chromatography to give **S12-4** (420 mg, 89%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.56 (d, *J*= 8.3 Hz, 1H), 6.04 (d, *J*= 2.5 Hz, 1H), 5.98 (dd, *J*= 2.5, 8.3 Hz, 1H), 4.19 (t, *J*= 4.4 Hz, 2H), 3.21 (t, *J*= 4.5 Hz, 2H), 2.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.8, 137.4, 137.0, 116.2, 104.8, 100.4, 64.6, 49.5, 38.7.

[0197] 6-Iodo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine [S12-5]. To solution of **S12-4** (2.1 g, 12.8 mmol) in 50 mL of acetic acid cooled in ice bath was added $NaNO_2$ (1.77g, 26.9 mmol) slowly in portions. The resulting mixture was stirred at 0 °C for 10 min and was added KI (4.24 g, 38.4 mmol) in portions. The reaction mixture was stirred at 0 °C for 30 min, allowed to warm up to rt and stirred for 2 h. The resulting mixture was quenched with 100 mL of water, extracted with ethyl acetate (3 x 150 mL). The organic layer was combined, treated with $Na_2S_2O_3$, washed with brine, dried over $MgSO_4$ and purified by flash chromatography to give **S12-5** (1.86 g, 53%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.64 (d, *J*= 8.3 Hz, 1H), 6.56 (s, 1H), 6.48 (d, *J*= 8.4 Hz, 1H), 4.25 (m, 2H), 3.24 (m, 2H), 2.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.1, 126.6, 120.5, 117.6, 111.9, 83.7, 64.8, 48.7, 36.5.



Reagents or conditions: (a) $(C_6H_5O)_2P(O)N_3$, *t*-BuOH, Et_3N, toluene, reflux; (b) *t*-BuLi, THF, -20°C, then ICH_2CH_2I, -78°C to rt; (c) TFA, CH_2Cl_2, rt; (d) 8-mercaptoadenine, neocuproine, CuI, NaOtBu, DMF, 115°C; (e) KI, $NaNO_2$, HCl, H_2O, < 5°C; (f) 1,3-dibromopropane, Cs_2CO_3, DMF, rt; (g) isopropylamine, DMF, rt.

Scheme 13. Synthesis of DZ4-52-N9.

[0198] ***tert*-Butyl naphthalen-2-ylcarbamate (S13-2).**2-Naphthoic acid **(S13-1;** 2.5 g, 14.3 mmol) in *tert*-BuOH (85 mL) and toluene (85 mL) was treated with Et_3N (2.3 mL, 16.4 mmol), 3 Å molecular sieves (16.7 g) and diphenyl phosphorylazide (3.5 mL, 16.4 mmol). The reaction mixture was refluxed for 24 h. After cooling to rt, solid was filtered off through Celite and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (75 mL) and washed with 1N aqueous HCl (2 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL), dried over sodium sulfate and concentrated under reduced pressure. Chromatography (10% EtOAc in hexanes) afforded 2.5 g (71%) of **S13-2.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.72-7.78 (m, 3H), 7.44 (t, *J*= 7.8 Hz, 1H), 7.31-7.38 (m, 2H), 6.61 (br s, 1H), 1.55 (s, 9H); MS (ESI) *m/z* 244.02 $[M+H]^+$.

[0199] 2-Amino-3-iodonaphthalene (S13-3). To a solution of **S13-2** (1.0 g, 4.11 mmol) in 20 mL dry THF under argon at -20°C was added *tert*-butyl lithium (1.5 M solution in pentane, 6.9 mL, 10.27 mmol) dropwise and was stirred for 2 h at -20 °C. After cooling to -78°C, a solution of diiodoethane (2.9 g, 10.27 mmol) in 10 mL dry THF was added dropwise and then allowed to warm to rt for 3 h. A saturated aqueous NH_4Cl solution was added, and the solution was extracted with diethyl ether. The organic layer was washed with 10% sodium thiosulfate solution and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the residue was purified by chromatography (3% EtOAc in hexanes) to afford 1.1 g of a 79/21 mixture (NMR) of regioisomeric 3-iodo and 1-iodo Boc-protected 2-aminonaphthalene, respectively. This mixture (1.1 g) was dissolved in dichloromethane (12.5 mL), and trifluoroacetic acid (12.5 mL) was added dropwise at rt. After stirring for 1 h at rt, the solution was neutralized with a concentrated NaOH solution. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, concentrated under reduced pressure and the resulting residue was purified by chromatography (0.5% EtOAc in hexanes) to afford 0.50 g (45%) of **S13-3.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.59 (d, *J*= 8.3 Hz, 1H), 7.56 (d, *J*= 8.3 Hz, 1H), 7.37 (dt, *J*= 1.0, 7.5 Hz, 1H), 7.22 (dt, *J*= 0.8, 7.5 Hz, 1H), 7.09 (s, 1H), 4.23 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 139.5, 135.3, 129.9, 127.5, 127.2, 126.3, 123.7, 109.0, 88.7; MS (ESI) *m/z* 269.96.

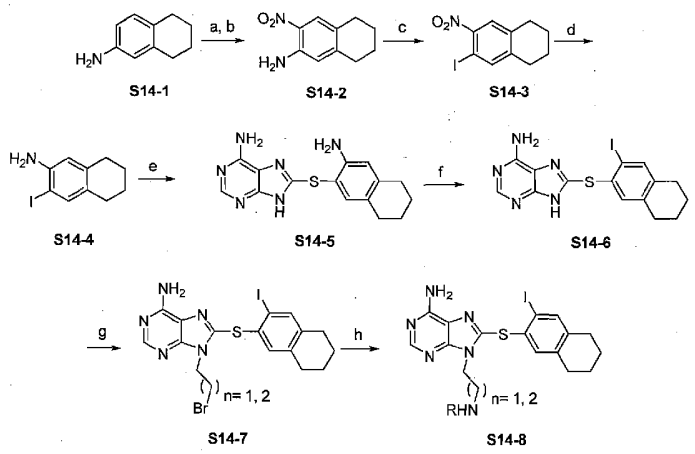
[0200] 8-(3-aminonaphthalen-2-ylthio)-9H-purin-6-amine (S13-4). A mixture of 8-mercaptoadenine (20.7 mg, 0.124 mmol), neocuproine hydrate (3.9 mg, 0.0185 mmol), CuI (3.5 mg, 0.0185 mmol), sodium *tert*-butoxide (23.7 mg, 0.24 mmol), **S13-3** (100 mg, 0.37 mmol) and DMF (2 mL) were heated at 115°C for 20 h. The solvent was removed under reduced pressure and the residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 10:1) to give 14 mg (37%) of **S13-4** as a solid. ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.18 (s, 1H), 8.12 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.40-7.46 (m, 1H), 7.24-7.30 (m, 1H), 7.20 (s, 1H); MS (ESI) *m/z* 308.95 $[M+H]^+$.

[0201] 8-(3-iodonaphthalen-2-ylthio)-9H-purin-6-amine (S13-5). To a suspension of **S13-4** (14 mg, 0.0454 mmol) in water

(150 µL) at 5°C was added 6 M HCl (140 µL) over 5 min. Then a solution of $NaNO_2$ (6.3 mg, 0.0908 mmol) in water (70 µL) was added dropwise over 30 min. at below 5°C. The mixture was stirred for an additional 10 min., then urea (1.9 mg, 0.0317 mmol) was added slowly. After 10 minutes, a solution of KI (22.6 mg, 0.136 mmol) in water (70 µL) was added dropwise over 5 min. and the mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 8:1) to give 8 mg (42%) of **S13-5** as a solid. ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.51 (s, 1H), 8.17 (s, 2H), 7.75-7.80 (m, 2H), 7.52-7.60 (m, 2H); MS (ESI) *m/z* 420.01 $[M+H]^+$.

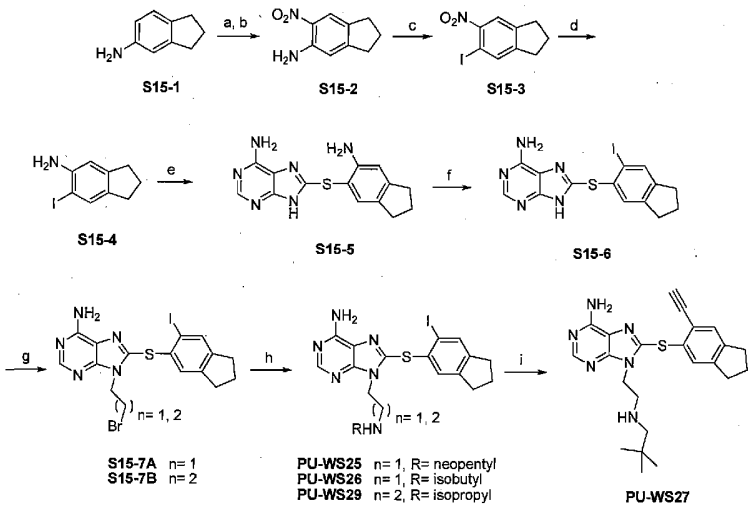
[0202] 9-(3-bromopropyl)-8-(3-iodonaphthalen-2-ylthio)-9H-purin-6-amine (S13-6). S13-5 (8 mg, 0.019 mmol), Cs_2CO_3 (7.4 mg, 0.0228 mmol), 1,3-dibromopropane (19.2 mg, 9.7 µL, 0.095 mmol) in DMF (0.2 mL) was stirred for 30 min. Then additional Cs_2CO_3 (7.4 mg, 0.0228 mmol) and 1,3-dibromopropane (19.2 mg, 9.7 µL, 0.095 mmol) was added and the mixture stirred for 30 min. The mixture was dried under reduced pressure and the residue purified by preparatory TLC (CH_2Cl_2:MeOH:AcOH, 15:1:0.5) to give 4.6 mg (45%) of **S13-6.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.51 (s, 1H), 8.27 (s, 1H), 8.05 (s, 1H), 7.74-7.80 (m, 2H), 7.53-7.60 (m, 2H), 4.42 (t, *J*= 7.1 Hz, 2H), 3.45 (t, *J*= 6.6 Hz, 2H), 2.45 (m, 2H); MS (ESI) *m/z* 539.84/541.89 $[M+H]^+$.

[0203] 8-(3-iodonaphthalen-2-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ4-52-N9]. S13-6 (4.6 mg, 0.0085 mmol) and isopropylamine (100 µL) in DMF (100 µL) was stirred overnight at rt. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 10:1) to give 4.0 mg (91 %) of **DZ4-52-N9.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.34 (s, 1H), 7.77 (s, 1H), 7.70-7.74 (m, 1H), 7.64-7.68 (m, 1H), 7.45-7.54 (m, 2H), 4.36 (t, *J*= 6.9 Hz, 2H), 2.74 (septet, *J*= 6.1 Hz, 1H), 2.58 (t, *J*= 6.8 Hz, 2H), 2.06 (m, 2H), 1.05 (d, *J*= 6.3 Hz, 6H); MS (ESI) *m/z* 518.82 $[M+H]^+$.



Reagents and conditions: (a)Ac_2O, dioxane, 0°C to rt; (b) KNO_3, H_2SO_4, 0°C to rt; (c) $NaNO_2$, KI, AcOH, 0°C to rt; (d) Fe, NH_4Cl, isopropanol, reflux; (e) 8-mercaptoadenine, CuI, nBu_4NBr, NaOt-Bu, mv; (f) $NaNO_2$, KI, AcOH, 0°C; (g) 1,3-dibromopropane or 1,2-dibromoethane, Cs_2CO_3, DMF, rt; (h) amine, DMF, rt.

Scheme 14.



Reagents and conditions: (a)Ac_2O, dioxane, 0°C to rt; (b) KNO_3, H_2SO_4, 0°C to rt; (c) $NaNO_2$, KI, AcOH, 0°C to rt; (d) Fe, NH_4Cl, isopropanol, reflux; (e) 8-mercaptoadenine, CuI, nBu_4NBr, NaOt-Bu, mv; (f) $NaNO_2$, KI, AcOH, 0°C; (g) 1,3-dibromopropane or 1,2-dibromoethane, Cs_2CO_3, DMF, rt; (h) isopropylamine or isobutylamine or neopentylamine, DMF, rt; (i) CuI, $PdCl_2(PPh_3)_2$, trimethylsilanylacetylene, Et_3N, DMF, 90°C.

Scheme 15. Synthesis of PU-WS25, PU-WS26, PU-WS29 and PU-WS27.

[0204] 5-amino-6-nitro-indane (S15-2). A solution of 5-aminoindane **(S15-1;** 10 g, 75 mmol) in 100 mL of dioxane cooled in ice bath was added acetic anhydride (15 mL) dropwise and kept stirring at room temperature for 2 days. The resulting mixture was condensed and dried under vacuum. The residue was dissolved in 100 mL of concentrated H_2SO_4, cooled in ice bath. KNO_3 in 15 mL of concentrated H_2SO_4 was added dropwise. The resulting solution was stirred at 0 °C for 2 h and then at rt for 2 h. The reaction mixture was poured into 150 g of ice and the resulting yellow precipitate was filtered and washed with cold water to give **S15-2** (7.1 g, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 6.65 (s, 1H), 6.02 (br, 2H), 2.83 (m, 4H), 2.06 (m, 2H); ^{13}CNMR(125 MHz, $CDCl_3$) δ 154.4, 144.2, 134.1, 131.2, 120.8, 113.5, 33.1, 31.4, 25.7.

[0205] 5-iodo-6-nitro-indane (S15-3). To a solution of **S15-2** (0.14 g, 0.78 mmol) in acetic acid cooled in ice bath was added $NaNO_2$ (65 mg, 0.94 mmol). The reaction mixture was stirred for 2 minutes. KI (0.39g, 2.45 mmol) was added and the mixture was stirred at rt for 20 minutes. The resulting suspension was quenched with water (15 mL) and extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with saturated aqueous $Na_2S_2O_3$ solution, brine and dried over MgSO4 and evaporated to dryness to give a residue that was purified by flash chromatography (ethyl acetate/hexane, gradient 0 to 50%) to give **S15-3** (0.12 g, 65%) as a yellow solid. ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.71 (s, 1H), 2.95 (m, 4H), 2.11 (m, 2H).

[0206] 5-amino-6-iodo-indane (S15-4). To a solution of **S15-3** (1.65 g, 5.7 mmol) in isopropanol (100 mL) and saturated aqueous NH_4Cl solution (20 mL) was added iron powder (1.1 g). The resulting suspension was refluxed for 1h. The reaction mixture was filtered and the filtrate was condensed and purified by flash chromatography (ethyl acetate/hexane, gradient 0 to 50%) to give **S15-4** (1.36 g, 92%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 6.59 (s, 1H), 3.88 (s, 2H), 2.74 (m, 4H), 1.98 (m, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 146.2, 144.9, 136.5, 134.1, 111.0, 32.8, 31.8, 26.1; MS (ESI): *m/z* 259.99 $[M+H]^+$.

[0207] 8-((6-amino-2,3-dihydro-1*H*-inden-5-yl)thio)-9-*H*-purin-6-amine (S15-5). The mixture of 8-mercaptoadenine (64 mg, 0.38 mmol), **S15-4** (100 mg, 0.38 mmol), CuI (14.7 mg, 0.07 mmol), sodium t-butoxide (111 mg, 1.15 mmol) and tetrabutylammonium bromide (24.9 mg, 0.07 mmol) in anhydrous DMF (4 mL) was vortexed and heated at 190 °C under microwave for 1h. The resulting mixture was condensed and purified by flash chromatography (methylene chloride/methanol, gradient 0 to 10%) to give **S15-5** (54 mg, 47%) as a while solid. ^{1}HNMR (500 MHz, MeOH-d_4/$CDCl_3$) δ 8.11 (s, 1H), 7.36 (s, 1H), 6.81 (s, 1H), 2.85 (m, 4H), 2.06 (m, 2H); MS (ESI): *m/z* 299.02 $[M+H]^+$.

[0208] 8-((6-iodo-2,3-dihydro-1*H*-inden-5-yl)thio)-9-*H*-purin-6-amine (S15-6). To a solution of **S15-5** (54 mg, 0.18 mmol) in acetic acid (5 mL) cooled in ice bath was added $NaNO_2$ (15 mg, 0.22 mmol) followed by KI (90 mg, 0.54 mmol). The reaction mixture was stirred at 0 °C for 15 min and quenched with water (10 mL). The resulting mixture was extracted with methylene chloride (2 x 20 mL). The organic layer was washed with saturated aqueous $Na_2S_2O_3$, brine, dried over $MgSO_4$ and evaporated to dryness. The residue was purified by flash chromatography (methylene chloride/methanol, gradient 0 to 10%) to give **S15-6** (42 mg, 56%) as a white solid. ^{1}HNMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.84 (s, 1H), 7.39 (s, 1H), 2.91 (m, 4H), 2.11 (m, 2H); MS (ESI) *m/z* 410.10 $[M+H]^+$.

[0209] 9-(2-bromoethyl)-8-((6-iodo-dihydro-1*H*-inden-5-yl)thio)-9*H*-purin-6-amine (S15-7A). To a solution of **S15-6** (70 mg, 0.17 mmol) in DMF (3 mL) was added 1,2-dibromoethane (74 uL, 0.86 mmol) and Cs_2CO_3 (111 mg, 0.34 mmol). The resulting mixture was stirred at rt for 2 h. **S15-7A** (36 mg, 41%) was obtained following preparatory TLC (methylene chloride/methanol, 20/1) as a white solid. ^{1}HNMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.75 (s, 1H), 7.18 (s, 1H), 4.62 (t, 2H), 3.68 (t, 2H), 2.88 (t, 2H), 2.81 (t, 2H), 2.06 (m, 2H); ^{13}CNMR (125 MHz, $CDCl_3$, δ): 155.9, 153.9, 152.4, 149.8, 148.9, 148.1, 137.6, 132.8, 131.1, 101.7, 46.3, 33.9, 29.7, 26.8; MS (ESI): *m/z* 516.15, 518.16 $[M, M+2]^+$.

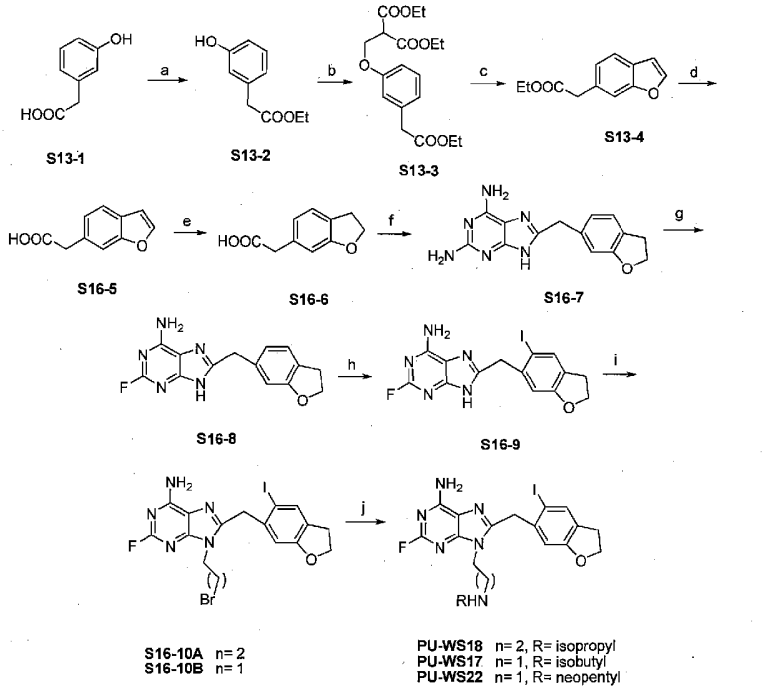
[0210] 8-((6-iodo-2,3-dihydro-*1H*-inden-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9*H*-purin-6-amine (PU-WS25). To a solution of **S15-7A** (31 mg, 0.06 mmol) in DMF (1.5 mL) was added neopentylamine (250 uL). The reaction mixture was stirred at rt overnight and condensed under vacuum. **PU-WS25** (28 mg, 89%) was obtained following preparatory TLC (methylene chloride/methanol, 10/1) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.73 (s, 1H), 7.1 (s, 1H), 5.63 (br, 2H), 4.38 (m, 2H), 3.03 (m, 2H), 2.87 (t, *J*= 7.4 Hz, 2H), 2.78 (t, *J*= 7.4 Hz, 2H), 2.37 (s, 2H), 2.04 (m, 2H), 0.93 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, δ):154.7, 152.9, 151.6, 147.1, 146.7, 146.4, 135.9, 133.5, 127.5, 120.2, 97.7, 61.8, 50.7, 49.7, 43.9, 32.5, 32.2, 31.5, 27.7, 25.5; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{28}IN_6S$, 523.1141; found 523.1140.

[0211] 8-((6-iodo-2,3-dihydro-1*H*-inden-5-yl)thio)-9-(2-(isobutylamino)ethyl)-9*H*-purin-6-amine (PU-WS26). To a solution of **S15-7A** (6 mg, 0.01 mmol) in DMF (1 mL) was added isobutylamine (150 uL). The reaction mixture was stirred at rt overnight and condensed under vacuum. **PU-WS26** (5.9 mg, 99%) was obtained following preparatory TLC (methylene chloride/methanol, 10/1) as a white solid. ^{1}HNMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.74 (s, 1H), 7.11 (s, 1H), 5.73 (br, 2H), 4.43 (m, 2H), 3.04 (m, 2H), 2.87 (t, *J*= 7.4 Hz, 2H), 2.78 (t, *J*=7.4 Hz, 2H), 2.49 (d, *J*= 6.6 Hz, 2H), 2.05 (m, 2H), 1.81 (m, 1H), 0.92 (m, 6H); HRMS *(m/z):* $[M+H]^+$ calcd for $C_{20}H_{26}IN_6S$ 509.0984; found 509.0990.

[0212] 9-(3-bromopropyl)-8-((6-iodo-2,3-dihydro-1*H*-inden-5-yl)thio)-9*H*-purin-6-amine (S15-7B). To a solution of **S15-6** (30 mg, 0.07 mmol) in DMF (3 mL) was added 1,3-dibromopropane (37 µL, 0.86 mmol) and Cs_2CO_3 (46 mg, 0.14 mmol). The resulting mixture was stirred at rt for 2 h. **S15-7B** (8 mg, 21%) was obtained following preparatory TLC (methylene chloride/methanol, 20/1) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.75 (s, 1H), 7.12 (s, 1H), 6.55 (br s, 2H), 4.33 (m, 2H), 2.88 (m, 2H), 2.79 (t, *J*= 7.4 Hz, 2H), 2.29 (m, 2H), 1.97 (m, 2H); MS (ESI): *m/z* 530.3, 532.3$[M, M+2]^+$.

[0213] 8-((6-iodo-2,3-dihydro-1*H*-inden-5-yl)thio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (PU-WS29). To a solution of **S15-7B** (8 mg, 0.015 mmol) in DMF (3 mL) was added isopropylamine (100 µL), stirred at rt overnight and condensed under vacuum. **PU-WS29** (5.9 mg, 99%) was obtained following preparatory TLC (methylene chloride/methanol, 10/1) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$)δ 8.32 (s, 1H), 7.75 (s, 1H), 7.12 (s, 1H), 5.73 (br s, 2H), 4.29 (t, 2H), 2.87 (t, *J*= 7.4 Hz, 2H), 2.7-2.79 (m, 3H), 2.55 (t, 2H), 2.03-2.09 (m, 4H), 1.05 *(d, J*= 11.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 152.9, 151.7, 147.2, 146.5, 135.9, 133.1, 127.6, 120.2, 97.9, 48.8, 43.7, 41.7, 32.5, 32.2, 30.0, 25.5, 22.7; HRMS *(m/z):* $[M+H]^+$ calcd for $C_{20}H_{26}IN_6S$ 509.0984; found 509.1003.

[0214] 8-((6-ethynyl-2,3-dihydro-1H-inden-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine **(PU-WS27).** Following the procedure to make **PU-WS8, PU-WS27** was obtained from **PU-WS25** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.32 (s, 1H), 7.41 (s, 1H), 7.13 (s, 1H), 5.67 (br s, 2H), 4.42 (m, 2H), 3.48 (s, 1H), 3.02 (m, 2H), 2.77-2.91 (m, 4H), 2.39 (s, 2H), 2.06 (m, 2H), 0.89 (s, 9H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{28}N_6S$, 421.2174; found 421.2164.



Reagents and conditions: (a)EtOH, H_2SO_4, reflux; (b) 2-bromomethylmalonate, NaH, DMF, 110°C; (c) PPA, toluene, reflux; (d) NaOH, MeOH, rt, then HCl; (e) Pd/C, H_2 (2 atm.), MeOH; (f) 2,4,5,6-tetraaminopyrimidine, triphenyl phosphite, pyridine, microwave, 210°C; (g) HF/pyridine, $NaNO_2$, 0°C to rt; (h) NIS, TFA, ACN; (i) 1,3-dibromopropane or 1,2-dibromoethane, Cs_2CO_3, DMF, rt; (h) isopropylamine or isobutylamine or neopentylamine, DMF, rt.

Scheme 16. Synthesis of PU-WS17, PU-WS18, PU-WS22.

[0215] Ethyl 2-(3-hydroxyphenyl)acetate (S16-2). To a solution of 2-(3-hydroxyphenyl)acetic acid (**S16-1**; 10 g, 65.8 mmol) in 200 mL of ethanol was added 8 mL of concentrated sulfuric acid. The resulting mixture was refluxed overnight and condensed under vacuum. The residue was dissolved in ethyl acetate and washed with water. The organic layer was combined, washed with brine, dried over $MgSO_4$, evaporated to dryness and purified by flash chromatography to give **S16-2** as a colorless oil in quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (br, 1H), 7.12 (m, 1H), 6.69-6.78 (m, 3H), 4.12 (m, 2H), 3.53 (s, 2H), 1.21 (m, 3H).

[0216] Diethyl 2-((3-ethoxy-2-oxoethyl)phenox)methyl)malonate (S16-3). To a solution of **S16-2** (11.8 g, 65.5 mmol) in 150 mL of DMF cooled in ice bath was added NaH (2.36 g, 98 mmol) and stirred at 0 °C under argon for 20 min. To the resulting mixture was added diethyl 2-bromomethylmalonate (11.8 mL, 78 mmol) dropwise. The reaction mixture was stirred at 110 °C overnight, evaporated to dryness and purified by flash chromatography to give compound **S16-3** (15.2 g, 66%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, 1H), 6.80-6.86 (m, 3H), 4.81 (m, 1H), 4.12 (m, 2H), 3.97 (m, 2H), 3.74 (m, 2H), 3.63 (m, 2H), 3.55 (s, 2H), 1.19 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 158.8, 135.6, 129.5, 121.8, 115.6, 113.3, 100.5, 68.5, 62.5, 60.7, 41.3, 15.4, 14.1.

[0217] Ethyl 2-(benzofuran-6-yl) acetate (S16-4). To a solution of **S16-3** (6 g, 17 mmol) in 100 mL of toluene was added 3 g of polyphosphoric acid. The resulting mixture was refluxed overnight, condensed and purified by flash chromatography to give **S16-4** (1.42 g, 41 %) as colorless oil.^{1}HNMR (500 MHz, $CDCl_3$) δ 7.31-7.42 (m, 3H), 6.95 (m, 1H), 6.51 (s, 1H), 3.94 (m, 2H), 3.51 (s, 2H), 1.02 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 155.2, 145.1, 130.6, 126.4, 124.3, 121.1, 112.2, 106.4, 60.9, 41.5, 14.2.

[0218] 2-(benzofuran-6-yl) acetic acid (S13-5). To a solution of **S16-4** (3 g, 14.7 mmol) in 100 mL methanol was add 25 mL of 1 N NaOH. The resulting mixture was stirred at rt for 2 h, neutralized with concentrated HCl, and adjusted pH to 2. The reaction mixture was condensed, purified by flash chromatography to yield **S16-5** as a white solid in quantitative yield. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.73 (s, 1H), 7.53 (d, J= 7.9 Hz, 1H), 7.43 (s, 1H), 7.15 (d, J= 8.0 Hz, 1H), 6.79 (s, 1H), 3.70 (s, 2H); ^{13}C NMR (125

MHz, MeOH-d_4) δ 175.7, 156.6, 146.6, 132.5, 127.7, 125.4, 121.9, 113.0, 107.4, 41.9.

[0219] 2-(2,3-dihydrobenzofuran-6-yl)acetic acid (S16-6). To a solution of **S16-5** (1.8 g, 10 mmol) in 20 mL of methanol was added Pd/C (10%, 120 mg) and stirred at rt under H_2 (2 atm) overnight. The reaction mixture was filtered, washed with cold methanol, evaporated to dryness and purified by flash chromatography to give **S16-6** (1.6 g, 88%) as a white solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.12 (d, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.71 (s, 1H), 4.55 (m, 2H), 3.56 (s, 2H), 3.16 (m, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 177.9, 160.4, 133.3, 126.2, 124.8, 121.5, 110.5, 71.5, 41.1, 29.4.

[0220] 8-((2,3-dihydrobenzofuran-6-yl)methyl)-9*H*-purine-2,6-diamine (S16-7). The mixture of 2,4,5,6-tetraaminopyrimidine (200 mg, 1.4 mmol), **S16-6** (254 mg, 1.4 mmol) and triphenyl phosphite (451 µL, 1.7 mmol) in 2 mL of pyridine was irradiated in the microwave for 15 min at 210 °C. After cooling, the reaction mixture was concentrated under vacuum and the residue purified by flash chromatography to give **S16-7** (350 mg, 89%) as a yellow solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.16 (m, 1H), 6.79 (m, 1H), 6.73 (s, 1H), 4.57 (m, 2H), 4.12 (s, 2H), 3.18 (m, 2H); MS: *m/z* 283.2 $(M+H)^+$.

[0221] 8-((2,3-dihydrobenzofuran-6-yl)methyl)-2-fluoro-9*H*-purin-6-amine (S16-8). A plastic tube charged with **S16-7** (0.72 g, 2.5 mmol) was cooled in ice bath, added HF/pyridine (73%, 1.76 mL) and stirred to dissolve. To the resulting mixture was added $NaNO_2$ (0.23 g, 3.3 mmol) in portions and kept stirring for 5 min. The reaction mixture was allowed to warm up to rt and stirred for 3 h. $CaCO_3$ (0.68 g) was added to quench excess HF. The resulting suspension was stirred for 1 h, filtered, concentrated in vacuo and purified by flash chromatography to give **S16-8** (0.45 g, 62%) as a yellow solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ: 7.16 (m, 1H), 6.77 (m, 1H), 6.71 (s, 1H), 4.57 (m, 2H), 4.12 (s, 2H), 3.19 (m, 2H); MS: *m/z* 286.0 $(M+H)^+$.

[0222] 2- fluoro-8-((5-iodo-2,3-dihydrobenzofuran-6-yl)methyl)-9H-purin-6-amine (S16-9). To a suspension of **S16-8** (0.45 g, 1.6 mmol) in 50 mL acetonitrile was added 1 mL of TFA. To the resulting solution was added NIS (1.06 g, 4.7 mmol) and the reaction mixture was stirred at rt for 3 h. It was then evaporated to dryness and purified by flash chromatography to give **S16-9** (0.408 g, 63%) as a yellow solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.67 (s, 1H), 6.76 (s, 1H), 4.59 (m, 2H), 4.28 (s, 2H), 3.21 (m, 2H); MS: *m/z* 412 $(M+H)^+$.

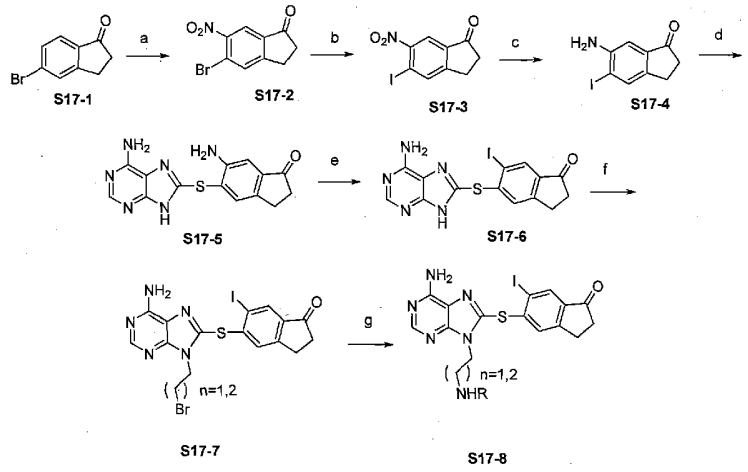
[0223] 9- (3-bromopropyl)-2-fluoro-8-((5-iodo-2,3-dihydrobenzofuran-6-yl)methyl)-9H-purin-6-amine (S16-10A). To a solution of **S16-9** (50 mg, 0.12 mmol) in 2 mL of DMF was added 1,3-dibromopropane (150 µL) and Cs_2CO_3 (80 mg, 0.24 mmol). The resulting mixture was stirred at rt for 2 h, evaporated to dryness and purified by preparatory TLC to give **S16-10A** (23 mg, 36%) as a white solid.^{1}H NMR (500 MHz, MeOH-d_4) δ 7.48 (s, 1H), 6.31 (s, 1H), 4.35 (m, 2H), 4.12 (s, 2H), 3.92 (m, 2h), 3.14 (m, 2H), 3.01 (m, 2H), 2.03 (m, 2H); MS: *m/z* 530, 532 (M, M+2)$^+$.

[0224] 2-fluoro-8-((5-iodo-2,3-dihydrobenzofuran-6-yl)methyl)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine (PU-WS18). To a solution of **S16-10A** (15 mg, 0.03 mmol) in 1 mL of DMF was added isopropylamine (0.5 mL), stirred at rt overnight, evaporated to dryness and purified by flash chromatography to give **PU-WS18** (13 mg, 90%) as a white solid. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.67 (s, 1H), 6.72 (s, 1H), 4.63 (m, 2H), 4.26 (m, 4H), 3.22-3.29 (m, 3H), 2.93 (t, *J* = 7.1 Hz, 2H), 2.27 (t, *J* = 7.0 Hz, 2H), 1.38 (d, *J* = 6.5 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{20}H_{25}N_6OFI$, 511.1119; found 511.1103.

[0225] 2-fluoro-8-((5-iodo-2,3-dihydrobenzofuran-6-yl)methyl)-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine [PU-WS17]. To a solution of **S16-9** (70 mg, 0.17 mmol) in 2 mL of DMF was added 1,2-dibromoethane (150 µL) and Cs_2CO_3 (110 mg, 0.34 mmol). The resulting mixture was stirred at rt for 2 h, evaporated to dryness and purified by preparatory TLC to give bromide intermediate **S16-10B.** To a solution of **S16-10B** (10 mg, 0.19 mmol) in 1 mL of DMF was added isobutylamine (100 uL), stirred at rt overnight, evaporated to dryness and purified by flash chromatography to give **PU-WS17** as a white solid. ^{1}H NMR (MeOH-d_4/$CDCl_3$, 500 MHz) δ: 7.67 (s, 1H), 6.62 (s, 1H), 4.59 (t, J = 8.7 Hz, 2H), 4.29 (s, 2H), 4.15 (t, J = 6.5 Hz, 2H), 3.22 (t, J = 8.7 Hz, 2H), 2.93 (t, J = 6.5 Hz, 2H), 2.45 (d, J = 6.9 Hz, 2H), 1.69 (m, 1H), 0.88 (d, J = 6.8 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{20}H_{25}FIN_6O$, 511.1119; found 511.1113.

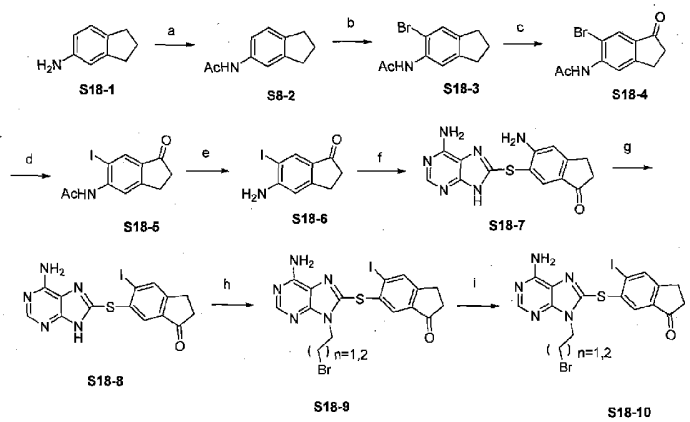
[0226] 2-fluoro-8-((5-iodo-2,3-dihydrobenzofuran-6-yl)methyl)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine [PU-WS22]. To a solution of **S16-9** (70 mg, 0.17 mmol) in 2 mL of DMF was added 1,2-dibromoethane (150 µL) and Cs_2CO_3 (110 mg,0.34 mmol). The resulting mixture was stirred at rt for 2 h, evaporated to dryness and purified by preparatory TLC to give bromide intermediate **S16-10B.** To a solution of **S16-10B** (65 mg, 0.13 mmol) in 1 mL of DMF was added neopentylamine (50 µL),

stirred at rt overnight, evaporated to dryness and purified by flash chromatography to give compound **PU-WS22** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (s, 1H), 6.53 (s, 1H), 5.79 (s, 2H), 5.52 (br, 2H), 4.52 (m, 2H), 4.09 (m, 2H), 3.19 (m, 2H), 2.94-3.02 (m, 2H), 2.34(s, 2H), 0.91 (s, 9H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{21}H_{27}FIN_6O$, 525.1275; found 525.1249.



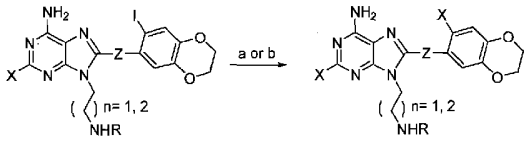
Reagents and conditions: (a) HNO_3, H_2SO_4; (b) NaI, CuI, N,N'-dimethylethylenediamine, dioxane, 110°C; (C) Fe, HCl; (d) 8-mercaptoadenine, neocuproine, CuI, NaOtBu, DMF, 115°C; (e) KI, $NaNO_2$, HCl, < 5°C ; (f) Cs_2CO_3, 1,3-dibromopropane, DMF, rt; (g) isopropylamine, DMF, rt.

Scheme 17.



Reagents and conditions: (a) Ac_2O, CH_2Cl_2, rt; (b) Br_2, AcOH, 10°C; (c) CrO_3, AcOH/H_2O, 50-55°C; (d) NaI, CuI, N,N'-dimethylethylenediamine, dioxane, 110°C; (e) 6M HCl (aq.), reflux; (f) 8-mercaptoadenine, neocuproine, CuI, NaOtBu, DMF, 115°C; (g) KI, $NaNO_2$, HCl, < 5°C ; (h) Cs_2CO_3, 1,3-dibromopropane, DMF, rt; (i) isopropylamine, DMF, rt.

Scheme 18.



PU-RK11 X= H, Z= S, n= 2, R= isopropyl
PU-HT165 X= H, Z= S, n= 1, R= isobutyl
DZ3-73 X= F, Z= CH_2, n= 1, R= isobutyl

PU-HJP18 X= H, Z= S, n= 2, R= isopropyl, X= 2-furanyl
PU-HJP19 X= H, Z= S, n= 2, R= isopropyl, X= 3-pyrazolyl
PU-HJP23 X= H, Z= S, n= 1, R= isobutyl, X= 2-furanyl
TT-VI-53A X= F, Z= CH_2, n= 1, R= isobutyl, X= 2-furanyl
TT-VI-54A X= F, Z= CH_2, n= 1, R= isobutyl, X= 3-pyrazolyl
PU-HJP20 X= H, Z= S, n= 2, R= isopropyl, X= 2-oxazolyl

Reagents or conditions: (a) boronic acid, $PdCl_2(PPh_3)_2$, $NaHCO_3$, H_2O, DMF; (b) $XSn(Bu)_3$, LiCl, $Pd(PPh_3)_4$, DMF, 90°C .

Scheme 19. Cross-coupling reactions of PU-RK11, PU-HT165 and DZ3-73.

[0227] 8-((7-(furan-2-yl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [HJP18]. 2-Furanylboronic acid (8 mg, 0.0712 mmol) was added to **PU-RK11** (25 mg, 0.0475 mmol) and $NaHCO_3$ (12 mg, 0.1425 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (6.7 mg, 0.0095 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 12 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 10.2 mg (45%) of **HJP18.** ^1H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.29 (s,1H), 7.47 (s, 1H), 7.26 *(d, J*= 3.8 Hz, 1H), 6.89 (s, 1H), 6.73 (d, *J*= 3.9 Hz, 1H), 6.46 (m, 1H), 4.25 (m, 4H), 4.16 (t, *J*= 6.2 Hz, 2H), 2.67 (m, 1H), 2.47 (t, *J* = 7.1 Hz, 2H), 1.86 (m, 2H), 1.01 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.4, 152.8, 151.7, 151.0, 146.7, 144.2, 143.7, 142.2, 126.6, 122.1, 119.9, 119.3, 117.6, 111.5, 109.5, 64.4, 64.3, 48.6, 43.8, 41.6, 30.1, 22.8; MS (ESI) *m/z* 467.14 $[M+H]^+$.

[0228] 8-((7-(1H-pyrazol-3-yl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [HJP19]. 1H-Pyrazole-3-boronic acid (6.4 mg, 0.057 mmol) was added to **PU-RK11** (20 mg, 0.038 mmol) and $NaHCO_3$ (9.8 mg, 0.117 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (5.3 mg, 0.0076 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 12 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 15:1) to give 7.6 mg (43%) o f **HJP19.** Additionally, 15.9 mg of unreacted PU-RK11 was recovered for an actual yield of 86%. ^1H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.18 (s, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.15 (s, 1H), 7.14 (s, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 4.29 (m, 4H), 4.19 (t, *J* = 6.6 Hz, 2H), 2.75 (septet, *J* = 6.1 Hz, 1H), 2.52 (t, *J*= 6.6 Hz, 2H), 1.93 (m, 2H), 1.06 (d, *J*= 6.1 Hz, 6H); MS (ESI) *m/z* 468.0 $[M+H]^+$.

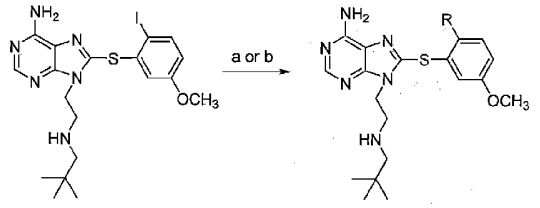
[0229] 8-((7-(furan-2-yl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thio)-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine [HJP23]. 2-Furanylboronic acid (5.4 mg, 0.0486 mmol) was added to **PU-HT165** (9 mg, 0.0171 mmol) and $NaHCO_3$ (5.7 mg, 0.0684 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (2.4 mg, 0.0034 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 12 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 1.8 mg (23%) **of HJP23.** ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.48 (d, *J* = 1.8 Hz, 1H), 7.26 (s, 1H), 6. 90 (s, 1H), 6.74 (d, *J* = 3.2 Hz, 1H), 6.47 (m, 1H), 5.63 (br s, 2H), 4.20-4.30 (m, 6H), 2.90 (t, *J*= 6.0 Hz, 2H), 2.38 (d, *J*= 6.8 Hz, 2H), 1.65 (m, 1H), 0.85 (d, *J*= 6.9 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}N_6O_3S$, 467.1865; found 467.1884.

[0230] 2-fluoro-8-((7-(furan-2-yl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine [TT-VI-53A]. 2-Furanylboronic acid (8 mg, 0.0712 mmol) was added to **DZ3-73** (25 mg, 0.0475 mmol) and $NaHCO_3$ (12 mg, 0.1425 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (6.7 mg, 0.0095 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 12 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 20.9 mg (94%) of **TT-VI-53A**. ^1H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 7.45 (d, *J* = 1.8 Hz, 1H), 7.13 (s, 1H), 6.60 (s, 1H), 6.44 (dd, *J*= 1.8, 3.3 Hz, 1H), 6.35 (d, *J* = 3.3 Hz, 1H), 4.34 (s, 2H), 4.26 (s, 4H), 4.05 (t, *J* = 6.4 Hz, 2H), 2.85 (t, *J* = 6.4 Hz, 2H), 2.35 (d, *J* = 6.9 Hz, 2H), 1.67 (m, 1H), 0.85 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-*d4*) δ 158.8 (d, *J* = 209.1 Hz), 156.3 (d, *J* = 19.5 Hz), 152.8, 152.2, 143.9, 142.9, 142.2, 126.0, 124.1, 118.7, 117.7, 117.6, 116.3, 111.6, 108.2, 64.6, 57.5, 48.6, 43.1, 31.8, 28.2, 20.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{24}H_{28}FN_6O_3$, 467.2207; found 467.2203; HPLC: method A R_t = 7.05, method B R_t = 8.74.

[0231] 8-((7-(1H-pyrazol-3-yl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine [TT-VI-54A]. 1H-Pyrazole-3-boronic acid (26 mg, 0.228 mmol) was added to **DZ3-**

73 (30 mg, 0.0570 mmol) and $NaHCO_3$ (29 mg, 0.342 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.2 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0114 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 12 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 15:1) to give 11.3 mg (42%) of **TT-VI-54A.** Additionally, 15.9 mg of unreacted DZ3-73 was recovered for an actual yield of 90%. ^1H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 7.60 (d, *J* = 2.1 Hz, 1H), 7.02 (s, 1H), 6.82 (s, 1H), 6.33 (d, *J*= 2.1 Hz, 1H), 4.32 (t, *J* = 6.8 Hz, 2H), 4.29 (s, 2H), 4.28 (s, 4H), 2.96 (t, *J* = 6.8 Hz, 2H), 2.59 (d, *J* = 7.0 Hz, 2H), 1.92 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 158.2 (d, *J* = 210.1 Hz), 156.5 (d, *J* = 19.9 Hz), 152.6, 152.2, 152.1, 144.0, 143.0, 126.5, 119.1, 118.9, 115.94, 115.91, 105.4, 64.65, 64.56, 56.5, 47.7, 41.0, 31.1, 27.2, 20.3; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{28}FN_8O_2$, 467.2319; found 467.2323; HPLC: method A R_t = 6.39, method B R_t = 7.03.

[0232] 9-(3-(isopropylamino)propyl)-8-((7-(oxazol-2-yl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thio)-9H-purin-6-amine [HJP20]. 2-(Tributyltin)oxazole (54 mg, 0.1518 mmol) was added to **PU-RK11** (20 mg, 0.038 mmol) and LiCl (3.2 mg, 0.076 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then $Pd(PPh_3)_4$ (6.7 mg, 0.0095 mmol) was added and the reaction mixture was heated under nitrogen at 90°C for 12 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 4.7 mg (27%) of **HJP20.** Additionally, 7 mg of unreacted PU-RK11 was recovered for an actual yield of 45%. ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.70 (s, 1H), 7.54 (s, 1H), 7.26 (s, 1H), 6.59 (s, 1H), 5.79 (br s, 2H), 4.20-4.34 (m, 6H), 2.67 (m, *J*= 6.1 Hz, 1H), 2.50 (t, *J*= 6.8 Hz, 2H), 1.93 (m, *J* = 7.1 Hz, 2H), 0.99 (d, *J* = 6.4 Hz, 6H); MS (ESI) *m/z* 468.15 $[M+H]^+$.



EC102

Reagents or conditions: (a) $RB(OH)_2$, $PdCl_2(PPh_3)_2$, $NaHCO_3$, H_2O, DMF; (b) CuI, $PdCl_2(PPh_3)_2$, trimethylsilanylacetylene, Et_3N, DMF, 90°C.

Scheme 20. Cross-coupling reactions of EC102.

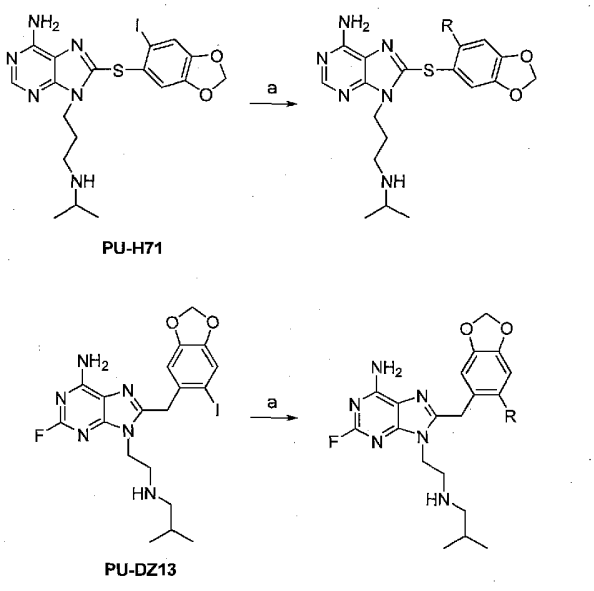
[0233] 8-(2-(furan-2-yl)-5-methoxyphenylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine [TT-V-138]. 2-Furanylboronic acid (8.2 mg, 0.0732 mmol) was added to **EC102** (25 mg, 0.0488 mmol) and $NaHCO_3$ (12.3 mg, 0.1464 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (6.8 mg, 0.00976 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 5 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 20.7 mg (94%) of **TT-V-138.** ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 6.86 (dd, *J*= 2.6, 8.7 Hz, 1H), 6.70-6.73 (m, 2H), 6.49 (dd, *J*= 1.8, 3.3 Hz, 1H), 5.98 (br s, 2H), 4.26 (t, *J*= 6.2 Hz, 2H), 3.70 (s, 3H), 2.89 (t, *J* = 6.2 Hz, 2H), 2.28 (s, 2H), 0.84 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 154.8, 153.2, 151.6, 151.2, 145.4, 142.0, 130.9, 130.2, 124.3, 120.1, 116.5, 113.4, 111.4, 109.1, 61.8, 55.3, 49.6, 43.9, 31.5, 27.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{29}N_6O_2S$, 453.2073; found 453.2071; HPLC: method A R_t = 6.76, method B R_t = 7.29.

[0234] 8-(5-methoxy-2-(thiophen-2-yl)phenylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine [TT-V-139]. 2-Thiopheneboronic acid (18.8 mg, 0.147 mmol) was added to **EC102** (25 mg, 0.0488 mmol) and $NaHCO_3$ (24.6 mg, 0.293 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.25 mL) and $Pd(PPh_3)_2Cl_2$ (10.4 mg, 0.0148 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 5 h. Solvent was removed under reduced

pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 16.2 mg (71%) of **TT-V-139.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.19 (s, 1H), 7.45 (d, *J*= 8.5 Hz, 1H), 7.30-7.33 (m, 1H), 6.99-7.04 (m, 3H), 6.97 (dd, *J*= 2.6, 8.5 Hz, 1H), 4.24 (t, *J*= 6.1 Hz, 2H), 3.82 (s, 3H), 2.97 (t, *J*= 6.1 Hz, 2H), 2.41 (s, 2H), 0.91 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 159.9, 154.6, 152.4, 150.9, 147.6, 140.4, 133.2, 130.8, 129.3, 127.6, 127.1, 126.2, 119.5, 118.9, 114.6, 61.4, 55.6, 49.3, 43.3, 31.3, 27.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{29}N_6OS_2$, 469.1844; found 469.1830; HPLC: method A R_t = 6.84, method B R_t = 7.48.

[0235] 8-(5-methoxy-2-(1H-pyrazol-3-yl)phenylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine [TT-V-140]. 1H-Pyrazole-3-boronic acid (26.2 mg, 0.234 mmol) was added to **EC102** (30 mg, 0.0585 mmol) and $NaHCO_3$ (29.5 mg, 0.351 mmol). DMF (1 mL) was added and the reaction mixture was evacuated and back filled with nitrogen. This was repeated four times then nitrogen was bubbled through the reaction mixture for 10 minutes. Then H_2O (0.2 mL) and $Pd(PPh_3)_2Cl_2$ (8.2 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for 7 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 15:1) to give 6.2 mg (23%) of **TT-V-140.** Additionally, 16.4 mg of unreacted EC102 was recovered for an actual yield of 52%. ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.19 (s, 1H), 7.58 (d, *J*= 2.1 Hz, 1H), 7.50 (d, *J*= 8.5 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.99 (dd, *J* = 2.6, 8.6 Hz, 1H), 6.40 (d, *J*= 2.1 Hz, 1H), 4.42 (t, *J*= 6.1 Hz, 2H), 3.81 (s, 3H), 3.02 (t, *J*= 6.1 Hz, 2H), 2.52 (s, 2H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.6,152.3,150.8,149.4,148.6, 148.5, 120.1, 119.2, 114.5, 110.9, 106.0, 102.3, 61.2, 49.1, 42.5, 31.1, 27.5; HRMS (ESI) m/z $[M+H]^+$ calcd. for $C_{22}H_{29}N_8OS$, 453.2185; found 453.2186; HPLC: method A R_t = 6.61, method B R_t = 6.82.

[0236] 8- ((2-ethynyl-5-methoxyphenyl)thio)-9-(2-(neopentylamino)ethyl)-9*H*-purin-6-amine (PU-WS31). Following the procedure to make PU-WS8, PU-WS31 was obtained from **EC102** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.35 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 6.75 (m, 2H), 5.65 (br, 2H), 4.35 (t, *J* = 6.3 Hz, 2H), 3.72 (s, 3H), 3.30 (s, 1H), 2.97 (t, *J* = 6.3 Hz, 2H), 2.31 (s, 2H), 0.87 (s, 9H); MS (ESI) *m/z* 411.3 $(M+H)^+$.



Reagents and conditions: (a) $RSn(Bu)_3$, LiCl, $Pd(PPh_3)_4$, DMF, 90°C.

Scheme 21. Stille coupling of PU-H71 and PU-DZ13.

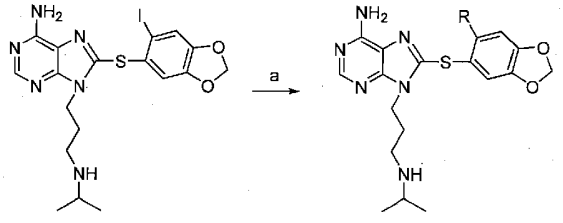
[0237] 9-(3-(isopropylamino)propyl)-8-(6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine [DZ4-20]. A mixture of **PU-H71** (30 mg, 0.0585 mmol), 2-(tri-*n*-butylstannyl)oxazole (83.8 mg, 49 µl, 0.234 mmol), LiCl (5 mg, 0.117 mmol) and $Pd(PPh_3)_4$ (6.7 mg, 0.0058 mmol) in DMF (1 mL) was evacuated and back filled with nitrogen. This was repeated four times then the reaction mixture was heated under nitrogen at 90°C for 18 h. Solvent was removed under reduced pressure and the resulting

residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAC:MeOH-NH_3 (7N), 2:2:1:0.5) to give 20.8 mg (78%) of **DZ4-20.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.25 (s, 1H), 7.75 (s, 1H), 7.46 (s, 1 H), 7.27 (s, 1H), 6.71 (s, 1 H), 6.06 (s, 2H), 4.26 (t, *J* = 6.9 Hz, 2H), 2.75 (septet, *J* = 6.3 Hz, 1H), 2.53 (t, *J*= 6.9 Hz, 2H), 1.98 (m, 2H), 1.06 *(d, J*= 6.3 Hz, 6H); HRMS (ESI) *m/z* [M+H:]$^+$ calcd. for $C_{21}H_{24}N_7O_3S$, 454.1661; found 454.1650; HPLC: method A R_t = 5.77, method B R_t = 5.28.

[0238] 9-(3-(isopropylamino)propyl)-8-(6-(thiazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine [DZ4-21]. A mixture of **PU-H71** (30 mg, 0.0585 mmol), 2-(tri-*n*-butylstannyl)thiazole (87.6 mg, 72.4 µl, 0.234 mmol), LiCl (5 mg, 0.117 mmol) and $Pd(PPh_3)_4$ (6.7 mg, 0.0058 mmol) in DMF (1 mL) was evacuated and back filled with nitrogen. This was repeated four times then the reaction mixture was heated under nitrogen at 90°C for 18 h. Then additional 2-(tri-*n*-butylstannyl)thiazole (21.9 mg, 18 µl, 0.0585 mmol) was added and the reaction mixture was heated under nitrogen at 90°C for an additional 18 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (hexane:CH_2Cl_2:EtOAC:MeOH-NH_3 (7N), 2:2:1:0.5) to give 17.6 mg (64%) of **DZ4-21.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.20 (s, 1H), 7.87 (d, *J* = 3.3 Hz, 1 H), 7.45 (s, 1H), 7.44 (d, *J* = 3.3 Hz, 1H), 6.98 (s, 1 H), 6.11 (s, 2H), 4.21 *(t, J* = 6.9 Hz, 2H), 2.78 (septet, *J*= 6.3 Hz, 1H), 2.55 (t, *J*= 6.9 Hz, 2H), 1.98 (m, 2H), 1.09 (d, *J*= 6.3 Hz, 6H); HRMS (ESI) *m/z* [M+H]$^+$ calcd. for $C_{21}H_{24}N_7O_2S_2$, 470.1433; found 470.1438; HPLC: method A R_t = 5.86, method B R_t = 5.66.

[0239] 2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine [DZ4-23]. A mixture of **PU-DZ13** (20 mg, 0.039 mmol), 2-(tri-*n*-butylstannyl)oxazole (55.9 mg, 32.7 µl, 0.156 mmol), LiCl (3.3 mg, 0.078 mmol) and $Pd(PPh_3)_4$ (4.5 mg, 0.0039 mmol) in DMF (1 mL) was evacuated and back filled with nitrogen. This was repeated four times then the reaction mixture was heated under nitrogen at 90°C for 18 h. Then additional LiCl (3.3 mg, 0.078 mmol) and $Pd(PPh_3)_4$ (4.5 mg, 0.0039 mmol) were added and the reaction mixture was heated under nitrogen at 90°C for an additional 18 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC two times (hexane:CH_2Cl_2:EtOAC:MeOH-NH_3 (7N), 2:2:1:0.5 then CH_2Cl_2:MeOH-NH_3 (7N), 20:1) to give 5.5 mg (31%) of **DZ4-23.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 7.68 (s, 1H), 7.53 (s, 1H), 7.12 (s, 1H), 6.84 (s, 1H), 6.07 (s, 2H), 4.74 (s, 2H), 4.41 (t, *J* = 6.4 Hz, 2H), 3.15 (t, *J* = 6.4 Hz, 2H), 2.59 (d, *J* = 6.9 Hz, 2H), 1.88 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 6H); HRMS (ESI) *m/z* [M+H]$^+$ calcd. for $C_{22}H_{25}FN_7O_3$, 454.2003; found 454.1995; HPLC: method A R_t = 6.61, method B R_t = 7.58.

[0240] 2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(thiazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine [DZ4-24]. A mixture of **PU-DZ13** (20 mg, 0.039 mmol), 2-(tri-*n*-butylstannyl)thiazole (58.3 mg, 48.2 µl, 0.156 mmol), LiCl (3.3 mg, 0.078 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.0078 mmol) in DMF (1 mL) was evacuated and back filled with nitrogen. This was repeated four times then the reaction mixture was heated under nitrogen at 90°C for 18 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC two times (hexane:CH_2Cl_2:EtOAC:MeOH-NH_3 (7N), 2:2:1:0.5 and CH_2Cl_2:MeOH:AcOH, 20:1:0.5) to give 10.2 mg (56%) of **DZ4-24.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 7.77 (d, *J* = 3.3 Hz, 1H), 7.36 (d, *J* = 3.3 Hz, 1H), 7.17 (s, 1H), 6.80 (s, 1H), 6.05 (s, 2H), 4.58 (s, 2H), 4.15 (t, *J* = 6.6 Hz, 2H), 2.85 (t, *J* = 6.6 Hz, 2H), 2.35 (d, *J* = 6.8 Hz, 2H), 1.64 (m, 1H), 0.86 (d, *J* = 6.8 Hz, 6H); HRMS (ESI) m/z [M+H]$^+$ calcd. for $C_{22}H_{25}FN_7O_2S$, 470.1774; found 470.1770; HPLC: method A R_t = 6.68, method B R_t = 7.79.



PU-H71

Reagents and conditions: (a) alkene (R), $Pd(PPh_3)_4$, *i*-Pr_2NEt, NMP, 55-100°C.

Scheme 22. Heck coupling of PU-H71.

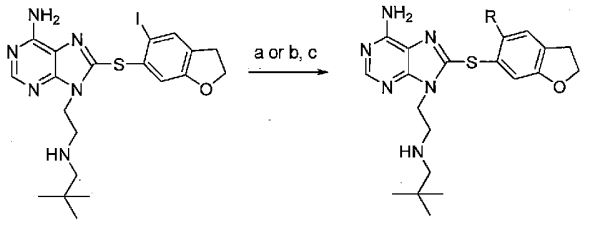
[0241] 8-(6-(cyclopent-2-enyl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [TT-VI-116]. A solution of **PU-H71** (30 mg, 0.0585 mmol) in NMP (1 mL) was evacuated and back filled with nitrogen. This was repeated four

times, then DIEA (15.1 mg, 21 µL, 0.117 mmol), cyclopentene (80 mg, 103 µL, 1.171 mmol) and $Pd(PPh_3)_4$ (6.8 mg, 0.00586 mmol) were added and the reaction mixture was heated under nitrogen at 100°C for 20 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC two times (CH_2Cl_2:MeOH-NH_3 (7N), 15:1 then CH_2Cl_2:MeOH, 7:3) to give 9.2 mg (35%) of **TT-VI-116.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.16 (s, 1H), 6.99 (s, 1H), 6.82 (s, 1H), 6.01 (s, 2H), 5.98 (m, 1H), 5.63 (m, 1H), 4.41 (t, *J*= 6.4 Hz, 2H), 3.39 (m, 1H), 3.34 (septet, *J* = 6.6 Hz, 1H), 2.95 (t, *J*= 6.4 Hz, 2H), 2.22-2.52 (m, 5H), 1.50-1.59 (m, 1H), 1.44 (d, *J* = 6.6 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{29}N_6O_2S$, 453.2073; found 453.2064; HPLC: method A R_t = 6.51, method B R_t = 7.79.

[0242] 8-(6-(2,5-dihydro-1H-pyrrol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ3-141]. A solution of **PU-H71** (30 mg, 0.0585 mmol) and N-Boc-2,3-dihydro-1H-pyrrole (19.8 mg, 20.2 µL, 0.117 mmol) in NMP (1.5 mL) was evacuated and back filled with nitrogen. This was repeated four times, then DIEA (15.1 mg, 21 µL, 0.117 mmol) and $Pd(PPh_3)_4$ (13.5 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 100°C for 20 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 15:1) and the resulting residue was dissolved into 2 mL of CH_2Cl_2:TFA (4:1) and stirred for 1 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2:MeOH-NH_3 (7N), 10:1) to give 6.0 mg (23%) of **DZ3-141.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.19 (s, 1H), 6.98 (s, 2H), 6.04 (m, 1H), 6.01 (s, 2H), 5.74 (m, 1H), 5.62 (d, *J*= 2.0 Hz, 1H), 4.31 (t, *J*= 6.9 Hz, 2H), 3.81-3.88 (m, 1H), 3.89-3.95 (m, 1H), 2.87 (septet, *J* = 6.3 Hz, 1H), 2.68 (t, *J* = 6.7 Hz, 2H), 2.14 (m, 2H), 1.15 (d, *J* = 6.3 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{28}N_7O_2S$, 454.2025; found 454.2046; HPLC: method A R_t = 5.27, method B R_t = 2.72.

[0243] 8-(6-(2,3-dihydrofuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ3-142]. A solution **of PU-H71** (30 mg, 0.0585 mmol) in NMP (1.5 mL) was evacuated and back filled with nitrogen. This was repeated four times, then DIEA (15.1 mg, 21 µL, 0.117 mmol), 2,3-dihydrofuran (82 mg, 88 µL, 1.17 mmol) and $Pd(PPh_3)_4$ (13.5 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 55°C for 20 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC two times (hexane:EtOAc:CH_2Cl_2:MeOH-NH_3 (7N), 2:1:2:0.5, then CH_2Cl_2:MeOH-NH_3 (7N), 15:1) to give 7.0 mg (26%) of **DZ3-142.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.06 (s, 1H), 6.96 (s, 1H), 6.43 (m, 1H), 6.01 (s, 2H), 5.94 (dd, *J*= 8.1, 10.8 Hz, 1H), 5.72 (br s, 2H), 4.93 (m, 1H), 4.35 (t, *J*= 6.8 Hz, 2H), 2.95-3.55 (m, 2H), 2.70 (t, *J*= 6.5 Hz, 2H), 2.39-2.47 (m, 1H), 2.22 (m, 2H), 1.25 (d, *J*= 6.2 Hz, 6H); HRMS (ESI) m/z $[M+H]^+$ calcd. for $C_{22}H_{27}N_6O_3S$, 455.1865; found 455.1865; HPLC: method A R_t = 6.07, method B R_t = 6.49.

[0244] 8-(6-(2,3-dihydrofuran-3-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine [DZ3-143]. A solution **of PU-H71** (30 mg, 0.0585 mmol) in NMP (1.5 mL) was evacuated and back filled with nitrogen. This was repeated four times, then DIEA (15.1 mg, 21 µL, 0.117 mmol), 2,5-dihydrofuran (82 mg, 88 µL, 1.17 mmol) and $Pd(PPh_3)_4$ (13.5 mg, 0.0117 mmol) were added and the reaction mixture was heated under nitrogen at 55°C for 20 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC two times (CH_2Cl_2:MeOH-NH_3 (7N), 10:1, then hexane:EtOAc:CH_2Cl_2:MeOH-NH_3 (7N), 2:1:2:0.5) to give 5.0 mg (19%) **of DZ3-143.** ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.18 (s, 1H), 7.02 (s, 1H), 7.00 (s, 1H), 6.55 (m, 1H), 6.04 (s, 2H), 4.99 (m, 1 H), 4.64-4.69 (m, 1 H), 4.45 (m, 1 H), 4.31 (t, *J*= 6.8 Hz, 2H), 4.05 (dd, *J*= 6.2, 9.2 Hz, 1H), 3.40 (m, 1H), 2.67 (t, *J*= 6.4 Hz, 2H), 2.14 (m, 2H), 1.16 (d, *J*= 6.1 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{27}N_6O_3S$, 455.1865; found 455.1862; HPLC: method A R_t = 6.04, method B R_t = 6.32.



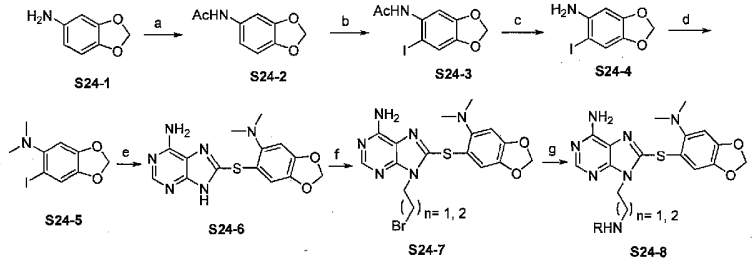
Reagents and conditions: (a) $RB(OH)_2$, $PdCl_2(PPh_3)_2$, $NaHCO_3$, H_2O, DMF, 90°C; (b) CuI, $PdCl_2(PPh_3)_2$, trimethylsilanylacetylene, Et_3N, DMF, 90°C; (c) KOH, MeOH, rt.

Scheme 23. Cross coupling reactions of PU-WS21.

[0245] **8-(5-(furan-2-yl)-2,3-dihydrobenzofuran-6-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine** [**PU-WS23**]. Following the procedure to make **PU-DZ3-4,** compound **PU-WS23** was obtained as a white solid. ^{1}HNMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.49 (s, 2H), 6.68 (d, *J*= 3.4 Hz, 1H), 6.58 (s, 1H), 6.49 (m, 1H), 5.60 (br s, 2H), 4.58 (t, *J*= 8.7 Hz, 2H), 4.25 (m, 2H), 3.22 (t, *J*= 8.7 Hz, 2H), 2.86 (m, 2H), 2.25 (s, 2H), 0.86 (s, 9H); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{29}N_6O_2$ 465.2073; found 465.2077.

[0246] **9-(2-(neopentylamino)ethyl)-8-(5-(thiophen-2-yl)-2,3-dihydrobenzofuran-6-ylthio)-9H-purin-6-amine** [**PU-WS24**]. Following the procedure to make **PU-DZ2-395,** compound **PU-WS24** was obtained as a white solid. ^{1}HNMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.32 (m, 1H), 7.27 (s, 1H), 7.03-7.07 (m, 2H), 6.67 (s, 1H), 5.59 (br s, 2H), 4.58 (t, *J*= 8.7 Hz, 2H), 4.15 (m, 2H), 3.21 (t, *J*= 8.7 Hz, 2H), 2.86 (m, 2H), 2.25 (s, 2H), 0.83 (s, 9H); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{29}N_6O_2$ 481.1844; found 481.1825.

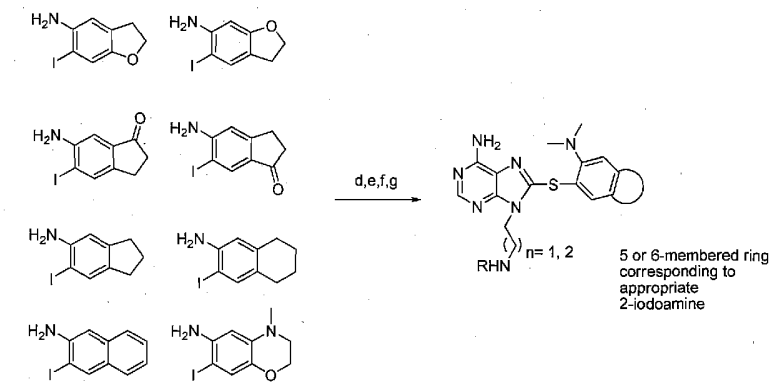
[0247] **8-(5-ethynyl-2,3-dihydrobenzofuran-6-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine** [**PU-WS28**]. Following the procedure to make **PU-WS8,** compound **PU-WS28** was obtained as a white solid. ^{1}HNMR (500 MHz, $CDCl_3$, δ): 8.33 (s, 1H), 7.36 (s, 1H), 6.59 (s, 1H), 5.70 (br, 2H), 4.58 (t, *J* = 8.7 Hz, 2H), 4.41 (m, 2H), 3.33 (t, *J*= 8.7 Hz, 2H), 3.49 (m, 2H), 3.02 (s, 2H), 2.44 (s, 2H), 0.91 (s, 9H); HRMS (m/z): $[M+H]^+$ calcd for $C_{22}H_{27}N_6OS$ 423.1967; found 423.1968.



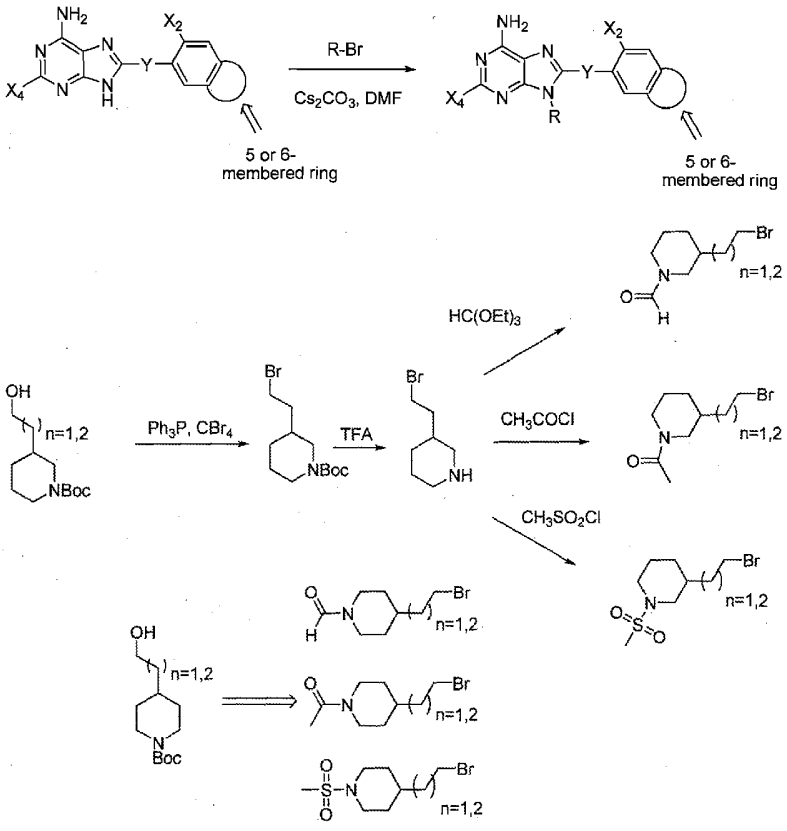
Reagents and conditions: (a) Ac_2O, AcOH, rt; (b) ICl, CH_2Cl_2, AcOH, rt; (c) NaOH, EtOH, H_2O, reflux; (d) paraformaldehyde, $NaBH_3CN$, MeOH, 50°C; (e) 8-mercaptoadenine, neocuproine, CuI, NaOtBu, DMF, 115°C; (f) Cs_2CO_3, 1,3-dibromopropane or 1,2-dibromoethane, DMF, rt; (g) amine, DMF, rt.

Scheme 24.

[0248] Similarly,



Scheme 25. Synthesis of various bromides required for alkylation of the purine skeleton.



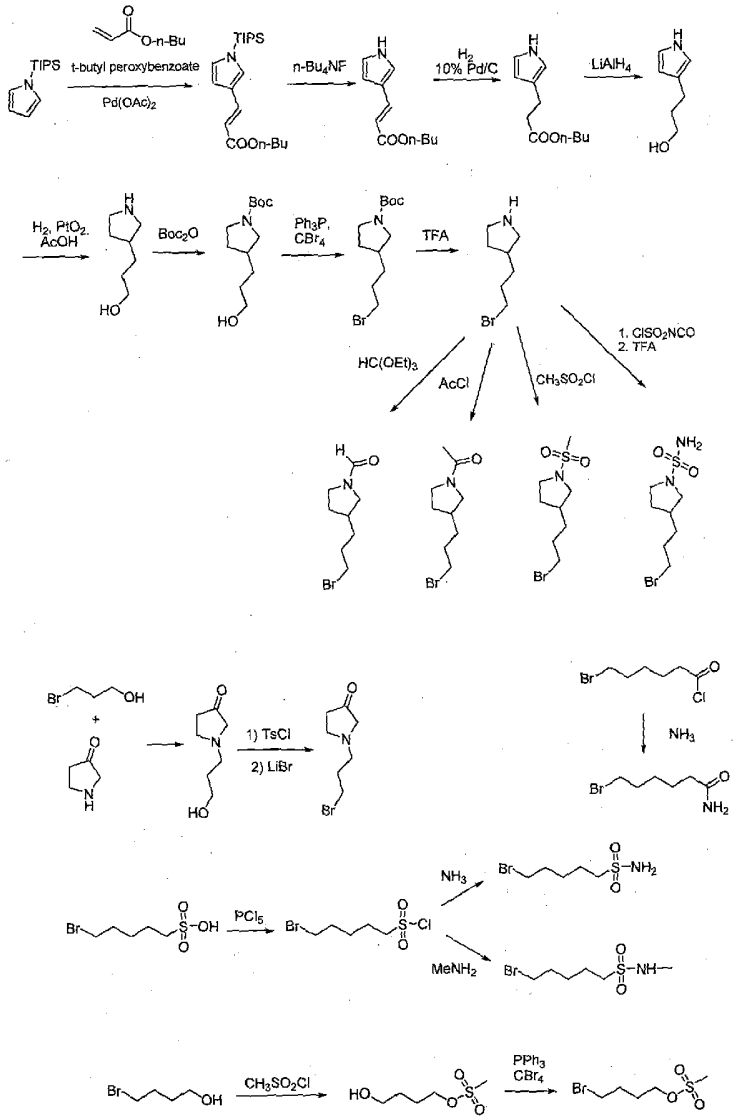


Table 2A

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
PU-WS9	5.5	ND
PU-WS4	8.0-14	ND
PU-WS10	132.9-346	ND

Table 2B

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
PU-WS17	17.3	ND
PU-WS18	33.3	ND
PU-WS21	10.8	ND
PU-WS22	8.0	ND

Table 2C

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
PU-WS23	12.2	ND
PU-WS24	25.4	ND

Table 2D

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
PU-WS28	8.1	ND

Table 2E

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
PU-WS26	3.6	ND
PU-WS25	7.2	ND
PU-WS29	4.5	ND

Table 2F

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
PU-WS27	15	ND

Table 2G

Compound #	Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
4A-1	DZ2-388	270	645
4A-2	DZ2-390	2,666	6,240
4A-3	DZ2-391	>100,000	>100,000
4A-4	TT-V-47B	8,287	15,010
4A-5	DZ2-392	1,388	2,520
4A-6	DZ3-3	438	1,030
4A-7	DZ3-6	732	1,385
4A-8	DZ3-50	2,333	>3000
4C-1	DZ3-4	11	22
4C-2	DZ3-27	48	86
4C-3	DZ3-25	3.9	5.2
4C-4	DZ3-26	14	26
4C-5	TT5-53A	5.3	6.5
4C-6	DZ3-33	56	141
4C-7	DZ3-34	82	142
4C-8	DZ3-35	23	37
4C-9	DZ3-36	6.0	12
4C-10	DZ3-49	>300	>300
4C-11	DZ3-51	153	185
4C-14	DZ3-60	ND	10.1
4C-16	DZ3-56	ND	10.2
4C-38	DZ4-20	ND	7.9
4C-39	DZ4-23	ND	11.4
4C-40	DZ3-142	ND	509
4C-41	DZ3-143	ND	2,081
4D-1	DZ2-395	43	80
4D-2	DZ3-48	24	59
4D-3	DZ3-58	ND	18.5
4D-16	DZ4-21	ND	47
4D-17	DZ4-24	ND	19.7

Compound #	Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
4F-1	DZ3-5	4,120	9,620

Table 2H

Compound #	Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
4B-1	PU-WS8	19.1	ND
4B-2	PU-WS6	403	ND
4B-3	PU-WS7	731	ND
4B-4	PU-WS16	13.7	ND
4B-13	PU-WS19	8.6	ND
4B-14	PU-WS20	<200	ND

Table 2I

Compound #	Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
4E-1	PU-WS3	218.8	ND
4E-2	PU-WS5	285	ND
4E-3	DZ3-39	542	1126
4E-4	DZ3-40	46	93

Table 2J

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
TT-VI-116	ND	394

Table 2K

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
DZ3-30	374	1024
DZ3-32	107	128
DZ3-43	2.6	7.2
DZ3-44	>300	>300
DZ3-45	>300	>300
DZ3-46	4.0	5.5
DZ3-61	ND	5.5

Table 2L

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
DZ3-29	309	740
DZ3-31	89	121
DZ3-41	57	161
DZ3-59	ND	24.6
DZ3-38	23	47
DZ3-141	ND	26,653

Table 2M

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
PU-RK11	ND	34.5
PU-HT165	ND	34.6
PU-HT175	ND	34.8

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
PU-RK12	ND	62.8
DZ3-73	ND	9.4
DZ4-84	45.1	ND

Table 2N

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
HJP18	ND	6.9
TT-VI-53A	ND	5.3
HJP23	46.3	ND
HJP20	ND	3.5

Table 20

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
HJP19	ND	11.2
TT-VI-54A	ND	7.7

Table 2P

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
DZ4-52-N9	ND	97.0

Table 2Q

Name	EC_{50}; binding to JNPL3 brain Hsp90 (nM)	EC_{50}; binding to SKBr3 cell Hsp90 (nM)
PU-WS31	<200	ND
TT-V-138	ND	84
TT-V-139	ND	240
TT-V-140	ND	32

Table 4A

No.	Name
4A-1	**DZ2-388**
	9-(3-(isopropylamino)propyl)-8-(6-phenylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine
4A-2	**DZ2-390**
	8-(6-(4-tert-butylphenyl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine
4A-3	**DZ2-391**
	8-(6-(3,5-bis(trifluoromethyl)phenyl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine
4A-4	**TT-V-47B**
	N1-(3-(6-amino-8-(6-(3,5-bis(trifluoromethyl)phenyl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)propyl)hexane-1,6-diamine
4A-5	**DZ2-392**
	8-(6-(4-(dimethylamino)phenyl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine
4A-6	**DZ3-3**
	9-(3-(isopropylamino)propyl)-8-(6-(4-methoxyphenyl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine
4A-7	**DZ3-6**
	8-(6-(4-bromophenyl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine
4A-8	**DZ3-50**
	4-(6-(6-amino-9-(3-(isopropylamino)propyl)-9H-purin-8-ylthio)benzo[d][1,3]dioxol-5-yl)benzaldehyde
4A-9	4-(2-(6-amino-8-(6-phenylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethyl)piperidine-1-carbaldehyde

No.	Name
4A-10	1-(4-(2-(6-amino-2-fluoro-8-((6-phenylbenzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4A-11	N-(2-((2-(6-amino-8-((6-phenylbenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)amino)ethyl)sulfamide
4A-12	3-(2-(6-amino-8-(6-phenylbenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethylamino)-N-hydroxypropanamide
4A-13	9-(3-aminopropyl)-8-(6-phenylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine

Table 4B

No.	Name
4B-1	**PU-WS8**
	8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine
4B-2	**PU-WS6**
	8-(6-(3,3-dimethylbut-1-ynyl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine
4B-3	**PU-WS7**
	9-(3-(isopropylamino)propyl)-8-(6-(phenylethynyl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine
4B-4	**PU-WS16**
	8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine
4B-5	1-(3-(2-(6-amino-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4B-6	8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9-(2-(1-(methylsulfonyl)piperidin-3-yl)ethyl)-9H-purin-6-amine
6B-7	1-(3-(4-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9H-purin-9-yl)butyl)pyrrolidin-1-yl)ethanone
4B-8	5-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9H-purin-9-yl)pentane-1-sulfonamide
4B-9	3-(2-(6-amino-2-chloro-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidine-1-carbaldehyde
4B-10	3-(2-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9H-purin-9-yl)ethyl)piperidine-1-sulfonamide
4B-11	N-(2-((2-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)amino)ethyl)sulfamide
4B-12	3-(2-(6-amino-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)-N-hydroxypropanamide
4B-13	**PU-WS19**
	8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine
4B-14	**PU-WS20**
	8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine
4B-15	9-(3-aminopropyl)-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine
4B-16	9-(2-aminoethyl)-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine
4B-17	9-(3-(tert-butylamino)propyl)-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine
4B-18	1-(3-(6-amino-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)propyl)pyrrolidin-3-one
4B-19	3-(2-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidine-1-sulfonamide
4B-20	6-(6-amino-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)hexanamide
4B-21	1-(6-amino-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)-3-(tert-butylamino)propan-2-ol
4B-22	6-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9H-purin-9-yl)hexanamide
4B-23	1-(2-((2-(6-amino-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)methyl)pyrrolidin-1-yl)ethanone
4B-24	5-(6-amino-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)pentane-1-sulfonamide
4B-25	1-(3-(2-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4B-26	8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine

No.	Name
4B-27	8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9-(3-(isopropylamino)propyl)-9H-purin-6-amine
4B-28	9-(3-(tert-butytamino)propyl)-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methy])-2-fluoro-9H-purin-6-amine
4B-29	8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9-(2-(1-(methylsulfonyl)piperidin-3-yl)ethyl)-9H-purin-6-amine
4B-30	1-(3-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methy])-2-fluoro-9H-purin-9-yl)propyl)pyrrolidin-3-one
4B-31	8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9-(2-(1-methylpiperidin-3-yl)ethyl)-9H-purin-6-amine
4B-32	8-(6-ethynyloenzo[d][1,3]dioxol-5-ylthio)-9-(2-(1-methylpiperidin-2-yl)ethyl)-9H-purin-6-amine
4B-33	1-(2-((2-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9H-purin-9-yl)ethylamino)methyl)pyrrolidin-1-yl)ethanone
4B-34	8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9-(2-(1-methylpiperidin-3-yl)ethyl)-9H-purin-6-amine
4B-35	8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9-(2-(1-methylpiperidin-2-yl)ethyl)-9H-purin-6-amine

Table 4C

No.	Name
4C-1	**DZ3-4**
	8-((6-(furan-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine
4C-2	**DZ3-27**
	8-((6-(furan)-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine
4C-3	**DZ3-25**
	2-fluoro-8-((6-(furan-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine
4C-4	**DZ3-26**
	2-fluoro-8-((6-(furan-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine
4C-5	**TT5-53A**
	8-((6-(furan-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine
4C-6	**DZ3-33**
	5-(6-((6-amino-9-(3-(isopropylamino)propyl)-9H-purin-8-yl)thio)benzo[d][1,3]diaxol-5-yl)furan-2-carbaldehyde
4C-7	**DZ3-34**
	5-(6-((6-amino-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-8-yl)methyl)benzo[d][1,3]dioxol-5-yl)furan-2-carbaldehyde
4C-8	**DZ3-35**
	9-(3-(isopropylamino)propyl)-8-((6-(5-methylfuran-2-yl)benzo[d][1;3]diexol-5-yl)thio)-9H-purin-6-amine
4C-9	**DZ3-36**
	2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
4C-10	**DZ3-49**
	9-(3-(isopropylamino)propyl)-8-((6-(isoxazol-4-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
4C-11	**DZ3-51**
	2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(isoxazol-4-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
4C-12	8-((6-(5-(aminomethyl)furan-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine
4C-13	8-((6-(5-(aminomethyl)furan-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-6-amine
4C-14	**DZ3-60**
	8-((6-(furan-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine
4C-15	8-(6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine

No.	Name
4C-16	**DZ3-56** 8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine
4C-17	1-(3-(6-amino-2-fluoro-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)propyl)pyrrolidin-3-one
4C-18	8-((6-(5-(aminomethyl)furan-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine
4C-19	1-(3-(2-(6-amino-8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4C-20	8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(2-(1-(methylsulfonyl)piperidin-3-yl)ethyl)-9H-purin-6-amine
4C-21	1-(3-(2-(6-amino-2-fluoro-8-((6-(5-methylfuran-2-yl)benzo[d] [1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4C-22	4-(2-(6-amino-2-fluoro-8-((6-(furan-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidine-1-carbaldehyde
4C-23	1-(3-(6-amino-8-(6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)propyl)pyrrolidin-3-one
4C-24	6-(6-amino-8-(6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)hexanamide
4C-25	6-(6-amino-2-fluoro-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)hexanamide
4C-26	1-(4-(2-(6-amino-2-fluoro-8-((6-(5-methylftlran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4C-27	1-(4-(2-(6-amino-2-chloro-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4C-28	1-(3-(2-(6-amino-8-(6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4C-29	1-(3-(2-(6-amino-2-fluoro-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidin-l-yl)ethanone
4C-30	3-(2-(6-ammo-2-chloro-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidine-1-sulfonamide
4C-31	1-(4-(2-(6-amino-8-((6-(5-(aminomethyl)furan-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4C-32	1-(3-(2-(6-amino-8-((6-(5-(aminomethyl)oxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-2-fluoro-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4C-33	5-(6-amino-2-fluoro-8-((6-(5-methyloxazot-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)pentane-1-sulfonamide
	2-fluoro-9-(3-(isopropylamino)propyl)-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
	9-(3-(tert-butylamino)propyl)-2-fluoro-8-((6-(5-methyloxazol-2-yl)benzo[d] [1,3] dioxol-5-yl)methyl)-9H-purin-6-amine
	N-(2-((2-(6-amino-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)amino)ethyl) sulfamide
	3-(2-(6-amino-8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)-N-hydroxypropanamide
	DZ4-20
	9-(3-(isopropylamino)propyl)-8-((6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
	DZ4-23
	2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
	DZ3-142
	8-((6-(2,3-dihydrofuran-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine
	DZ3-143
	8-((6-(2,3-dihydrofuran-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine

No.	Name
	9-(3-aminopropyl)-8-(6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine
	9-(2-aminoethyl)-2-fluoro-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
	9-(3-(tert-butylamino)propyl)-8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine
	9-(3-(tert-butylamino)propyl)-8-((6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
	1-(4-(2-(6-amino-8-((6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
	8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(1-(methylsulfonyl)piperidin-3-yl)ethyl)-9H-purin-6-amine
	9-(3-(tert-butylamino)propyl)-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
	1-(6-amino-8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)-3-(tert-butylamino)propan-2-ol
	1-(6-amino-8-((6-(5-methloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)-3-(isopropylamino)propan-2-ol
	2-(3-(6-amino-8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)propyl)aziridine-1-carbaldehyde
	5-(6-amino-8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)pentane-1-sulfonamide
	5-(6-amino-8-(6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)pentane-1-sulfonamide
	8-(6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(3-(1-(methylsulfonyl)pyrrolidin-3-yl)propyl)-9H-purin-6-amine
	1-(3-(6-amino-8-(6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)propyl)pyrrolidin-3-one
	9-(3-(tert-butylamino)propyl)-2-fluoro-8-((6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
	5-(6-amino-2-fluoro-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)pentane-1-sulfonamide
	6-(6-amino-2-fluoro-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)hexanamide
	2-fluoro-9-(3-(isopropylamino)propyl)-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
	9-(3-(tert-butylamino)propyl)-2-fluoro-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
	9-(3-aminopropyl)-2-fluoro-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
	9-(3-aminopropyl)-2-fluoro-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine

Table 4D

No.	Name
4D-1	**DZ2-395**
	9-(3-(isopropylamino)propyl)-8-((6-(thiophen-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
4D-2	**DZ3-48**
	2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(thiophen-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
4D-3	**DZ3-58**
	9-(2-(neopentylamino)ethyl)-8-((6-(thiophen-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
4D-4	9-(3-(isopropylamino)propyl)-8-((6-(thiophen-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
4D-5	2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(thiophen-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
4D-6	9-(2-(neopentylamino)ethyl)-8-((6-(thiophen-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
4D-7	1-(4-(2-(6-amino-8-((6-(thiophen-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4D-8	4-(2-(6-amino-8-((6-(thiophen-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidine-1-carbaldehyde
4D-9	1-(4-(2-(6-amino-2-fluoro-8-((6-(thiophen-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone

No.	Name
4D-10	4-(2-(6-amino-2-fluoro-8-((6-(thiophen-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidine-1-carbaldehyde
4D-11	4-(2-(6-amino-8-((6-(thiophen-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidine-1-carbaldehyde
4D-12	4-(2-(6-amino-2-fluoro-8-((6-(thiophen-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidine-1-carbaldehyde
6D-13	4-(2-(6-amino-2-chloro-8-((6-(thiophen-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)ethyl)piperidine-1-carbaldehyde
4D-14	N-(2-((2-(6-amino-8-((6-(thiophen-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)amino)ethyl) sulfamide
4D-15	3-((2-(6-amino-8-((6-(thiophen-2-yl)benzo[d][l,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)amino)-N-hydroxypropanamide
4D-16	**DZ4-21**
	9-(3-(isopropylamino)propyl)-8-((6-(thiazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
4D-17	**DZ4-24**
	2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(thiazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
4D-18	9-(3-aminopropyl)-8-((6-(thiophen-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
4D-19	9-(3-(tert-butylamino)propyl)-8-((6-(thiophen-2-yl)benzo[d][1,3]cioxol-5-yl)thio)-9H-purin-6-amine
4D-20	9-(3-(tert-butylamino)propyl)-8-((6-(thiazol-2-yl)benzo[d][1,3]dioxol-5yl)thio)-9H-purin-6-amine
4D-21	9-(3-(tert-butylamino)propyl)-8-((6-(5-methylthiophen-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
4D-22	9-(3-(tert-butylamino)propyl)-8-((6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine
4D-23	1-(3-(2-(6-amino-8-(6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethyl)piperidin-1-yl)ethanone
4D-24	1-(6-amino-8-((6-(5-methylthiophen-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)-3-(isopropylamino)propan-2-ol
4D-25	1-(6-amino-8-((6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)-3-(isopropylamino)propan-2-ol
4D-26	6-(6-amino-8-(6-(5-methylthiophen-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)hexanamide
4D-27	5-(6-amino-8-(6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)pentane-1-sulfonamide
4D-28	9-(3-(1-(methylsulfonyl)pyrrolidin-3-yl)propyl)-8-(6-(5-methylthiophen-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine
4D-29	2-(2-(6-amino-8-(6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethyl)pyrrolidine-1-carbaldehyde
4D-30	2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(5-methylthiophen-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
4D-31	8-((6-(5-methylthiophen-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine
4D-32	2-fluoro-9-(2-(isobutylamino)ethyl)-8-((6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amine
4D-33	8-((6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amine

Table 4E

No.	Name
4E-1	**PU-WS3**
	6-((6-amino-2-fluoro-9-(3-(isopropylamino)propyl)-9H-purin-8-yl)methyl)benzo[d][1,3]dioxole-5-carbonitrile
4E-2	**PU-WS5**
	6-((6-amino-9-(3-(isopropylamino)propyl)-9H-purin-8-yl)thio)benzo[d][1,3]dioxole-5-carbonitrile
4E-3	**DZ3-39**
	2-(6-((6-amino-9-(3-(isopropylamino)propyl)-9H-purin-8-yl)thio}benzo[d][1,3]dioxol-5-yl)acetonitrile

No.	Name
4E-4	DZ3-40
	2-(6-((6-amino-2-fluoro-9-(2-(isobutylamino)ethyl)-9H-purin-8-yl)methyl)benzo[d][1,3]dioxol-5-yl)acetonitrile
6E-5	N-(2-((2-(6-amino-8-((6-(cyanomethyl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)amino)ethyl)sulfamide
4E-6	3-((2-(6-amino-8-((6-cyanobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)amino)-N-hydroxypropanamide
4E-7	6-((6-amino-2-chloro-9-(3-(isopropylamino)propyl)-9H-purin-8-yl)methyl)benzo[d][1,3]dioxole-5-carbonitrile

Table 4F

No.	Name
4F-1	DZ3-5
	9-(3-(isopropylamino)propyl)-8-(6-(pyridin-4-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine

REFERENCES CITED IN THE DESCRIPTION

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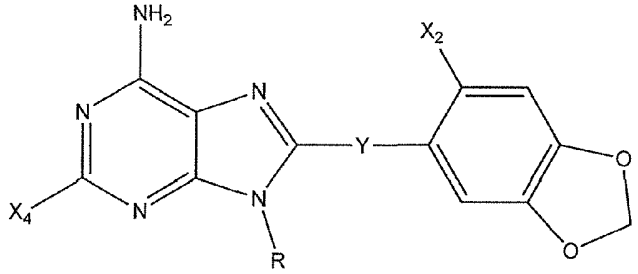
Patentkrav

1. Forbindelse med formlen:



hvor

(a) Y er $-CH_2-$ eller -S-;

(b) X_4 er hydrogen eller halogen; og

(c) X_2 og R er en kombination, der er udvalgt blandt:

(i) X_2 er en substitueret eller ikke-substitueret, lineær, forgrenet eller cyklisk cyanoalkyl, og R er en substitueret eller ikke-substitueret, lineær, forgrenet primær aminoalkyl, sekundær alkylaminoalkyl, tertiær alkylaminoalkyl eller trialkylammonioalkylgruppe; eller

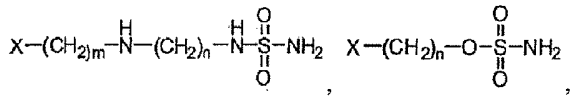
(ii) X_2 er en aryl, en alkynyl, en cycloalkyl eller en cycloalkenylgruppe, og R er:

(a) hydrogen; eller

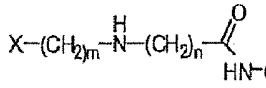
(b) en ligekædet eller forgrenet C_1 til C_{10}-alkyl, C_2 til C_6-alkenyl eller C_2 til C_6-alkynyl, der er usubstitueret eller substitueret; eller

(c) aminoalkyl, sekundær eller tertiær alkylaminoalkyl eller trialkylammonioalkyl;

(d)



eller



hvor m er 2-3, n er 1-6, og X er 9*N*-påhæftningsstedet.

2. Forbindelse ifølge krav 1, hvor X_2 er alkynyl.

3. Forbindelse ifølge krav 2, hvor forbindelsen er udvalgt fra gruppen, der består af: 8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amin; 8-(6-

ethynylbenzo[d][1,3]dioxol-5-ylthio)-9-(2-(isobutylamino)ethyl)-9H-purin-6-amin; N-(2-((2-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)amino)ethyl)sulfamid; 3-(2-(6-amino-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)-N-hydroxypropanamid; 8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amin; 8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluor-9-(2-(isobutylamino)ethyl)-9H-purin-6-amin; 9-(3-aminopropyl)-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amin; 9-(2-aminoethyl)-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amin; 9-(3-(tert-butylamino)propyl)-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amin; 6-(6-amino-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)hexanamid; 1-(6-amino-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)-3-(tert-butylamino)propan-2-ol; 5-(6-amino-8-(6-ethynylbenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)pentan-1-sulfonamid; 5-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluor-9H-purin-9-yl)pentan-1-sulfonamid; 8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluor-9-(2-(isobutylamino)ethyl)-9H-purin-6-amin; 6-(6-amino-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluor-9H-purin-9-yl)hexanamid; 8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluor-9-(2-(neopentylamino)ethyl)-9H-purin-6-amin; 8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluor-9-(3-(isopropylamino)propyl)-9H-purin-6-amin; 9-(3-(tert-butylamino)propyl)-8-((6-ethynylbenzo[d][1,3]dioxol-5-yl)methyl)-2-fluor-9H-purin-6-amin;

4. Forbindelse ifølge krav 1, hvor X_2 er en heteroarylgruppe.

5. Forbindelse ifølge krav 4, hvor X_2 er furanyl.

6. Forbindelse ifølge krav 5, hvor forbindelsen er udvalgt fra gruppen, der består af: 8-((6-(furan-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(3-

(isopropylamino)propyl)-9H-purin-6-amin; 8-((6-(furan-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amin; 5-(6-((6-amino-9-(3-(isopropylamino)propyl)-9H-purin-8-yl)thio)benzo[d][1,3]dioxol-5-yl)furan-2-carbaldehyd; 9-(3-(isopropylamino)propyl)-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amin; 8-((6-(5-(aminomethyl)furan-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amin; 8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amin; 8-((6-(5-(aminomethyl)furan-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amin; N-(2-((2-(6-amino-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)amino)ethyl)-sulfamid; 3-(2-(6-amino-8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)-N-hydroxypropanamid; 9-(3-(tert-butylamino)propyl)-8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amin; 1-(6-amino-8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)-3-(tert-butylamino)propan-2-ol; 5-(6-amino-8-(6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)pentan-1-sulfonamid; 2-fluor-8-((6-(furan-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9-(2-(isobutylamino)ethyl)-9H-purin-6-amin; 5-(6-((6-amino-2-fluor-9-(2-(isobutylamino)ethyl)-9H-purin-8-yl)methyl)benzo[d][1,3]dioxol-5-yl)furan-2-carbaldehyd; 2-fluor-9-(2-(isobutylamino)ethyl)-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin; 8-((6-(5-(aminomethyl)furan-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-2-fluor-9-(2-(isobutylamino)ethyl)-9H-purin-6-amin; 5-(6-amino-2-fluor-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)pentan-1-sulfonamid; 6-(6-amino-2-fluor-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)hexanamid; 2-fluor-9-(3-(isopropylamino)propyl)-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin; 9-(3-(tert-butylamino)propyl)-2-fluor-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin; og 9-(3-

aminopropyl)-2-fluor-8-((6-(5-methylfuran-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin.

7. Forbindelse ifølge krav 4, hvor X_2 er oxazolyl.

8. Forbindelse ifølge krav 7, hvor forbindelsen er udvalgt fra gruppen, der består af: 8-(6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amin; 6-(6-amino-8-(6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)hexanamid; 9-(3-(isopropylamino)propyl)-8-((6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amin; 9-(3-aminopropyl)-8-(6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amin; 9-(3-(tert-butylamino)propyl)-8-((6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amin; 9-(3-(tert-butylamino)propyl)-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amin; 1-(6-amino-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)-3-(isopropylamino)propan-2-ol; 5-(6-amino-8-(6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)pentan-1-sulfonamid; 2-fluor-9-(2-(isobutylamino)ethyl)-8-((6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin; 6-(6-amino-2-fluor-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)hexanamid; 5-(6-amino-2-fluor-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-9-yl)pentan-1-sulfonamid; 2-fluor-9-(3-(isopropylamino)propyl)-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin; 9-(3-(tert-butylamino)propyl)-2-fluor-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin; 9-(3-(tert-butylamino)propyl)-2-fluor-8-((6-(oxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin; og 9-(3-aminopropyl)-2-fluor-8-((6-(5-methyloxazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin.

9. Forbindelse ifølge krav 4, hvor X_2 er pyrazolyl.

10. Forbindelse ifølge krav 9, hvor forbindelsen er udvalgt

fra gruppen, der består af: 8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amin; 8-((6-(5-methyl-1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amin; 8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amin; N-(2-((2-(8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-6-amino-9H-purin-9-yl)ethyl)amino)ethyl)-sulfamid; N-(2-((2-(8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-6-amino-9H-purin-9-yl)ethyl)amino)ethyl)-sulfamid; 3-((2-(8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-6-amino-9H-purin-9-yl)ethyl)amino)-N-hydroxypropanamid; 8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(3-aminopropyl)-9H-purin-6-amin; 8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(3-(tert-butylamino)propyl)-9H-purin-6-amin; 1-(8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)thio)-6-amino-9H-purin-9-yl)-3-(isopropylamino)propan-2-ol; 5-(8-(6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-ylthio)-6-amino-9H-purin-9-yl)pentan-1-sulfonamid; 6-(8-(6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-ylthio)-6-amino-9H-purin-9-yl)hexanamid; 8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-2-fluor-9-(2-(isobutylamino)ethyl)-9H-purin-6-amin; 2-fluor-9-(2-(isobutylamino)ethyl)-8-((6-(5-methyl-1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin; 8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9-(2-aminoethyl)-2-fluor-9H-purin-6-amin; 5-(8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-6-amino-2-fluor-9H-purin-9-yl)pentan-1-sulfonamid; 6-(8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-6-amino-2-fluor-9H-purin-9-yl)hexanamid; og 8-((6-(1H-pyrazol-3-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9-(3-(tert-butylamino)propyl)-2-fluor-9H-purin-6-amin.

11. Forbindelse ifølge krav 4, hvor X_2 er furan, thiophen, 3-pyrazol, oxazol eller thiazolyl.

12. Forbindelse ifølge krav 11, hvor forbindelsen er udvalgt

fra gruppen, der består af: 9-(3-(isopropylamino)propyl)-8-((6-(thiazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amin; 2-fluor-9-(2-(isobutylamino)ethyl)-8-((6-(thiazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin; 9-(3-(tert-butylamino)propyl)-8-((6-(thiazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amin; 9-(3-(tert-butylamino)propyl)-8-((6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amin; 1-(6-amino-8-((6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)-3-(isopropylamino)propan-2-ol; 5-(6-amino-8-(6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)pentan-1-sulfonamid; 2-fluor-9-(2-(isobutylamino)ethyl)-8-((6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-yl)methyl)-9H-purin-6-amin; og 8-((6-(5-methylthiazol-2-yl)benzo[d][1,3]dioxol-5-yl)thio)-9-(2-(neopentylamino)ethyl)-9H-purin-6-amin.

13. Forbindelse ifølge krav 1, hvor R er 2-(methyl, t-butylamino)ethyl, 2-(methyl, isopropylamino)ethyl, 3-(neopentylamino)propyl, 2-(isobutylamino)ethyl, 2-(ethyl, isopropylamino)ethyl, 3-(isopropylamino)propyl, 3-(t-butylamino)propyl, 2-(isopropylamino)ethyl, 2-(hydroxyethyl, isopropylamino)ethyl, 3-(ethylamino)propyl, 3-(ethyl, methylamino)propyl, 2-(neopentylamino)ethyl, 3-(methyl, isopropylamino)propyl, 3-(ethyl, isopropylamino)propyl, 3-(hydroxyethyl, isopropylamino)propyl, 3-(methyl, propargylamino)propyl, 2-(methyl, propargylamino)ethyl, 3-(allyl, methylamino)propyl og 2-(methyl, isobutylamino)ethyl.

14. Forbindelse ifølge krav 13, hvor R er 3-(isopropylamino)propyl.

15. Forbindelse ifølge krav 13 eller 14, hvor Y er S, X_4 er H, og X_2 er acetylenyl, 2-furanyl, 3-furanyl, 5-methyl-2-furanyl, 2-thiophen, 3-thiophen, 2-pyrazolyl, 3-pyrazolyl, 2-thiazolyl, 5-methyl-2-thiazolyl, 2-oxazolyl, 5-methyl-2-oxazolyl eller eventuelt substitueret imidazol.

16. Forbindelse ifølge krav 13 eller 14, hvor Y er S, X_4 er H, og X_2 er acetylenyl, 2-furanyl, 3-furanyl, 5-methyl-2-furanyl, 2-pyrazolyl, 3-pyrazolyl, 2-thiazolyl, 5-methyl-2-thiazolyl, 2-oxazolyl eller 5-methyl-2-oxazolyl.

17. Anvendelse af en forbindelse ifølge et hvilket som helst af ovennævnte krav til formulering af en farmaceutisk sammensætning til inhibering af Hsp90.

18. Anvendelse af en forbindelse ifølge et hvilket som helst af kravene 1-16 til formulering af en farmaceutisk sammensætning til behandling af cancer eller neurodegenerativ sygdom.

DRAWINGS

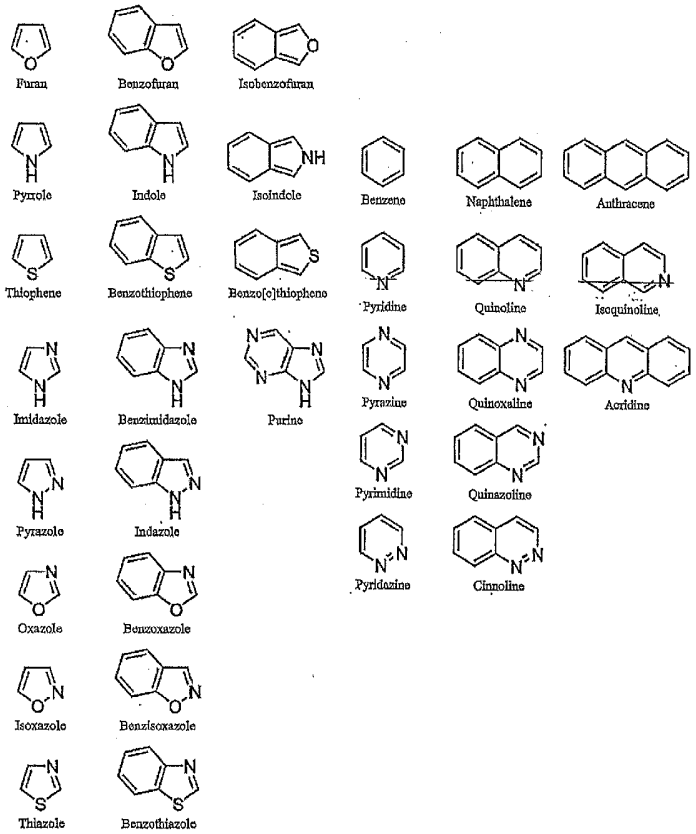


Fig. 1

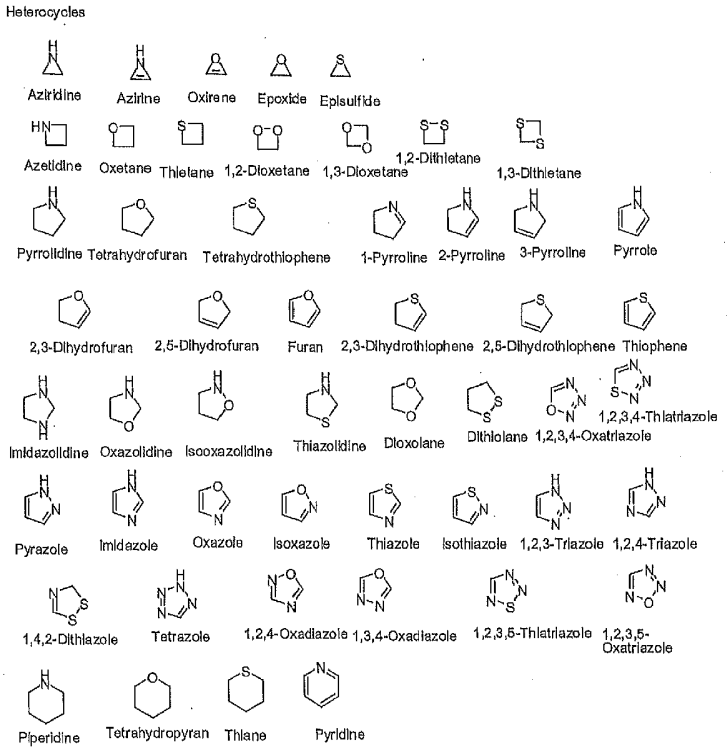
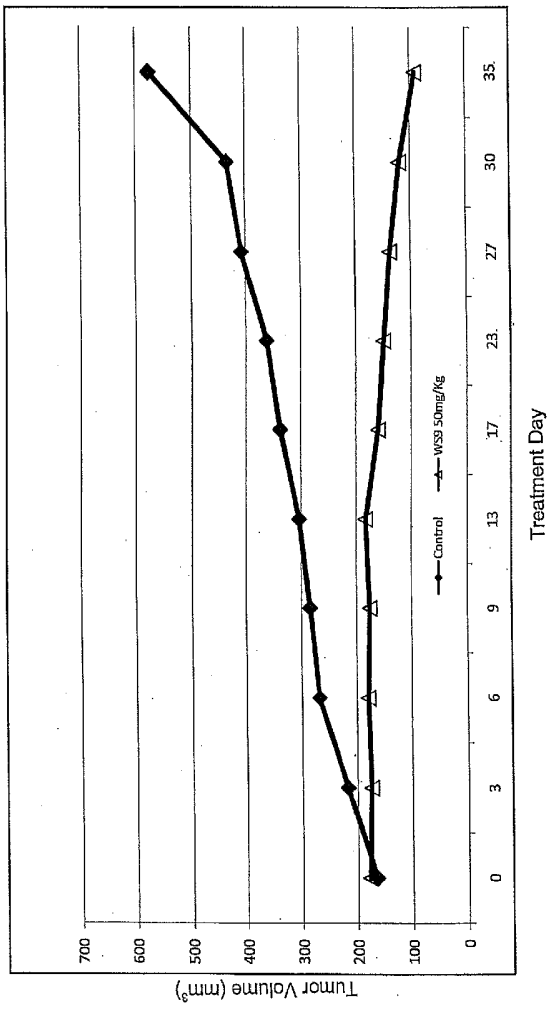

Heterocycles
Aziridine
Azirine
Oxirene
Epoxide
Episulfide
Azetidine
Oxetane
Thietane
1,2-Dioxetane
1,3-Dioxetane
1,2-Dithietane
1,3-Dithietane
Pyrrolidine
Tetrahydrofuran
Tetrahydrothiophene
1-Pyrroline
2-Pyrroline
3-Pyrroline
Pyrrole
2,3-Dihydrofuran
2,5-Dihydrofuran
Furan
2,3-Dihydrothiophene
2,5-Dihydrothiophene
Thiophene
Imidazolidine
Oxazolidine
Isooxazolidine
Thiazolidine
Dioxolane
Dithiolane
1,2,3,4-Oxatriazole
1,2,3,4-Thiatriazole
Pyrazole
Imidazole
Oxazole
Isoxazole
Thiazole
Isothiazole
1,2,3-Triazole
1,2,4-Triazole
1,4,2-Dithiazole
Tetrazole
1,2,4-Oxadiazole
1,3,4-Oxadiazole
1,2,3,5-Thiatriazole
1,2,3,5-Oxatriazole
Piperidine
Tetrahydropyran
Thiane
Pyridine

Fig. 2

Fig. 3


Tumor Volume (mm³)
700
600
500
400
300
200
100
0
0
3
6
9
13
17
23
27
30
35
Treatment Day
Control
WS9 50mg/kg