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PREPARATION OF A DIVERSE PURINE-SCAFFOLD LIBRARY VIA ONE-STEP PALLADIUM CATALYZED CROSS-COUPLING

Tony Taldone,[a,*] Danuta Zatorska,[a] Hardik J. Patel,[a] Weilin Sun,[a] Maulik R. Patel,[a] and Gabriela Chiosis[a,b,c]

a. Molecular Pharmacology and Chemistry Program, Sloan-Kettering Institute, New York, NY, U.S.A. Email: taldonet@mskcc.org
b. Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, U.S.A.
c. Department of Pharmacology, Weill Cornell Medical College, New York, NY U.S.A.

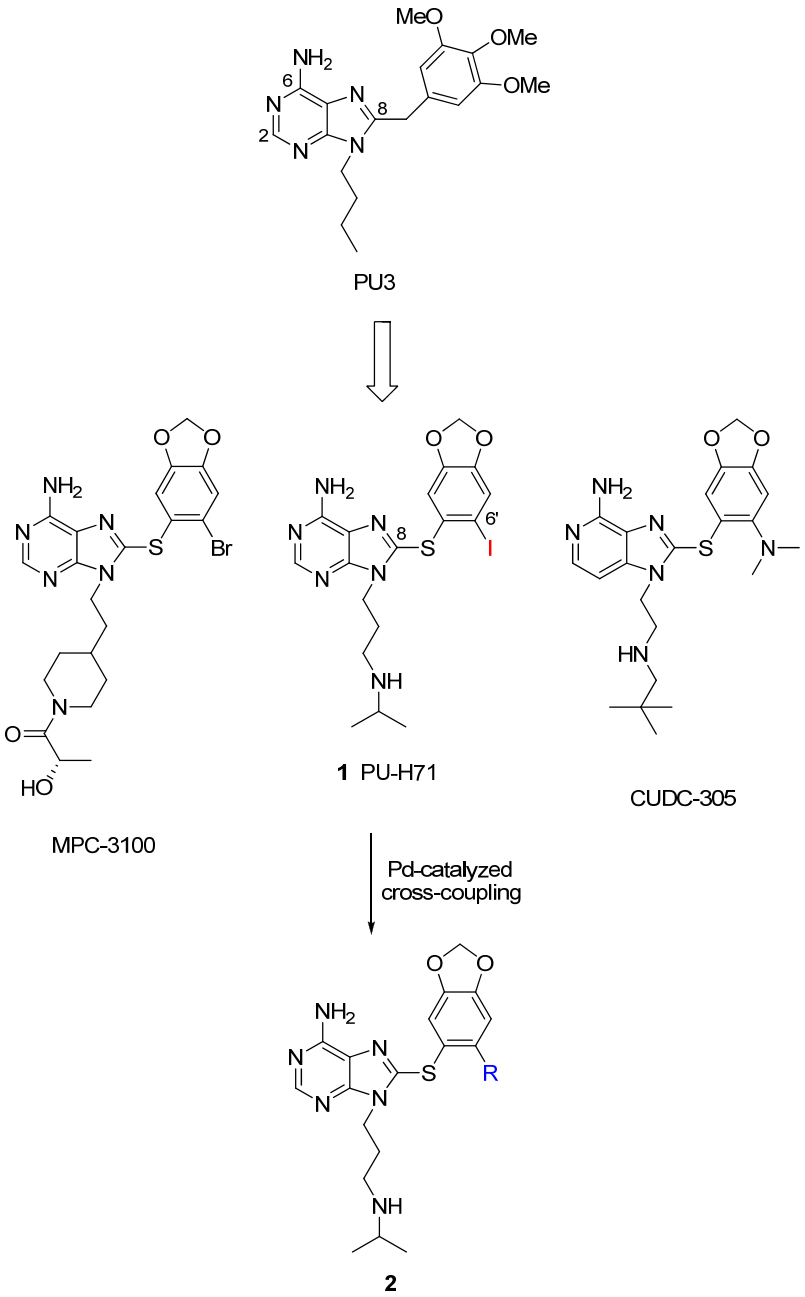
Abstract – In our ongoing efforts to prepare Hsp90 inhibitors, various cross-coupling reactions (Suzuki, Stille, Heck, and Sonogashira) were used to construct a diverse library of substituted purines in a single step from PU-H71 (**1**). We show that these reactions, particularly Suzuki coupling, are highly efficient, do not require protection of the pendant amine, and due to the wide variety of commercially available substrates, allow for the rapid development of a diverse purine library. The products derived from these reactions will enable us to explore the chemical space occupied by the key 6'-iodine of PU-H71 through molecules with diverse physical and chemical properties with the potential to be useful for diseases in which Hsp90 is implicated.

INTRODUCTION

The biological significance of purines and their derivatives as the endogenous ligand to a multitude of receptors, kinases, and ATPases implicated in disease has made it an attractive scaffold for chemical modification.[1] As a result of this, as well as its ease of access to structural diversity, the purine ring has become a privileged structure in medicinal chemistry. Towards this goal, cross-coupling reactions have been used extensively to directly attach C-substituents (i.e. aryl, heteroaryl, alkenyl, alkyl) at positions 2, 6, or 8 of the purine-scaffold starting from the corresponding halopurine.[2-4] In addition, these reactions may also be used to introduce diversity to purine-scaffolds whereby the purine ring remains unmodified.

A protein of significant interest to us that requires ATP for its function is heat shock protein 90 (Hsp90). Hsp90 is a molecular chaperone which assists in the conformational activation of its client proteins. Many of its clients (i.e. HER2, EGFR, mutant ER, HIF1α, Raf-1, AKT and mutant p53) function in the

development and progression of cancer. As a result of this, as well as the ability to simultaneously inhibit multiple oncogenic signals, Hsp90 has emerged as an intriguing target in cancer and potentially in neurodegenerative diseases.[5,6] One class of Hsp90 inhibitor discovered through rational design is based on the purine-scaffold, and in particular on 8-substituted adenines, as exemplified by the prototype PU3 (Scheme 1).[7] Extensive medicinal chemistry efforts aimed at optimizing the potency and pharmacokinetic properties of PU3 have resulted in a number of agents currently in clinical trials for cancer including PU-H71 (**1**), MPC-3100 and CUDC-305 (Scheme 1).[8] Each of these molecules have in common a purine or



Scheme 1. Development of clinical agents targeting Hsp90 derived from PU3 and modifications to the 6'-position of **1** through Pd-catalyzed cross-coupling

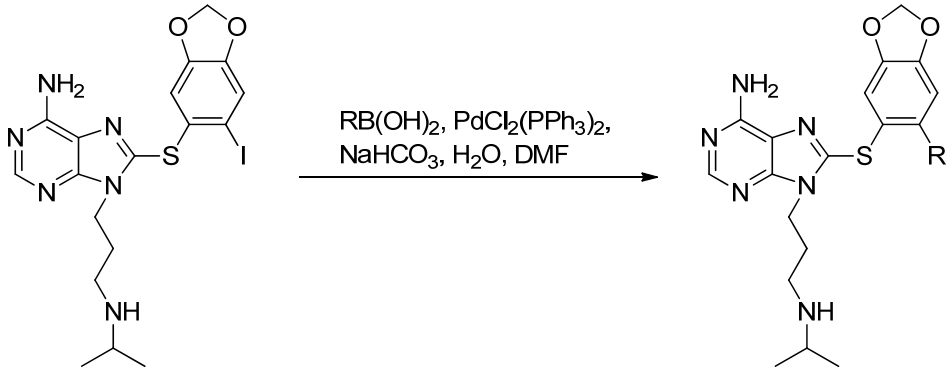
purine-like core attached to a benzo[*d*][1,3]dioxolyl moiety at the 8-position through a sulfur linker. The benzo[*d*][1,3]dioxolyl moiety is substituted with a relatively small hydrophobic group in the 6'-position such as iodine, bromine or dimethylamine, which combined occupies a hydrophobic pocket of Hsp90 where it makes many critical interactions.[9] The 6'-position, key for high-affinity binding to Hsp90 for this scaffold, has largely been unexplored because chemistry has not yet been developed. The presence of iodine in the 8-thioaryl substituent of **1** offered to us the intriguing possibility of performing single-step metal catalyzed cross-coupling reactions in an attempt to create a targeted and diverse library exploring the chemical space around the 6'-position (**2**; Scheme 1). In this paper we show that the Suzuki, Stille, Heck and Sonogashira coupling reactions can be used with great effect to generate a focused library of 6'-substituted 8-(benzo[*d*][1,3]dioxol-5-yl)thio purine analogs of the potent Hsp90 inhibitor PU-H71 (**1**) in a single step without the need for wasteful protection-deprotection steps (Scheme 1).

RESULTS AND DISCUSSION

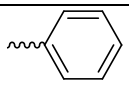
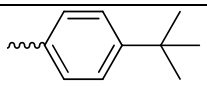
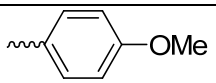
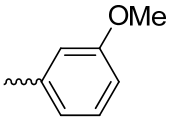
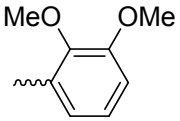
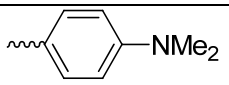
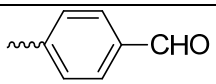
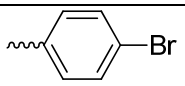
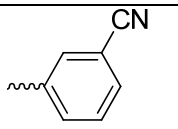
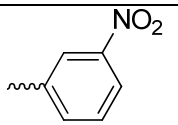
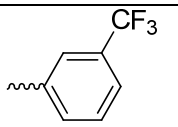
Palladium catalyzed cross-coupling reactions have revolutionized the field of organic synthesis by enabling for the efficient construction of carbon-carbon bonds under mild conditions and with high functional group tolerance.[10] Suzuki, Stille, Heck and Sonogashira coupling are some of the most commonly applied palladium-catalyzed cross-coupling reactions and their usefulness extends to the synthesis of complex natural products and of biologically active molecules. In this regard, these reactions have been used to construct novel scaffolds and to investigate structure activity relationships (SARs) through the rapid development of diverse molecular libraries. While there are numerous palladium catalyzed cross-coupling reactions available, we have chosen to focus on the Suzuki, Stille, Heck and Sonogashira reactions. Combined, these reactions complement one another and have enabled us access to a wide variety of derivatives of PU-H71 (**1**) through the direct substitution of the 6'-iodine on the 8-aryl ring (Tables 1-4). We show that these reactions are applicable to a complex heterocycle such as **1** and that they are tolerant of the secondary amine, thereby avoiding the necessity of tedious protection-deprotection steps.

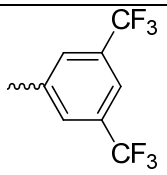
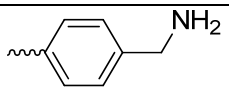
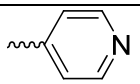
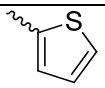
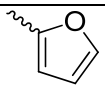
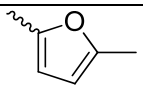
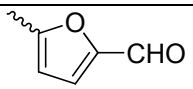
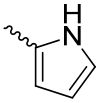
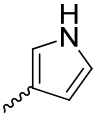
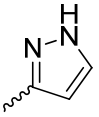
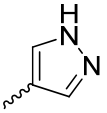
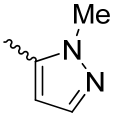
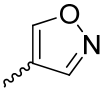
Our general conditions for Suzuki coupling were heating a mixture of **1** with boronic acid (1.5-3 eq.), $PdCl_2(PPh_3)_2$ (10-20 mol%) and $NaHCO_3$ (3 eq.) in DMF/H_2O at 90 °C for 2-24 h (Table 1). For the most part, 1.5 eq. of boronic acid and 10 mol% of $PdCl_2(PPh_3)_2$ were sufficient, however, in cases where the reaction was noticeably sluggish, additional catalyst and/or boronic acid was added to ensure complete consumption of **1**. Progress of the reaction was monitored by LC-MS as TLC proved inadequate for many of the reactions. Accordingly, it was essential to ensure complete reaction in order to efficiently isolate pure product. Therefore, the conditions reported including reaction time have not been optimized for yield, but rather reflect our requirement for complete consumption of starting material. As can be seen in Table 1, a

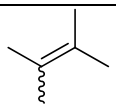
Table 1. Suzuki-Miyaura coupling of **1**



1 **3-29**

Compound	R	conditions	yield (%)
3		90 °C, 4 h	73
4		90 °C, 3 h	83
5		90 °C, 4 h	71
6		90 °C, 9 h	71
7		90 °C, 9 h	77
8		90 °C, 3 h	85
9		90 °C, 4 h	66
10		90 °C, 4 h	44
11		90 °C, 20 h	64
12		90 °C, 20 h	69
13		90 °C, 24 h	54

14		90 °C, 3 h	70
15		90 °C, 20 h	30[a]
16		90 °C, 4 h	55
17		90 °C, 5 h	45
18		90 °C, 4 h	72
19		90 °C, 4 h	42[b]
20		90 °C, 4 h	34
21		90 °C, 4 h	90
22		90 °C, 4 h	22[c]
23		90 °C, 4 h	30[b,c]
24		90 °C, 4 h	8
25		90 °C, 4 h	53[b,c]
26		90 °C, 2 h	74[b]
27		rt, 24 h	43[d]
28	-CH_2CN	90 °C, 4 h	49[d]

29		90 °C, 7 h	66

a. The primary amino formyl product (-CH_2NHCHO) was also obtained in 17% yield.
b. from boronic acid pinacol ester
c. from Boc protected boronic acid or pinacol ester
d. from reaction with 4-isoxazoleboronic acid pinacol ester

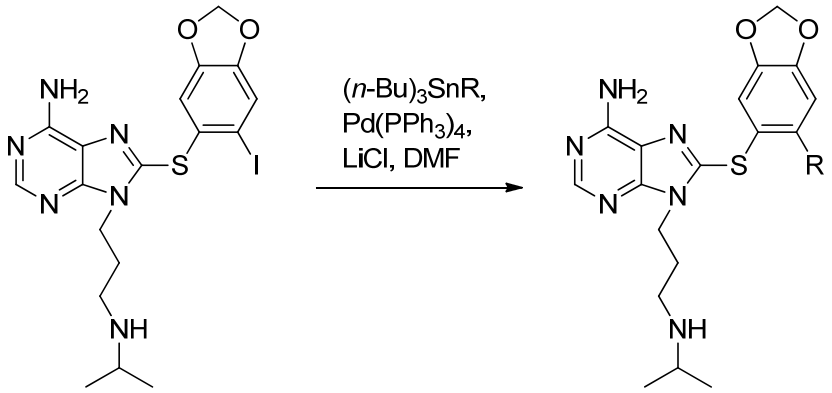
large number of products were obtained from the reaction of **1** with 5- and 6-membered aromatic and heteroaromatic boronic acids as well as with an alkenyl boronic acid.

Reaction of **1** with phenylboronic acid and 4-*tert*-butylphenylboronic acid yielded **3** and **4**, respectively, in good yields. The reaction was tolerant to a wide variety of functional groups and was unaffected by the presence of electron donating or withdrawing groups on the phenyl ring. The 4-methoxy, 3-methoxy, 2,3-dimethoxy and 4-dimethylamino derivatives **5-8** were each prepared in good yield. The 4-formyl and 4-bromo derivatives **9-10**, as well as the strongly electron withdrawing 3-cyano, 3-nitro, 3-trifluoromethyl and 3,5-di-trifluoromethyl derivatives **11-14** were formed in moderate to good yields. The reaction of **1** with 4-aminomethylphenylboronic acid yielded **15** in 30% and its *N*-formyl derivative in 17% as a by-product from the further reaction of the primary amine with the DMF solvent. Heterocyclic boronic acids also reacted with **1** to give pyridine **16**, thiophene **17**, furans **18-21**, pyrroles **22-23**, and pyrazoles **24-26**. Under the general conditions employed, the product **27** desired in the reaction with 4-isoxazoleboronic acid pinacol ester was not obtained. Instead, nitrile **28** was isolated, presumably as a result of CO elimination from isoxazole **27**, in 49% yield. A similar occurrence has been mentioned previously in the coupling of 4-isoxazoleboronic acid pinacol ester with a fused 2-bromoimidazole.[11] Furthermore, acetonitrile and CO were identified as the major products from the thermal decomposition of isoxazole.[12] In an attempt to isolate isoxazole **27**, the reaction temperature was lowered to 60 °C, however, an inseperable mixture of isoxazole **27** and nitrile **28** was obtained in a ratio of 71:29, respectively, as determined by LC-MS. However, conducting the reaction at rt for 24 h yielded **27** in 43% yield with no formation of nitrile **28**.

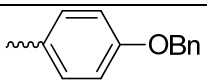
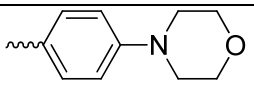
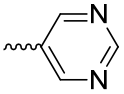
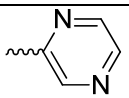
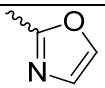
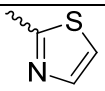
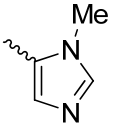
While reaction of **1** with a substituted alkenyl boronic acid yielded vinylic compound **29** in 66% yield, alkyl boronic acids failed to react under our general conditions. Reactions with methylboronic acid, 2-methylpropylboronic acid, phenethylboronic acid and cyclopropylboronic acid resulted in no product as determined by LC-MS. Using conditions previously described as optimal for the coupling of cyclopropylboronic acid with aryl bromides (($Pd(OAc)_2$, tricyclohexylphosphine, toluene, H_2O, K_3PO_4, 100 °C)[13] resulted in no reaction after 3 h. Prolonged heating for 24-48 h with excess cyclopropylboronic acid (3 eq.), $Pd(OAc)_2$, (20 mol%) and tricyclohexylphosphine (0.2 eq.) resulted in an inseparable mixture of unreacted starting material **1**, product and deiodinated reduced material.

Although Stille coupling accomplishes similar transformations to Suzuki coupling, they complement each other through the availability of respective starting materials and hence expand the scope of products that may be obtained in one-step reactions. Our initial attempts of Stille coupling aryl tin compounds with **1** or even Boc-protected **1** were unsuccessful and resulted in significant protodestannylation as well as

Table 2. Stille coupling of **1**



1 **30-38**

compound	R	conditions	yield (%)
30		100 °C, 18 h	42
31		100 °C, 18 h	48
32		100 °C, 18 h	33
33		100 °C, 18 h	46
34		90 °C, 18 h	78
35		90 °C, 18 h	64
36		90 °C, 18 h	31
37		90 °C, 18 h	68
38		90 °C, 18 h	72

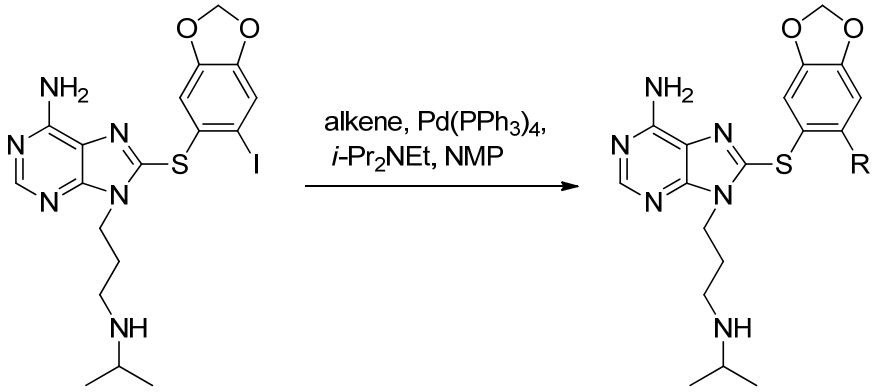
unreacted starting material, with only very minor amount of product detectable. However, the addition of LiCl to the reaction resulted in smooth conversion to product with no detectable protodestannylation and was the key to the success of this reaction. LiCl is commonly used to promote Stille couplings[14,15] and is believed to function through the exchange of chloride ion with the coordinated iodide ion in the oxidative addition product. The resulting chloro complex facilitates transmetalation with arylstannane through the formation of stable Bu_3SnCl. The general conditions we adopted ((n-Bu)$_3$SnR (4 eq.), LiCl (2 eq.), $Pd(PPh_3)_4$ (10-20 mol%), DMF, 90-100 °C, 18 h) were used to prepare a number of 5- and 6-membered aromatics as well as the vinyl and allyl derivatives (Table 2). In order to demonstrate the usefulness of Stille coupling and to expand the diversity of our library, the compounds formed (Table 2) were chosen to be distinct from those produced by Suzuki coupling (Table 1).

The 4-benzyloxy and 4-morpholine substituted phenyl derivatives **30** and **31**, respectively, as well as pyrimidine **32** and pyrazine **33** were obtained by reaction with respective tri-*n*-butyltin compounds in moderate yields. Other heterocycles including oxazole **34**, thiazole **35**, and imidazole **36** were similarly prepared. The vinyl and allyl groups can also be added through Stille coupling by reaction with tri-*n*-butylvinyltin or tri-*n*-butylallyltin to give **37** or **38**, respectively. Although Stille and Suzuki reactions complement each other well, a major disadvantage of the Stille reaction is the use of toxic organotin compounds. In comparison to the boronic acids used in Suzuki coupling, organotin compounds are much more toxic and must be handled with great care.

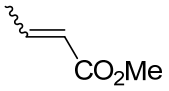
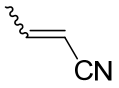
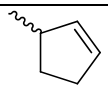
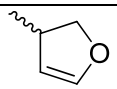
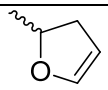
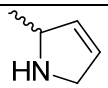
Our general conditions for Heck coupling consisted of heating a mixture of purine **1** with alkene (1.1-20 eq.), $Pd(PPh_3)_4$ (10-20 mol%) and *N,N*-diisopropylethylamine (1.2-2 eq.) in NMP at 55-100 °C for 20-24 h (Table 3). Reaction with methyl acrylate and acrylonitrile yielded the *trans*-substituted products **39** and **40**, respectively. As expected, reaction with each of the cyclic alkenes occurred with migration of the double bond.[16,17] The major isolatable product obtained from the reaction with cyclopentene is the 2,3-alkene **41**, whereas in the reaction with 2,5-dihydrofuran, the double bond flips to the 2,3-position to give **42**. In the case of the unsymmetrical alkenes, enol ether 2,3-dihydrofuran and *N*-protected enamine 2,3-dihydropyrrole, reaction occurs at the carbon adjacent to the heteroatom. **43** was obtained as the major product from reaction with 2,3-dihydrofuran, while reaction with *N*-Boc-2,3-dihydropyrrole results in the double bond flipping to the 3,4-position of the pyrrolidine ring, yielding **44** as the major product following deprotection.

1 can also undergo the Sonogashira reaction with a variety of alkynes without protection of the amine in moderate to good yields (Table 4). Our general conditions consisted of heating a mixture of purine **1** with alkyne (2-2.5 eq.), $PdCl_2(PPh_3)_2$ (15 mol%), CuI (0.5 eq.) and triethylamine (5 eq.) in DMF at 90-100 °C for 24 h (Table 4). The unsubstituted alkyne derivative **45** was prepared from trimethylsilanylacetylene

Table 3. Heck coupling of **1**



1 **39-44**

compound	R	conditions	yield (%)
39		100 °C, 24 h	35
40		100 °C, 24 h	51
41		100 °C, 20 h	35[a]
42		55 °C, 20 h	19[b]
43		55 °C, 20 h	26[c]
44		100 °C, 20 h	23[d]

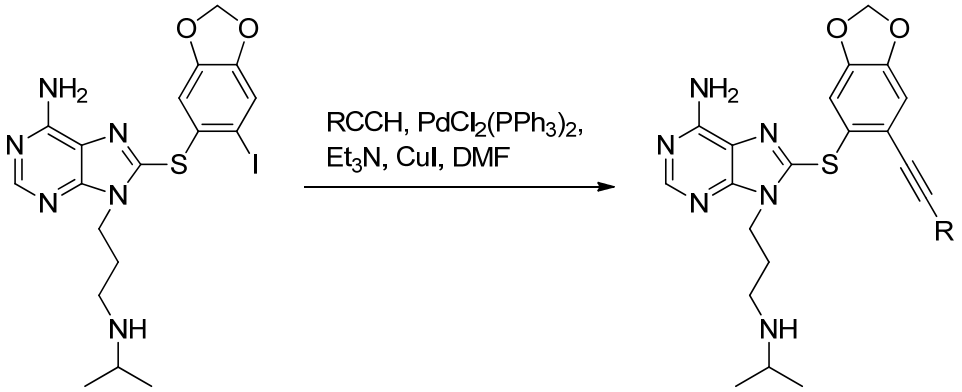
a. from cyclopentene
b. from 2,5-dihydrofuran
c. from 2,3-dihydrofuran
d. from *N*-Boc-2,3-dihydro-1*H*-pyrrole

following removal of the trimethylsilyl group. Other acetylene derivatives of **1** obtained in moderate to good yields using our general conditions include *n*-butyl **46**, *t*-butyl **47**, cyclopentyl **48**, cyclohexyl **49** and phenyl **50**.

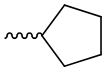
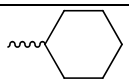
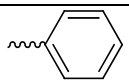
CONCLUSION

We have shown that Pd-catalyzed cross-coupling reactions can be used to prepare a library of derivatives of PU-H71 (**1**) in a single step with commercially available reagents. These reactions occur on an "advanced intermediate" without the need of protecting groups and enable for late stage introduction of chemical diversity to generate a focused library of 6'-substituted 8-(benzo[*d*][1,3]dioxol-5-yl)thio purines. Suzuki

Table 4. Sonogashira coupling of **1**



1 **45-50**

compound	R	conditions	yield (%)
45	H	90 °C, 24 h	69[a]
46	—$(CH_2)_3Me$	100 °C, 24 h	66
47		90 °C, 24 h	77
48		100 °C, 24 h	55
49		100 °C, 24 h	46
50		100 °C, 24 h	61

a. from trimethylsilylacetylene

and Stille coupling were used to introduce a variety of aryl or alkenyl groups to **1**. Heck coupling enabled for the reaction with a variety of olefins, while Sonogashira coupling was used to introduce a variety of alkynes. In general, Suzuki coupling occurred with smooth conversion to the desired product and only in the case of 4-isoxazoleboronic acid pinacol ester was the expected product **27** not isolated using the general conditions. However, performing the reaction at rt allowed for the isolation of **27** and prevented its decomposition to nitrile **28**. In the case of Stille coupling, the addition of LiCl was found to be essential for the success of the reaction by enabling efficient transmetalation. The wide variety and ready availability of boronic acids, as well as their non-toxic nature, has made Suzuki coupling the most useful reaction of those reported here to construct the library of substituted purines in a single step from PU-H71 (**1**). Because of the significance of **1** as a potent Hsp90 inhibitor which has entered clinical trials as an

anticancer agent,[8] we believe that this library has significant value for biological investigations which Hsp90 has been associated with.

EXPERIMENTAL

GENERAL METHODS

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 or 600 MHz instrument. Chemical shifts are reported in δ values in ppm downfield from TMS as the internal standard. ^{1}H 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 (HRMS) 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 min 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 min at 1.0 mL/min. PU-H71 was prepared as previously reported.[18] All reagents were purchased from Aldrich, Acros, Combi-blocks or Frontier Scientific.

SUZUKI-MIYAURA COUPLING

General conditions. Boronic acid or pinacol ester (1.5-3 eq.) was added to **1** (30 mg, 0.0585 mmol, 1 eq.) and $NaHCO_3$ (3 eq.) in a 10 mL RBF equipped with a magnetic stir bar and rubber septum. 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 min. Then H_2O (0.1 mL) and $PdCl_2(PPh_3)_2$ (10-20 mol%) were added and the reaction mixture was heated under nitrogen at 90 °C for 2-24 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC to yield compounds **3-26**, **28** and **29**. **27** was obtained by performing the reaction at rt as is described below.

9-(3-(Isopropylamino)propyl)-8-(6-phenylbenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (3). ^{1}H 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.

8-(6-(4-*tert*-Butylphenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (4). ^{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.

9-(3-(Isopropylamino)propyl)-8-(6-(4-methoxyphenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (5). ^{1}H 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.

9-(3-(Isopropylamino)propyl)-8-(6-(3-methoxyphenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (6). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.16 (t, J = 8.0 Hz, 1H), 6.91 (s, 1H), 6.73-6.81 (m, 3H), 6.70 (s, 1H), 5.93 (s, 2H), 5.82 (br s, 2H), 3.91 (t, J = 6.9 Hz, 2H), 3.63 (s, 3H), 2.59 (septet, J = 6.2 Hz, 1H), 2.32 (t, J = 6.8 Hz, 2H), 1.66-1.75 (m, 2H), 0.93 (d, J = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 154.9, 153.2, 152.1, 149.2, 148.3, 142.1, 139.8, 129.7, 122.3, 121.4, 120.5, 115.5, 113.9, 111.5, 102.6, 55.8, 49.4, 44.2, 41.8, 30.5, 23.4; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{25}H_{29}N_6O_3S$, 493.2022; found 493.2036.

8-(6-(2,3-Dimethoxyphenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (7). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 6.88-6.94 (m, 2H), 6.86 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 6.62 (d, J = 7.5 Hz, 1H), 5.92 (s, 2H), 5.88 (br s, 2H), 3.75-4.05 (m, 2H), 3.82 (s, 3H), 3.54 (s, 3H), 2.59 (septet, J = 6.2 Hz, 1H), 2.30 (t, J = 6.6 Hz, 2H), 1.64-1.74 (m, 2H), 0.93 (d, J = 6.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 153.4, 153.2, 152.2, 148.8, 148.4, 148.3, 147.3, 135.5, 134.9, 124.3, 123.3, 122.9, 120.5, 113.5, 112.9, 111.6, 102.5, 61.4, 56.5, 49.4, 44.2, 41.7, 30.4, 23.3; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{26}H_{31}N_6O_4S$, 523.2128; found 523.2107.

8-(6-(4-(Dimethylamino)phenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (8). ^{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.

4-(6-(6-Amino-9-(3-(isopropylamino)propyl)-9*H*-purin-8-ylthio)benzo[*d*][1,3]dioxol-5-yl)benzaldehyde (9). ^{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.

8-(6-(4-Bromophenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (10). ^{1}H 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.

3-(6-(6-Amino-9-(3-(isopropylamino)propyl)-9*H*-purin-8-ylthio)benzo[*d*][1,3]dioxol-5-yl)benzonitrile (11). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.55 (s, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.31-7.36 (m, 1H), 6.95 (s, 1H), 6.73 (s, 1H), 5.97 (s, 2H), 5.74 (br s, 2H), 3.97 (t, *J* = 6.9 Hz, 2H), 2.63 (septet, *J* = 6.2 Hz, 1H), 2.39 (t, *J* = 6.7 Hz, 2H), 1.72-1.81 (m, 2H), 0.96 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 153.2, 152.2, 149.8, 149.0, 148.0, 142.0, 138.0, 134.4, 133.6, 131.8, 129.5, 120.8, 120.5, 119.1, 114.8, 112.9, 111.4, 102.9, 49.5, 44.1, 41.8, 30.4, 23.3; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{25}H_{26}N_7O_2S$, 488.1869; found 488.1878.

9-(3-(Isopropylamino)propyl)-8-(6-(3-nitrophenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (12). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.16 (s, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.37-7.43 (m, 1H), 6.99 (s, 1H), 6.78 (s, 1H), 5.99 (s, 2H), 5.77 (br s, 2H), 3.97 (t, *J* = 6.7 Hz, 2H), 2.60 (septet, *J* = 6.1 Hz, 1H), 2.37 (t, *J* = 6.6 Hz, 2H), 1.70-1.80 (m, 2H), 0.94 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 153.2, 152.2, 149.9, 149.1, 148.5, 148.0, 142.3, 138.0, 136.1, 129.6, 125.1, 123.1, 120.7, 120.4, 115.0, 111.4, 102.9, 49.5, 44.1, 41.8, 30.5, 23.2; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{24}H_{26}N_7O_4S$, 508.1767; found 508.1772.

9-(3-(Isopropylamino)propyl)-8-(6-(3-(trifluoromethyl)phenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (13). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.45-7.51 (m, 2H), 7.32-7.40 (m, 2H), 6.99 (s, 1H), 6.76 (s, 1H), 5.98 (s, 2H), 5.70 (br s, 2H), 3.91 (t, *J* = 6.9 Hz, 2H), 2.60 (septet, *J* = 6.3 Hz, 1H), 2.34 (t, *J* = 6.7 Hz, 2H), 1.68-1.76 (m, 2H), 0.94 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

154.8, 153.2, 152.2, 149.7, 148.8, 148.2, 141.5, 138.9, 133.3, 131.1 (q, J = 33 Hz), 129.1, 126.8 (q, J = 4 Hz), 125.0 (q, J = 4 Hz) 124.6 (q, J = 271 Hz), 120.9, 120.4, 114.8, 111.6, 102.8, 49.5, 44.1, 41.7, 30.4, 23.2; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{25}H_{26}F_3N_6O_2S$, 531.1790; found 531.1780.

8-(6-(3,5-Bis(trifluoromethyl)phenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (14). ^{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.

8-(6-(4-(Aminomethyl)phenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (15). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.91 (s, 1H), 6.75 (s, 1H), 5.95 (s, 2H), 5.59 (br s, 2H), 3.90 (t, J = 6.9 Hz, 2H), 3.81 (s, 2H), 2.60 (septet, J = 6.3 Hz, 1H), 2.33 (t, J = 6.8 Hz, 2H), 1.65-1.74 (m, 2H), 0.94 (d, J = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 153.3, 152.2, 149.2, 148.29, 148.26, 143.4, 139.7, 139.3, 130.1, 127.5, 121.4, 120.6, 113.8, 111.6, 102.6, 49.4, 46.8, 44.2, 41.9, 30.5, 23.3; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{25}H_{30}N_7O_2S$, 492.2182; found 492.2170.

From above reaction 4.8 mg (17%) of *N*-formyl derivative of **15** was also obtained.

***N*-(4-(6-(6-Amino-9-(3-(isopropylamino)propyl)-9*H*-purin-8-ylthio)benzo[*d*][1,3]dioxol-5-yl)benzyl) formamide.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.15 (s, 1H), 7.11 (d, J = 7.9 Hz, 2H), 7.08 (s, 1H), 7.02 (d, J = 7.9 Hz, 2H), 6.73 (s, 1H), 5.98 (s, 2H), 5.59 (br s, 2H), 4.40 (d, J = 6.0 Hz, 2H), 3.73 (t, J = 6.8 Hz, 2H), 2.75 (septet, J = 6.3 Hz, 1H), 2.37 (t, J = 6.8 Hz, 2H), 1.64-1.73 (m, 2H), 1.04 (d, J = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 154.9, 153.0, 151.8, 149.7, 148.9, 148.3, 140.4, 140.2, 138.3, 130.2, 128.2, 121.0, 120.5, 115.2, 111.7, 102.7, 50.0, 43.7, 42.3, 41.5, 29.7, 22.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{26}H_{30}N_7O_3S$, 520.2131; found 520.2145.

9-(3-(Isopropylamino)propyl)-8-(6-(pyridin-4-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (16). ^{1}H 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.

9-(3-(Isopropylamino)propyl)-8-(6-(thiophen-2-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (17). ^{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.

8-(6-(Furan-2-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (18). ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.18 (s, 1H), 7.49 (d, *J* = 1.8 Hz, 1H), 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.

9-(3-(Isopropylamino)propyl)-8-(6-(5-methylfuran-2-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (19). ^{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.

5-(6-(6-Amino-9-(3-(isopropylamino)propyl)-9*H*-purin-8-ylthio)benzo[*d*][1,3]dioxol-5-yl)furan-2-carbaldehyde (20). ^{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.

8-(6-(Furan-3-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (21). ^{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.

8-(6-(1*H*-Pyrrol-2-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (22). ^{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.

8-(6-(1*H*-Pyrrol-3-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (23). ^{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.

8-(6-(1*H*-Pyrazol-3-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (24). ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.17 (s, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 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.

8-(6-(1*H*-Pyrazol-4-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (25). ^{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 $C_{21}H_{25}N_8O_2S$, 453.1821; found 453.1819; HPLC: method A R_t = 5.60, method B R_t = 4.87.

9-(3-(Isopropylamino)propyl)-8-(6-(1-methyl-1*H*-pyrazol-5-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (26). ^{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.

9-(3-(Isopropylamino)propyl)-8-(6-(isoxazol-4-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (27). 4-Isoxazoleboronic acid pinacol ester (34.2 mg, 0.1755 mmol) was added to **1** (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 min. Then H_2O (0.1 mL) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.0117 mmol) were added and the reaction mixture was stirred at rt for 24 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 11.5 mg (43%) of **27**. ^{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 = 5.87; method B R_t = 5.57.

2-(6-(6-Amino-9-(3-(isopropylamino)propyl)-9*H*-purin-8-ylthio)benzo[*d*][1,3]dioxol-5-yl)acetonitrile (28). ^{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.

9-(3-(Isopropylamino)propyl)-8-(6-(3-methylbut-2-en-2-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (29). ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.22 (s, 1H), 6.80 (s, 1H), 6.62 (s, 1H), 5.99 (s, 2H), 4.24 (t, J = 6.8 Hz, 2H), 2.77 (septet, J = 6.2 Hz, 1H), 2.54 (t, J = 6.8 Hz, 2H), 2.02 (m, 2H), 1.85 (s, 3H), 1.74 (s, 3H), 1.36 (s, 3H), 1.09 (d, J = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.3, 152.3, 151.3, 149.0, 148.5, 147.2, 142.3, 130.7, 128.2, 119.3, 119.1, 112.6, 110.1, 101.9, 43.2, 41.1, 29.2, 21.9, 21.8, 20.1, 19.9; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{23}H_{31}N_6O_2S$, 455.2229; found 455.2215; HPLC: method A R_t = 6.66, method B R_t = 8.07.

STILLE COUPLING

General conditions. A mixture of **1** (30 mg, 0.0585 mmol, 1 eq.), (n-Bu)$_3$SnR (4 eq.), LiCl (2 eq.) and $Pd(PPh_3)_4$ (10-20 mol%) in DMF (1 mL) in a 10 mL RBF equipped with a magnetic stir bar and rubber septum was evacuated and back filled with nitrogen. This was repeated four times then the reaction mixture was heated under nitrogen at 90-100 °C for 18 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC to yield compounds **30-38**.

8-(6-(4-(Benzyloxy)phenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (30). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.47 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 7.3 Hz, 2H), 7.36 (t, J = 7.1 Hz, 1H), 7.22 (d, J = 8.5 Hz, 2H), 6.93-6.98 (m, 3H), 6.84 (s, 1H), 6.02 (s, 2H), 5.79 (br s, 2H), 5.09 (s, 2H), 4.03 (t, J = 6.7 Hz, 2H), 2.73 (septet, J = 6.1 Hz, 1H), 2.44 (t, J = 6.6 Hz, 2H), 1.79-1.88 (m, 2H), 1.06 (d, J = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 154.9, 153.2, 152.2, 149.2, 148.4, 148.1, 139.6, 137.5, 133.4, 131.1, 129.3, 128.7, 128.2, 121.2, 120.5, 115.0, 113.7, 111.7,

102.5, 70.7, 49.6, 44.0, 41.7, 30.2, 23.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{31}H_{33}N_6O_3S$, 569.2335; found 569.2352.

9-(3-(Isopropylamino)propyl)-8-(6-(4-morpholinophenyl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (31). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.95 (s, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.84 (s, 1H), 6.01 (s, 2H), 5.81 (br s, 2H), 4.02 (t, *J* = 6.8 Hz, 2H), 3.85-3.92 (m, 4H), 3.16-3.24 (m, 4H), 2.71 (septet, *J* = 6.2 Hz, 1H), 2.43 (t, *J* = 6.7 Hz, 2H), 1.78-1.86 (m, 2H), 1.04 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 153.2, 152.2, 151.2, 149.2, 148.4, 148.0, 139.7, 132.0, 130.8, 121.4, 120.5, 115.4, 113.6, 111.6, 102.5, 67.5, 49.56, 49.51, 44.1, 41.8, 30.3, 23.2; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{28}H_{34}N_7O_3S$, 548.2444; found 548.2454.

9-(3-(Isopropylamino)propyl)-8-(6-(pyrimidin-5-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (32). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.68 (s, 2H), 8.17 (s, 1H), 7.07 (s, 1H), 6.82 (s, 1H), 6.05 (s, 2H), 5.45 (br s, 2H), 4.07 (t, *J* = 6.7 Hz, 2H), 2.68-2.77 (m, 1H), 2.45 (t, *J* = 6.6 Hz, 2H), 1.80-1.88 (m, 2H), 1.04 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.6, 156.7, 153.9, 152.3, 151.7, 149.9, 149.0, 147.8, 134.1, 133.4, 119.7, 119.5, 115.6, 110.8, 102.5, 49.3, 43.1, 40.9, 29.7, 22.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_8O_2S$, 465.1821; found 465.1820.

9-(3-(Isopropylamino)propyl)-8-(6-(pyrazin-2-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (33). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (d, *J* = 1.5 Hz, 1H), 8.56 (dd, *J* = 1.5, 2.5 Hz, 1H), 8.46 (d, *J* = 2.5 Hz, 1H), 8.21 (s, 1H), 7.03 (s, 1H), 6.88 (s, 1H), 5.98 (s, 2H), 5.74 (br s, 2H), 4.05 (t, *J* = 7.0 Hz, 2H), 2.60 (septet, *J* = 6.2 Hz, 1H), 2.38 (t, *J* = 6.8 Hz, 2H), 1.72-1.80 (m, 2H), 0.94 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.3, 153.2, 152.8, 151.6, 149.2, 148.9, 147.2, 145.2, 143.4, 143.0, 133.9, 122.2, 119.9, 113.6, 110.4, 102.3, 48.8, 43.7, 41.4, 30.0, 22.8; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_8O_2S$, 465.1821; found 465.1798.

9-(3-(Isopropylamino)propyl)-8-(6-(oxazol-2-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (34). ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.25 (s, 1H), 7.75 (s, 1H), 7.46 (s, 1H), 7.27 (s, 1H), 6.71 (s, 1H), 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); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 160.0, 154.7, 152.8, 151.3, 150.1, 148.5, 146.8, 139.0, 128.3, 123.7, 122.3, 120.0, 112.1, 109.7, 102.7, 43.2, 41.5, 29.3, 22.0; 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.

9-(3-(Isopropylamino)propyl)-8-(6-(thiazol-2-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (35). ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.20 (s, 1H), 7.87 (d, *J* = 3.3 Hz, 1H), 7.45 (s, 1H), 7.44 (d, *J* = 3.3 Hz, 1H), 6.98 (s, 1H), 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); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.5, 152.5, 152.4, 151.4, 149.75, 149.69, 148.0, 142.7, 121.13, 121.07, 120.1, 119.4, 114.6, 110.9, 102.9, 43.2,

41.3, 29.2, 21.9; 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.

9-(3-(Isopropylamino)propyl)-8-(6-(1-methyl-1*H*-imidazol-5-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (36). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.40 (s, 1H), 6.93 (s, 1H), 6.82 (s, 1H), 6.73 (s, 1H), 6.00 (s, 2H), 5.53 (br s, 2H), 4.04 (t, *J* = 6.8 Hz, 2H), 3.38 (s, 3H), 2.66 (septet, *J* = 6.2 Hz, 1H), 2.42 (t, *J* = 6.8 Hz, 2H), 1.76-1.84 (m, 2H), 0.98 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.0, 151.7, 150.6, 148.0, 147.5, 145.9, 137.2, 129.2, 128.1, 124.8, 123.6, 118.8, 112.0, 111.1, 101.2, 47.9, 42.5, 40.2, 30.8, 28.6, 21.4; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{27}N_8O_2S$, 467.1978; found 467.1957.

8-(6-Vinylbenzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (37). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.29 (s, 1H), 7.23 (dd, *J* = 17.3, 10.9 Hz, 1H), 7.10 (s, 1H), 6.92 (s, 1H), 5.99 (s, 2H), 5.64 (br s, 2H), 5.61 (d, *J* = 17.3 Hz, 1H), 5.29 (d, *J* = 11.0 Hz, 1H), 4.26 (t, *J* = 7.1 Hz, 2H), 2.73 (septet, *J* = 6.3 Hz, 1H), 2.57 (t, *J* = 6.8 Hz, 2H), 1.97 (m, 2H), 1.05 (d, *J* = 6.3Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.1, 152.6, 148.0, 133.7, 115.7, 113.6, 106.0, 101.9, 48.8, 47.2, 43.8, 41.5, 30.0, 29.7, 22.7, 19.2; MS (ESI) *m/z* 412.9 $[M+H]^+$.

8-(6-Allylbenzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (38). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.27 (s, 1H), 6.92 (s, 1H), 6.80 (s, 1H), 5.99 (s, 2H), 5.84-5.91 (m, 1H), 5.59 (br s, 2H), 4.98-5.07 (m, 2H), 4.28 (t, *J* = 6.9 Hz, 2H), 3.54 (m, 2H), 2.77 (septet, *J* = 6.3 Hz, 1H), 2.58 (t, *J* = 6.8 Hz, 2H), 1.94-2.04 (m, 2H), 1.07 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.0, 152.4, 151.9, 147.8, 146.9, 136.9, 136.2, 119.5, 116.6, 113.9, 110.3, 101.7, 48.9, 43.5, 41.2, 38.3, 29.7, 22.5; MS (ESI) *m/z* 426.8 $[M+H]^+$.

HECK COUPLING

General conditions. A solution of **1** (30 mg, 0.0585 mmol, 1 eq.) in NMP (1.5 mL) in a 10 mL RBF equipped with a magnetic stir bar and rubber septum was evacuated and back filled with nitrogen. This was repeated four times, then *N,N*-diisopropylethylamine (1.2-2 eq.), alkene (1.1-20 eq.) and $Pd(PPh_3)_4$ (10-20 mol%) were added and the reaction mixture was heated under nitrogen at 55-100 °C for 20-24 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC to yield compounds **39-43**. **44** was similarly prepared and obtained following Boc removal as is described below.

(*E*)-Methyl-3-(6-(6-amino-9-(3-(isopropylamino)propyl)-9*H*-purin-8-ylthio)benzo[*d*][1,3]dioxol-5-yl)acrylate (39). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.17 (d, *J* = 15.8 Hz, 1H), 7.14 (s, 1H), 7.03 (s, 1H), 6.27 (d, *J* = 15.8 Hz, 1H), 6.05 (s, 2H), 5.66 (br s, 2H), 4.37 (t, *J* = 6.4 Hz, 2H), 3.77 (s, 3H), 2.99-3.08 (m, 1H), 2.73 (t, *J* = 6.5 Hz, 2H), 2.27-2.33 (m, 2H), 1.27 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 167.0, 154.2, 152.5, 151.7, 149.9, 149.7, 147.0, 141.1, 131.6, 123.3, 119.8, 119.0, 114.5, 106.6, 102.4, 51.9, 49.4, 43.2, 41.1, 31.9, 22.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{22}H_{27}N_6O_4S$, 471.1815; found 471.1808; HPLC: method A R_t = 6.07, method B R_t = 6.39.

(*E*)-3-(6-(6-Amino-9-(3-(isopropylamino)propyl)-9*H*-purin-8-ylthio)benzo[*d*][1,3]dioxol-5-yl)-acrylonitrile (40). ^1H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.18 (s, 1H), 7.94 (d, *J* = 16.5 Hz, 1H), 7.19 (s, 1H), 7.08 (s, 1H), 6.12 (s, 2H), 5.86 (d, *J* = 16.5 Hz, 1H), 4.30 (t, *J* = 6.4 Hz, 2H), 2.88 (m, 1H), 2.68 (t, *J* = 6.7 Hz, 2H), 2.27-2.33 (m, 2H), 1.14 (d, *J* = 6.1 Hz, 6H); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{21}H_{24}N_7O_2S$, 438.1712; found 438.1725; HPLC: method A R_t = 5.83, method B R_t = 5.64.

8-(6-(Cyclopent-2-enyl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (41). ^1H 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); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.3, 151.9, 151.5, 150.7, 149.9, 147.0, 145.6, 133.4, 129.8, 119.1, 116.0, 115.2, 108.5, 102.1, 50.9, 42.2, 41.9, 40.5, 39.9, 29.9, 26.9, 19.6; 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.

8-(6-(2,3-Dihydrofuran-3-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (42). ^1H 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, 1H), 4.64-4.69 (m, 1H), 4.45 (m, 1H), 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.4, 152.0, 150.2, 148.1, 147.4, 146.9, 142.6, 119.7, 117.6, 114.5, 108.6, 104.0, 101.9, *, 48.9, 45.3, 43.7, 41.3, 30.0, 22.8, *signal overlaps with solvent; ^{13}C NMR (125 MHz, CD_2Cl_2) δ 154.4, 152.64, 152.61, 150.7, 148.8, 147.9, 147.4, 143.3, 120.2, 118.3, 115.0, 109.0, 104.4, 102.6, 77.6, 49.7, 45.8, 43.9, 41.7, 30.2, 22.6; 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.

8-(6-(2,3-Dihydrofuran-2-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (43). ^1H 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 152.1, 151.8, 150.0, 147.8, 147.6, 145.1, 141.3, 119.5, 116.3, 114.5, 106.9, 102.0, 99.3, 79.7, 50.1, 42.4, 40.6, 37.9, 29.7, 20.9; 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.

8-(6-(2,5-Dihydro-1*H*-pyrrol-2-yl)benzo[*d*][1,3]dioxol-5-ylthio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (44). A solution of **1** (30 mg, 0.0585 mmol) and *N*-Boc-2,3-dihydro-1*H*-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 *N,N*-diisopropylethylamine (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 **44**. ^{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); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.0, 152.0, 151.7, 150.7, 149.4, 147.8, 142.8, 131.0, 129.8, 119.2, 116.8, 115.3, 108.7, 102.2, 66.1, 53.6, 43.4, 41.2, 40.4, 29.8, 22.2; 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.

SONOGASHIRA COUPLING

General conditions. To a solution of **1** (20 mg, 0.039 mmol, 1 eq.) in DMF (2 mL) in a sealed tube flushed with argon was added CuI (0.5 eq.), $PdCl_2(PPh_3)_2$ (15 mol%), alkyne (2-2.5 eq.) and triethylamine (5 eq.). The reaction mixture was heated at 90-100 °C for 24 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC to yield compounds **46-50**. **45** was similarly prepared and obtained following trimethylsilyl removal as is described below.

8-(6-Ethynyl-benzo[1,3]dioxol-5-ylsulfanyl)-9-(3-isopropylamino-propyl)-9*H*-purin-6-ylamine (45). To a solution of **1** (20 mg, 0.039 mmol) in 2 ml of DMF in a sealed tube, was added CuI (3.8 mg, 0.019 mmol), $PdCl_2(PPh_3)_2$ (4.2 mg, 0.006 mmol), trimethylsilylacetylene (14 μL, 0.098 mmol) and triethylamine (13.7 μL, 0.1866 mmol). The reaction mixture was heated at 90 °C for 24 h. The reaction mixture was concentrated under reduced pressure to give a white solid to which was added MeOH (1 mL) and KOH (10 mg) and was stirred at rt for 2 h. Solvent was removed under reduced pressure and the resulting residue was purified by preparatory TLC (CH_2Cl_2: *n*-hexane: EtOAc: MeOH-NH_3 (7N), 4:4:2:1) to give 11 mg (69%) of **45**. ^{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); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{20}H_{23}N_6O_2S$, 411.1603; found 411.1605.

8-((6-(Hex-1-yn-1-yl)benzo[*d*][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (46). ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.23 (s, 1H), 6.81 (s, 1H), 6.68 (s, 1H), 5.87 (s, 2H), 4.24 (t, *J* = 6.9 Hz, 2H), 2.66 (septet, *J* = 6.2 Hz, 1H), 2.48 (t, *J* = 6.2 Hz, 2H), 2.31 (t, *J* = 6.9 Hz, 2H), 1.90 (quintet, *J* = 7.6 Hz, 2H), 1.44 (quintet, *J* = 6.2 Hz, 2H), 1.34 (sextet, *J* = 7.6 Hz, 2H), 0.98 (d, *J* = 6.2 Hz,

6H), 0.82 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.4, 152.8, 151.6, 148.1, 147.9, 146.6, 127.8, 119.8, 114.8, 112.5, 111.4, 101.9, 96.1, 77.9, 48.8, 43.6, 41.5, 30.6, 29.9, 22.6, 21.9, 19.3, 13.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{24}H_{31}N_6O_2S$, 467.2229; found 467.2227.

8-[6-(3,3-Dimethylbut-1-ynyl)benzo[1,3]dioxol-5-ylsulfanyl]-9-(3-isopropylamino-propyl)-9*H*-purin-6-ylamine (47). ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) 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); HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{24}H_{31}N_6O_2S$, 467.2229; found 467.2233.

8-((6-(Cyclopentylethynyl)benzo[*d*][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (48). ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.16 (s, 1H), 6.85 (s, 1H), 6.76 (s, 1H), 5.92 (s, 2H), 4.27 (t, *J* = 6.2 Hz, 2H), 2.81 (septet, *J* = 6.9 Hz, 1H), 2.69 (quintet, *J* = 6.9 Hz, 1H), 2.56 (t, *J* = 6.2 Hz, 2H), 2.03 (quintet, *J* = 6.2 Hz, 2H), 1.79-1.85 (m, 2H), 1.60-1.63 (m, 2H), 1.48-1.53 (m, 4H), 1.09 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.5, 152.5, 151.5, 148.6, 148.2, 147.6, 124.2, 121.2, 119.5, 112.7, 112.5, 102.2, 100.5, 77.7, 49.7, 42.8, 41.1, 33.9, 30.9, 28.8, 25.1, 21.4; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{25}H_{31}N_6O_2S$, 479.2229; found 479.2235.

8-((6-(Cyclohexylethynyl)benzo[*d*][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine (49). ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) δ 8.13 (s, 1H), 6.87 (s, 1H), 6.78 (s, 1H), 5.94 (s, 2H), 4.29 (t, *J* = 6.9 Hz, 2H), 2.98 (septet, *J* = 6.6 Hz, 1H), 2.66 (t, *J* = 6.6 Hz, 2H), 2.48 (quintet, *J* = 4.6 Hz, 1H), 2.11 (quintet, *J* = 6.6 Hz, 2H), 1.57-1.67 (m, 4H), 1.30-1.36 (m, 2H), 1.22-1.26 (m, 2H), 1.19 (d, *J* = 5.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$/MeOH-d_4) δ 154.5, 152.6, 151.6, 148.1, 148.0, 146.8, 125.4, 119.9, 112.5, 111.3, 101.9, 101.8, 100.2, 77.9, 49.6, 42.8, 41.1, 33.6, 32.5, 29.7, 25.9, 25.1, 24.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{26}H_{33}N_6O_2S$, 493.2386; found 493.2381.

9-(3-Isopropylaminopropyl)-8-(6-phenylethynylbenzo[1,3]dixool-5-ylsulfanyl)-9*H*-purin-6-ylamine (50). ^{1}H NMR (500 MHz, $CDCl_3$/MeOH-d_4) 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, $CDCl_3$/MeOH-d_4) 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; HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{26}H_{27}N_6O_2S$, 487.1903; found 487.1913.

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