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ScienceDirect
Bioorganic & Medicinal Chemistry 15 (2007) 130–141
Bioorganic & Medicinal Chemistry

A Pd(0) based cross-coupling approach to the synthesis of 2-amidopurines and their evaluation as CDK inhibitors

Lucie Vandromme,[a] Michel Legraverend,[a,*] Sergio Kreimerman,[a] Olivier Lozach,[b] Laurent Meijer[b] and David S. Grierson[a]

[a]*UMR 176, Institut Curie, Bât. 110-112, Centre Universitaire, 91405 Orsay, France*
[b]*CNRS, Cell Cycle Group, Station Biologique, BP 74, 29682 Roscoff, France*

Received 26 June 2006; revised 27 September 2006; accepted 4 October 2006
Available online 6 October 2006

Abstract—Two new series of 2-amido- and 2-aminocarbonylpurines have been synthesized using a Pd catalyst cross-coupling reaction either with amides or amines in the presence of CO. Moderate in vitro inhibitory activity against CDK1 and CDK5 was observed with IC_{50} of 0.9 μM for the most active compound (**18c**).

1. Introduction

The cyclin-dependent kinases (CDKs) are a family of serine/threonine kinases that play a crucial role in cell cycle division.[1] In many forms of cancer a deregulation of CDK function and consequent loss of cell cycle control are observed. This suggests that the development of pharmacological inhibitors of CDKs may be an anticancer strategy.[2] Abnormalities in CDK activity and regulation are similarly observed in pain signaling and in neurodegenerative disorders such as Alzheimer's, Parkinson's, and Nieman-Pick's diseases. This provides further impetus for the development of potent and selective pharmacological inhibitors of these kinases.[3,4] However, it remains to be established what selectivity profile a CDK inhibitor, and in particular CDK1 inhibitors, should have for anti-cancer activity.[5] Although many families of CDK inhibitors are already known,[6–12] purine CDK inhibitors[3,13–16] are attractive because the purine scaffold allows a great variety of structural modifications to be made at the 2, 6, and 9 positions. Indeed, the synthesis and screening of a wide range of polyfunctionalized purine compounds (purine libraries) has permitted an optimization of their activity relative to the CDK's, and it has also brought to light an impressive number of other potential applications of purines as therapeutic agents and/or biological tools.[17]

Given the important influence of the side chain at C-2, C-6, and N-9 on the potency and selectivity profile in purine CDK inhibitors,[4,13,18,19] it is of continued interest to study new types of substituents at these positions in order to delineate the specificity profile and scope of applications of purine inhibitors. One option that has received relatively little attention are purine compounds with an amide or urea functions in their structure (Fig. 1).[20–27] In this context, compounds **1** and **2** were found to be potent p38 MAP kinase inhibitors,[26] and unlike other trisubstituted purine analogues, compound **3** shows a good affinity for GSK3.[27] The related furopyrimidine **4** is also a potent inhibitor of GSK-3β[21] and displays submicromolar activity (IC_{50} = 457 nM) against CDK2. The presence of amide functionality is central to the affinity of the Sugen type indolinones **5** and **6** for different kinases, and it was found that inhibition of CDK4/cyclin D1 and CDK2/cyclin E by compound **7** was dramatically improved by incorporation of an amide containing motif in its structure (**7** → **8** → **9**).[23] Replacing the anilinophthalizine unit in the KDR/Flt1 inhibitor **10** by a simple benzamide system as in **11** was also found to be possible.[20]

Based upon these results, it was considered pertinent to develop methodology for the synthesis of 2,6,9-trisubstituted purines incorporating either a –NHCOR or a CONHR motif at C-2, and to evaluate such compounds

Keywords: Purine; CDK inhibitors; Amidation; Carbonylative amination; Amidopurine.
* Corresponding author. Tel.: +1 69 86 30 85; fax: +1 69 0753 81; e-mail: Michel.Legraverend@curie.u-psud.fr

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doi:10.1016/j.bmc.2006.10.003

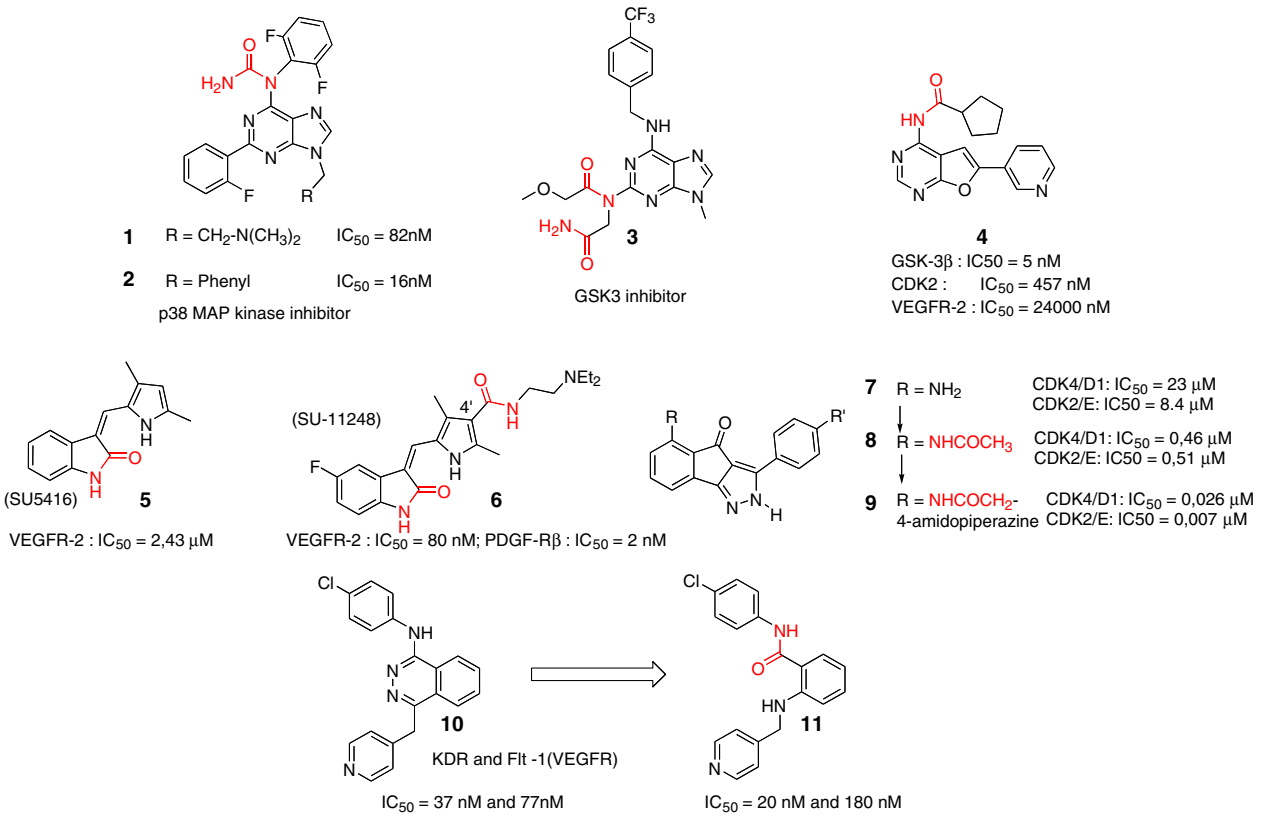


Figure 1. Examples of kinase inhibitors which have been improved by the presence of an amide chain in their structure.

for their capacity to inhibit CDK1/cyclinB, CDK5/p25, and GSK-3β. Given the ready availability of 2-iodo-6-chloro and 6-benzylsulfanylpurines bearing diverse functionality at N-9, attention was directed to the use of Pd(0)-catalyzed cross-coupling reactions involving these 2-iodo purines for this purpose. Palladium-catalyzed amidations of aryl halides have been reported by Buchwald,[28–31] Hartwig[32–34] and others[35,36] and were recently applied to 6-bromopurine.[37] To our knowledge, the Pd(0)-mediated amidation and carbonylative amination of purine substrates at C-2 have not been reported.

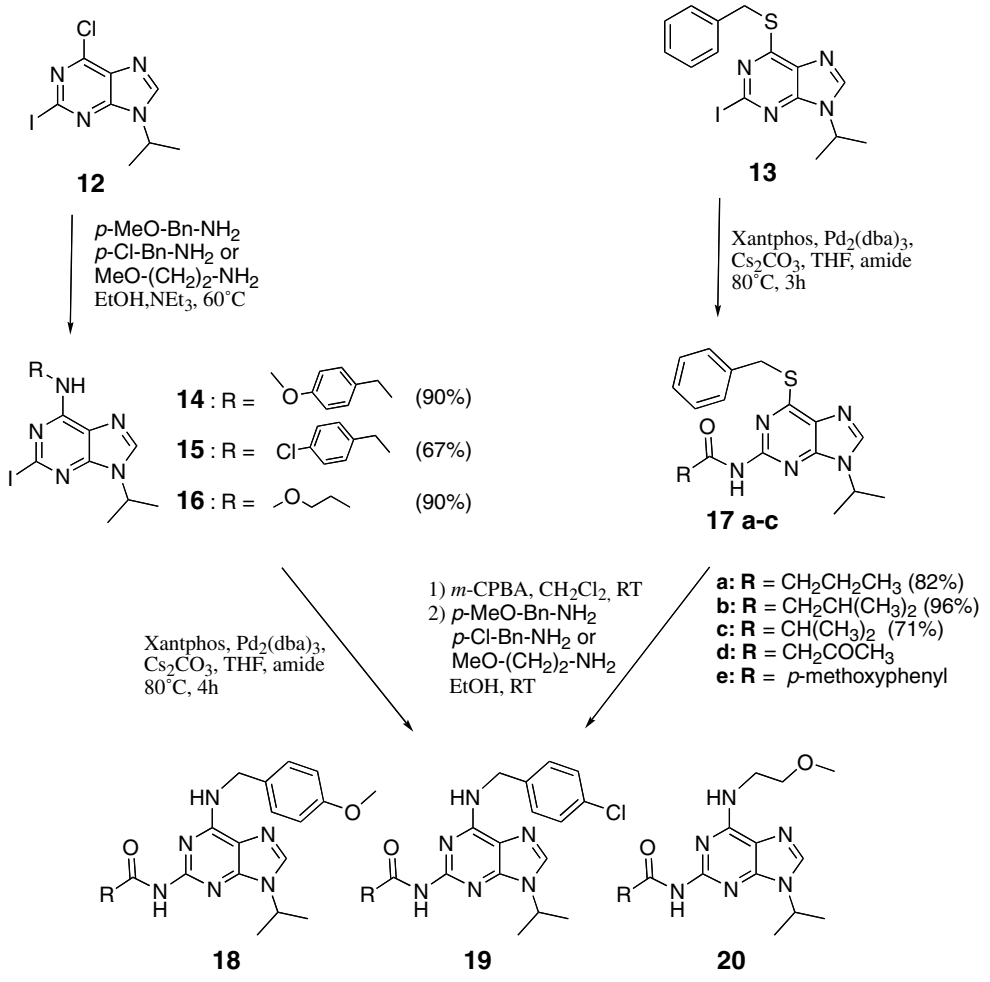
2. Chemistry

The objective initially set in our study was to determine whether compound **12**, available in four steps and high yield from commercial 6-chloropurine,[38–40] would react in the desired manner under Pd(0)-catalyzed amidation conditions to give the C-2 amide product. This reaction was of particular interest as it would provide a means to introduce an amine/amide type motif at C-2 in a 2,6-dihalopurine rather than at the more reactive C-6 position, as is observed under S_NAr conditions. The fact that this intermediate reacts in Sonogashira,[41] Stille,[42] and Suzuki[43] type palladium-catalyzed reactions to regioselectively give the C-2 cross-coupling products suggested that this would be the case. In preliminary experiments, however, the reaction of purine **12** in THF with different amides using $Pd_2(dba)_3$ as catalyst, Xantphos as the ligand, and cesium carbonate as the base (Buchwald conditions)[30,31] led to the expected 2-mono-substituted derivative along with a 2-amido-6-oxo purine derivative in low yield.

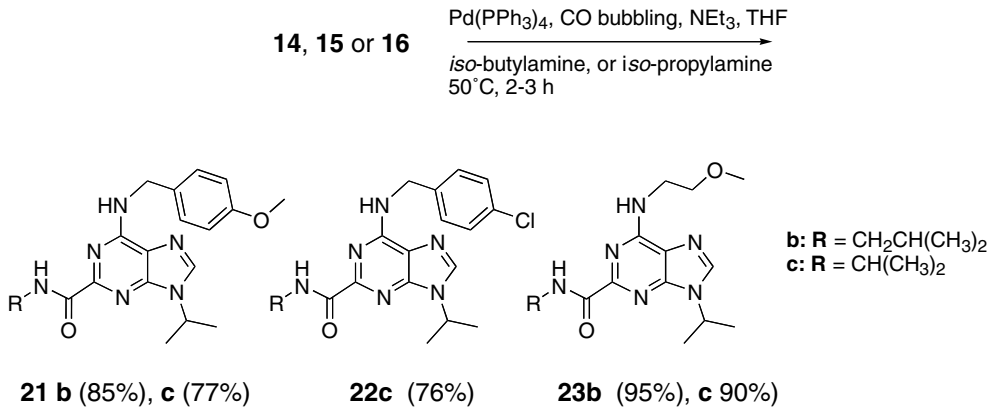
To obtain the trisubstituted 'amidopurines' **18**, **19**, and **20** the option was thus taken to functionalize the C-6 position prior to the key amidation reaction at C-2 through reaction of **12** with *p*-methoxybenzylamine, *p*-chlorobenzylamine, and methoxyethylamine in EtOH containing Et_3N at 60 °C. Intermediates **14**–**16** were obtained in this way in 67–90% yields. Subsequent reaction of **14** with isovaleramide, isobutyramide, acetoacetamide, and *p*-methoxybenzamide as representative amides using the Buchwald conditions led to formation of purines **18b**–**e** (57–82%). In the same way compounds **19e** and **20d**,**e** were obtained.

Returning to the idea of introducing the amide function at C-2 in the first step, the 6-benzylsulfanyl purine derivative **13**[38] was reacted with *n*-butyramide and the four other test amides under the Pd(0) catalysis conditions to give compounds **17a-e** in good to excellent yields (65–98%). The interest in using compound **13** as the starting material is that the C-6 S-benzyl substituent is much less susceptible to displacement (S_NAr) reactions than is the chloro substituent in **12**, and as the results show, this motif is also not reactive in the cross-coupling reactions. The other interesting attribute to the use of compound **13** is that, as we[44] and Schultz et al.[45] independently showed, the S-benzyl group can be activated with respect to reaction with amine nucleophiles by simple S-oxidation. Indeed, the corresponding sulfones obtained by reacting intermediates **17a**–**c** with *m*-CPBA

underwent facile conversion to products **19a**–**c** and **20a**–**c** upon reaction with the requisite amine in EtOH at room temperature. In a similar way, compound **18a** was prepared in two steps from **17a** in 67% overall yield. However, a limiting feature which surfaced in this study was that amides **17d** and **17e** were unstable toward the treatment with *m*-CPBA during the S-oxidation step. Perhaps with other oxidants and lower temperature con-



Scheme 1. Routes to 2-amidopurine derivatives **18**–**20**.



Scheme 2. Synthesis of amides **21**–**23**.

ditions this will no longer be a problem for these and other amide-containing derivatives which are of interest for certain biological applications.

The Pd(0)-catalyzed amino carbonylation of aryl halides proved to be particularly well adapted and direct method for the preparation of the corresponding inverted C-2 amides (Scheme 2). In the experiments, the reaction of the 2-iodopurine intermediates **14**, **15**, and **16** with isopropylamine or isobutylamine and CO (atmospheric pressure) in the presence of $Pd(PPh_3)_4$ (cat) led to the formation of the mono-carbonylated compounds **21b**,**c**, **22c**, and **23b**,**c** in a single step and in high yields.

As shown in Table 1 the new amide substituents at position 2 did not improve the inhibitory activity, as compared to other 2-iodo- or 2-pyrrolidine methanol purine derivatives,[46] but this structural modification is not detrimental to the inhibitory activity. The best inhibitors (**18c**, **19c**, and **22c**) bear a short amide chain (isopropyl) at C2, and a *p*-methoxybenzylamino- or a *p*-chlorobenzylamino- group at C6. They inhibit CDK1 and CDK5 to a similar extent. In contrast, the presence of a bulky *p*-methoxyphenyl substituent at C-2 (**18e**, **19e**, and **20e**) decreases the anti-CDK activity. The presence of the acyclic methoxyethyl-amino substituent at C-6[47] gave consistently less active inhibitors as compared to the corresponding C-6 benzylamino derivatives (**20** less active than **18** or **19**; **23** less active than **21** or **22**). In addition, as the majority of non-purine inhibitors of CDK1/Cyclin B inhibit GSK-3β to a similar extent[48] it was of interest to screen our compounds against GSK3. As found for Roscovitine and Purvalanol no inhibition of GSK3 was observed.[48] As suggested by the structure of N-9 methyl substituted purine compound **3** (Scheme 1), this may simply be the consequence of unfavorable interactions between the bulky N-9 *i*-propyl group in our purine derivatives with the gatekeeper residue and the hydrophobic 1 pocket. This intriguing point requires further investigation.

3. Biological results

See Table 1.

Table 1. Enzymatic evaluation (IC_{50}, μM) on CDK1 and CDK5

Compound	CDK1/cyclin B	CDK5/p25
18a	4.4	3.9
18b	2.3	1.8
18c	0.94	1.3
18d	2.4	1.6
18e	4.6	3.4
19a	2.9	2.1
19b	3	1.6
19c	1.2	0.9
19e	40	19
20a	13	10
20b	9.6	6.6
20c	7	7
20d	>10	NT
20e	>10	NT
21b	2.4	2.1
21c	2.3	2.4
22c	1.7	2
23b	7.2	16
23c	8.3	13

4. Experimental

4.1. Biochemical reagents

Sodium orthovanadate, EGTA, EDTA, Mops, β-glycerophosphate, phenylphosphate, sodium fluoride, dithiothreitol (DTT), glutathione–agarose, glutathione, bovine serum albumin (BSA), nitrophenylphosphate, leupeptin, aprotinin, pepstatin, soybean trypsin inhibitor, benzamidine, and histone H1 (type III-S) were obtained from Sigma Chemicals. [γ-^{33}P]ATP was obtained from Amersham. The GS-1 peptide (YRRAAVPPSPSLSRHSSPHQSpEDEEE) was synthesized by the Peptide Synthesis Unit, Institute of Biomolecular Sciences, University of Southampton, Southampton SO16 7PX, U.K.

4.2. Buffers

Homogenization buffer: 60 mM β-glycerophosphate, 15 mM *p*-nitrophenylphosphate, 25 mM Mops (pH 7.2), 15 mM EGTA, 15 mM $MgCl_2$, 1 mM DTT, 1 mM sodium vanadate, 1 mM NaF, 1 mM phenylphosphate, 10 μg leupeptin/ml, 10 μg aprotinin/ml, 10 μg soybean trypsin inhibitor/ml, and 100 μM benzamidine.

Bead buffer: 50 mM Tris, pH 7.4, 5 mM NaF, 250 mM NaCl, 5 mM EDTA, 5 mM EGTA, 0.1% Nonidet P-40, 10 μg leupeptin/ml, 10 μg aprotinin/ml, 10 μg soybean trypsin inhibitor/ml, and 100 μM benzamidine.

Buffer A: 10 mM $MgCl_2$, 1 mM EGTA, 1 mM DTT, 25 mM Tris–HCl, pH 7.5, and 50 μg heparin/ml.

Buffer C: homogenization buffer but 5 mM EGTA, no NaF, and no protease inhibitors.

Tris-buffered saline–Tween 20 (TBST): 50 mM Tris, pH 7.4, 150 mM NaCl, and 0.1% Tween 20.

Hypotonic lysis buffer (HLB): 50 mM Tris–HCl, pH 7.4, 120 mM NaCl, 10% glycerol, 1% Nonidet-P40, 5 mM DTT, 1 mM EGTA, 20 mM NaF, 1 mM orthovanadate, 5 μM microcystin, and 100 μg/ml each of leupeptin, aprotinin, and pepstatin.

4.3. Kinase preparations and assays

Kinase activities were assayed in Buffer A or C (unless otherwise stated), at 30 °C, at a final ATP concentration of 15 μM. Blank values were subtracted and activities calculated as pmoles of phosphate incorporated for a 10 min. incubation. The activities are usually expressed in % of the maximal activity, that is, in the absence of inhibitors. Controls were performed with appropriate dilutions of dimethylsulfoxide. In a few cases phosphorylation of the substrate was assessed by autoradiography after SDS–PAGE.

GSK-3β was purified from porcine brain.[49] It was assayed, following a 1/100 dilution in 1 mg BSA/ml of 10 mM DTT, with 5 μl of 40 μM GS-1 peptide as a substrate, in buffer A, in the presence of 15 μM [γ-^{33}P] ATP (3,000 Ci/mmol; 1 mCi/ml) in a final volume of 30 μl. After 30 min incubation at 30 °C, 25 μl aliquots of supernatant were spotted onto 2.5 × 3 cm pieces of Whatman P81 phosphocellulose paper, and, 20 s later, the filters were washed five times (for at least 5 min each time) in a solution of 10 ml phosphoric acid/liter of water. The wet filters were counted in the presence of 1 ml ACS (Amersham) scintillation fluid.

CDK1/cyclin B was extracted in homogenization buffer from M phase starfish (*Marthasterias glacialis*) oocytes and purified by affinity chromatography on p9^{CKShs1}-Sepharose beads, from which it was eluted by free p9^{CKShs1} as previously described.[50,51] The kinase activity was assayed in buffer C, with 1 mg histone H1/ml, in the presence of 15 μM [γ-^{33}P] ATP (3000 Ci/mmol; 1 mCi/ml) in a final volume of 30 μl. After 10 min. incubation at 30 °C, 25 μl aliquots of supernatant were spotted onto P81 phosphocellulose papers and treated as described above.

CDK5/p25 was reconstituted by mixing equal amounts of recombinant mammalian CDK5 and p25 expressed in *E. coli* as GST (glutathione-*S*-transferase) fusion proteins and purified by affinity chromatography on glutathione–agarose (vectors kindly provided by Dr. J.H. Wang) (p25 is a truncated version of p35, the 35 kDa CDK5 activator). Its activity was assayed in buffer C as described for CDK1/cyclin B.

4.4. Chemistry

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300 spectrometer (300 and 75.3 MHz, respectively). Mass spectra were recorded on a WATERS ZQ 2000 spectrometer with direct injection.

4.5. 6-Benzylsulfanyl-2-iodo-9-isopropyl-9*H*-purine (13)

To a stirred solution of 6-chloro-2-iodo-9-tetrahydropyranepurine[38] (5 g, 13.7 mmol) in ethanol (50 mL) were added benzylmercaptan (2 equiv, 27.4 mmol, 3.2 mL) and triethylamine (2 equiv, 27.4 mmol, 3.8 mL). The reaction mixture was stirred at 60 °C for 10 min. Then the resultant white precipitate was filtered and washed with absolute ethanol to afford the expected product, 97%; R_f: 0.53 (EtOAc/heptane 6:4); mp: 186–187 °C. ^{1}H NMR ($CDCl_3$) δ: 8.06 (s, 1H, H8); 7.52–7.48 (m, 2H ar); 7.35–7.22 (m, 3H ar); 5.71 (dd, 1H, NCHO, J = 10.4 Hz, J' = 2.1 Hz); 4.57 (s, 2H, CH_2S); 4.75 (dd, 1H, CHO, J = 10.0 Hz, J' = 2.1 Hz); 4.14 (td, 1H, CHO, J = 11.5 Hz, J' = 3.2 Hz); 1.94–1.63 (m, 6H, 3CH_2). ^{13}C NMR ($CDCl_3$) δ: 161.6 (C6); 148.4 (C4); 140.3 (CH, C8); 137.2 (Cq ar); 131.0 (C5); 129.5 (2CH ar); 128.4 (2CH ar); 127.4 (CH ar); 118.4 (C2); 81.8 (NCHO a); 68.8 (CH_2O e); 33.3 (CH_2S); 32.2 (CH_2 b); 24.8 (CH_2 d); 22.6 (CH_2 c). MS (IC/NH_3): *m/z* 453 [M+H]. Anal. Calcd for $C_{17}H_{17}IN_4OS$: C, 45.14; H, 3.79; N, 12.39; S, 7.09. Found: C, 44.81; H, 3.71; N, 12.14; S, 7.21.

To a solution of 6-benzylsulfanyl-2-iodo-9-(tetrahydropyran-2-yl)-9*H*-purine (5.5 g, 12.1 mmol) described above, in dry CH_2Cl_2 was added dropwise TFA 99% (9 equiv, 109 mmol, 8 mL). The resultant solution was stirred at room temperature for 10 min and turned deep red. Then the solution was concentrated, the residue dissolved in EtOAc and washed with a saturated solution of $NaHCO_3$. The organic layers were combined, dried on $MgSO_4$, and concentrated, and the resultant solid was washed with CH_2Cl_2 to afford the expected product (2-iodo-6-benzylsulfanylpurine) as a white solid, 77%; R_f: 0.45 (EtOAc/heptane 6:4); mp: 251 °C. ^{1}H NMR (DMSO) δ: 13.64 (br s, 1H, NH); 8.38 (s, 1H, H8); 7.50–7.22 (m, 5H ar); 4.56 (s, 2H, CH_2S). ^{13}C NMR (DMSO) δ: 159.4 (C6); 150.3 (C4); 143.1 (CH, C8); 137.6 (Cq ar); 130.0 (C5); 129.9 (2CH ar); 128.3 (2CH ar); 127.2 (CH ar); 118.9 (C2); 32.2 (CH_2S). MS (electrospray): *m/z* 759.1 [2M+Na]; 391.1 [M+Na]; 369.1 [M+H]. Anal. Calcd for $C_{12}H_9IN_4S$: C, 39.15; H, 2.46; N, 15.22; S, 8.71. Found: C, 38.91; H, 2.44; N, 15.11; S, 8.29.

To a stirred solution of PPh_3 (1.3 equiv, 17.7 mmol, 4.63 g) in dry THF (40 mL) under argon, cooled at −50 °C, was added dropwise DIAD (1.3 equiv, 17.7 mmol, 3.48 mL). The reaction mixture was stirred for 10 min (a yellow precipitate appears). Then, isopropanol (1.3 equiv, 17.7 mmol, 1.35 mL) was added. After stirring at −50 °C for 10 min, 2-iodo-6-benzylsulfanylpurine (1 equiv, 13.6 mmol, 5 g) in a solution of dry THF (20 mL) was added, and the resultant solution was stirred at room temperature overnight. After concentration of the reaction mixture, the resultant yellow oil was purified by silica gel column chromatography (CH_2Cl_2) to afford the expected product (**13**) as a slightly yellow solid, 80%; R_f: 0.63 (CH_2Cl_2/EtOH 95:5); mp: 124 °C. ^{1}H NMR ($CDCl_3$) δ: 7.89 (s, 1H, H8); 7.52 (d, 2H ar, J = 7.2 Hz); 7.50–7.22 (m, 3H ar); 4.84 (sept, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 4.57 (s, 2H, CH_2Ph); 1.58 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 161.3 (C6); 148.9 (C4); 140.0 (CH, C8); 137.2 (Cq ar); 131.1 (C5); 129.3 (2CH ar); 128.5 (2CH ar); 127.2 (CH ar); 118.0 (C2); 47.3 (*C*H-*i*-PrN); 33.4 (CH_2S); 22.7 (2*C*H_3-*i*-Pr). MS (electrospray): *m/z* 433.1 [M+Na]; 411.1 [M+H]. Anal. Calcd for $C_{15}H_{15}IN_4S$: C, 43.91; H, 3.69; N, 13.66; S, 7.82. Found: C, 43.75; H, 3.64; N, 13.68; S, 7.71.

4.6. (2-Iodo-9-isopropyl-9*H*-purin-6-yl)-(4-methoxybenzyl)-amine (14)

A solution of 6-chloro-2-iodo-9-isopropylpurine (**12**)[38–40] (4 g, 12.4 mmol), triethylamine (1 equiv), and *p*-methoxybenzylamine (1.5 equiv, 18.6 mmol, 2.42 mL) in absolute ethanol (60 ml) was stirred for 18 h at 60 °C. The mixture was evaporated to dryness and the resulting solid was purified by flash chromatography (CH_2Cl_2/EtOH: 95:5) to give **14** (3.8 g, 90%) as a white solid after washing with pentane: R_f: 0.68 (CH_2Cl_2/EtOH 98:2); mp: 165 °C. ^{1}H NMR ($CDCl_3$) δ: 7.67 (s, 1H, H8); 7.31 (d, 2H ar, J = 8.5 Hz); 6.88 (d, 2H ar, J = 8.5 Hz); 6.00 (br s, 1H, NH); 4.82 (m, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 4.72 (br s, 2H, CH_2N); 3.81 (s, 3H, CH_3O); 1.56 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 159.1 (*C*q ar-OMe); 153.9 (C4); 149.2 (C6);

136.9 (CH, C8); 130.1 (Cq ar); 120.2 (C5); 114.2 (C2); 114.0 (4CH ar); 55.3 (CH_3O); 46.8 (*C*H-*i*-PrN); 44.2 (CH_2N); 22.8 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 424 (100%) [M+H]; 316 (29%) [M−CH_2OPh]; HRMS calcd for $C_{16}H_{18}IN_5O$: *m*/*z* [M+H], 424.0629, Found 424.0628. Anal. Calcd for $C_{16}H_{18}IN_5O$: C, 45.40; H, 4.29; N, 16.55. Found: C, 45.69; H, 4.37; N, 16.87.

4.7. (4-Chlorobenzyl)-(2-iodo-9-isopropyl-9*H*-purin-6-yl)-amine (15)

A solution of 6-chloro-2-iodo-9-isopropylpurine (**12**) (500 mg, 1.55 mmol) in absolute ethanol (20 mL) was stirred at 60 °C for 2 days in the presence of triethylamine (1 equiv, 1.55 mmol, 216 μL), *p*-chlorobenzylamine (2 equiv, 3.1 mmol, 378 μL). After concentration in vacuo, the oily residue was purified by silica gel column chromatography, eluting with CH_2Cl_2/EtOH (100:0–98:2) to give **15** as a white solid after washing with heptane, 67%; R_f: 0.44 (CH_2Cl_2/EtOH 98:2); mp: 116 °C; ^{1}H NMR ($CDCl_3$): δ: 7.59 (s, 1H, H8); 7.33 (d, 2H ar, J = 8.4 Hz); 7.25 (d, 2H ar, J = 8.4 Hz); 4.94 (m, 2H, CH_2N, J = 6.2 Hz); 4.76 (sept, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 1.52 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 156.2 (C4); 148.0 (C6); 137.2 (CH, C8); 133.4 (Cq ar); 129.4 (Cq ar); 128.8 (4CH ar); 120.4 (C5); 116.0 (C2); 46.9 (*C*H-*i*-PrN); 43.5 (CH_2N); 22.8 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 428 (100%) [M+H]; *m*/*z* 301 (25%) [M−I]. HRMS calcd for $C_{15}H_{15}ClIN_5$: *m*/*z* [M+H], 428.0133. Found: 428.0135.

4.8. (2-Iodo-9-isopropyl-9*H*-purin-6-yl)-(methoxyethyl)-amine (16)

A solution of **12** (500 mg, 1.55 mmol) in absolute ethanol (20 mL) was stirred at 60 °C for 2 days in the presence of triethylamine (1 equiv, 1.55 mmol, 216 μL), 2-methoxyethylamine (2 equiv, 3.1 mmol, 404 μL). After concentration in vacuo, the crude yellow solid was washed with pentane to give **16** as a white solid, 90%; R_f: 0.42 (CH_2Cl_2/EtOH 98:2); mp: 112 °C. ^{1}H NMR ($CDCl_3$) δ: 7.70 (s, 1H, H8); 6.16 (br s, NH); 4.80 (sept, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 3.80 (br s, 2H, CH_2N); 3.59 (t, 2H, CH_2O, J = 5.1 Hz); 3.38 (s, 3H, CH_3O); 1.55 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 154.1 (C4); 149.1 (C6); 137.0 (CH, C8); 120.1 (C5); 119.7 (C2); 71.0 (CH_2O); 58.7 (CH_3O); 46.7 (*C*H-*i*-PrN); 40.3 (CH_2N); 22.8 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 362 (100%) [M+H]; 330 (25%) [M+H–CH_3O]; 320 (39%) [M−*i*-Pr]. HRMS calcd for $C_{11}H_{16}IN_5O$: *m*/*z* [M+H] 362.0472. Found: 362.0479.

4.9. *N*-(6-Benzylsulfanyl-9-isopropyl-9*H*-purin-2-yl)-butyramide (17a)

A mixture of 2-iodopurine **13** (1 g, 2.44 mmol), Cs_2CO_3 (3 equiv, 7.32 mmol, 2.38 g), butyramide (2 equiv, 4.88 mmol, 425 mg), $Pd_2(dba)_3$ (0.02 equiv, 0.05 mmol, 45 mg), and XantPhos (0.03 equiv, 0.07 mmol, 42 mg) in dry and degassed THF (23 mL) was stirred at 80 °C for 3 h. The solution was concentrated, and, after the usual work up, the red oil was purified by silica gel column chromatography (CH_2Cl_2/EtOH 1:0 to 95:5) to afford the expected product as a white solid: 739 mg, 82%. R_f: 0.31 (CH_2Cl_2/EtOH 98:2). Mp: 118 °C. ^{1}H NMR ($CDCl_3$) δ: 7.96 (br s, 1H, NHCO); 7.89 (s, 1H, H8); 7.44 (d, 2H ar, J = 7.0 Hz); 7.34–7.22 (m, 3H ar); 4.76 (sept, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 4.59 (s, 2H, CH_2S); 2.89 (t, 2H, CH_2 a, J = 7.4 Hz); 1.80 (sext, 2H, CH_2 b, J = 7.4 Hz); 1.61 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz); 1.03 (t, 3H, CH_3 c, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 173.4 (CO); 161.4 (C6); 151.6 (C2); 149.1 (C4); 139.9 (CH, C8); 137.2 (C5); 129.0 (2CH ar); 128.5 (2CH ar); 128.1 (Cq ar); 127.3 (CH ar); 47.5 (*C*H-*i*-PrN); 39.2 (CH_2 a); 32.9 (CH_2S); 22.4 (2*C*H_3-*i*-Pr); 18.3 (CH_2 b); 13.9 (CH_3 c). MS (electrospray): *m*/*z* 392 (17%) [M+Na]; 371 (24%) [M+2H]; 370 (100%) [M+H]. HRMS calcd for $C_{19}H_{23}N_5OSN$: *m*/*z* 370.1696 [M+H]. Found: 370.1704.

4.10. *N*-(6-Benzylsulfanyl-9-isopropyl-9*H*-purin-2-yl)-3-methyl-butyramide (17b)

In the same conditions as for the preparation of **17a**, the 3-methylbutyramide derivative **17b** was obtained from **13** as a slightly orange solid, 96%. R_f: 0.29 (CH_2Cl_2/EtOH 98:2). Mp: 97 °C. ^{1}H NMR ($CDCl_3$) δ: 8.41 (s, 1H, NHCO); 7.92 (s, 1H, H8); 7.45–7.21 (m, 5H ar); 4.77 (sept, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 4.59 (s, 2H, CH_2S); 2.78 (d, 2H, CH_2CO, J = 6.9 Hz); 1.60 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 1.04 (d, 6H, 2CH_3-*i*-PrCH_2, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 172.7 (CO); 161.4 (C6); 151.6 (C2); 149.1 (C4); 139.9 (CH, C8); 137.2 (Cq ar); 129.0 (2CH ar); 128.5 (2CH ar); 128.1 (C5); 127.3 (CH ar); 47.4 (*C*H-*i*-PrN); 46.2 (*C*H_2, CH_2CO); 32.9 (CH_2S); 25.3 (*C*H-*i*-Pr); 22.6 (2*C*H_3-*i*-PrN); 22.4 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 406 (100%) [M+Na]; 384 (39%) [M+H]. HRMS calcd for $C_{20}H_{25}N_5OS$: *m*/*z* 406.1672 [M+Na]. Found: 406.1682.

4.11. *N*-(6-Benzylsulfanyl-9-isopropyl-9*H*-purin-2-yl)-isobutyramide (17c)

In the same conditions as for the preparation of **17a**, the isobutyramide derivative **17c** was obtained from **13** as a white solid, 71%. R_f: 0.34 (CH_2Cl_2/EtOH 98:2). Mp: 124 °C. ^{1}H NMR ($CDCl_3$) δ: 8.13 (br s, 1H, NHCO); 7.90 (s, 1H, H8); 7.45 (d, 2H ar, J = 6.9 Hz); 7.34–7.22 (m, 3H ar); 4.78 (sept, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 4.60 (s, 2H, CH_2S); 2.04 (br s, 1H, CHCO); 1.60 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 1.29 (d, 6H, 2CH_3-*i*-PrCO, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 161.3 (C6); 151.5 (C2); 149.2 (C4); 139.9 (CH, C8); 137.2 (Cq ar); 129.0 (2CH ar); 128.5 (2CH ar); 128.2 (C5); 127.3 (CH ar); 47.4 (*C*H-*i*-PrN); 35.3 (CHCO); 32.9 (CH_2S); 22.5 (2*C*H_3-*i*-PrN); 19.3 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 392 (10%) [M+Na]; 370 (100%) [M+H] HRMS calcd for $C_{19}H_{23}N_5OS$: *m*/*z* 370.1696 [M+H]. Found: 370.1706.

4.12. *N*-[9-Isopropyl-6-(4-methoxy-benzylamino)-9*H*-purin-2-yl]-butyramide (18a)

A solution of **17a** (664 mg, 1.79 mmol) and 3 equiv of *m*-CPBA (621 mg, 3.59 mmol) in dry CH_2Cl_2 (10 ml) was stirred at room temperature for 2 h. After addition

of water (2 ml), the organic layer was separated, dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography eluting with CH_2Cl_2 followed by CH_2Cl_2/EtOH 95:5 to afford *N*-(9-isopropyl-6-phenylmethanesulfonyl-9*H*-purin-2-yl)-butyramide as a white solid: 504 mg, 70%. R_f: 0.64 (CH_2Cl_2/EtOH 95:5). Mp: 116 °C. ^{1}H NMR ($CDCl_3$) δ: 8.48 (br s, 1H, NHCO); 8.28 (s, 1H, H8); 7.45–7.22 (m, 5H ar); 4.95 (m, 1H, C*H*-*i*-PrN); 4.91 (s, 2H, CH_2S); 2.70 (t, 2H, CH_2 a, J = 7.3 Hz); 1.80 (sext, 2H, CH_2 b, J = 7.4 Hz); 1.67 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz); 1.04 (t, 3H, CH_3 c, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 172.8 (CO); 155.2 (C2); 151.5 (C4); 145.1 (CH, C8); 131.2 (2CH ar); 129.0 (CH ar); 128.8 (2CH ar); 126.9 (C6); 126.4 (C5); 59.7 (CH_2S); 48.3 (*C*H-*i*-Pr); 39.4 (CH_2 a); 22.4 (2*C*H_3-*i*-Pr); 18.3 (CH_2 b); 13.8 (CH_3 c). MS (electrospray): *m*/*z* 424 (100%) [M+Na]; 402 (12%) [M+H]. HRMS calcd for $C_{19}H_{23}N_5O_3S$: *m*/*z* 424.1414 [M+Na]. Found: 424.1418. It was used without further purification in the next step.

A solution of the preceding 6-benzylsulfonepurine (190 mg, 0.47 mmol), 4-methoxybenzylamine (1.5 equiv, 0.94 mmol, 124 μL) in absolute ethanol (10 mL) was stirred at room temperature for 1 h. After evaporation to dryness, the crude solid was purified by silica gel column chromatography (CH_2Cl_2/EtOH 1:0–98:2) to afford the expected product (**18a**) as a white solid: 172 mg, 95%. R_f: 0.28 (CH_2Cl_2/EtOH 98:2). Mp: 115 °C. ^{1}H NMR ($CDCl_3$) δ: 7.81 (br s, 1H, NHCO); 7.66 (s, 1H, H8); 7.30 (d, 2H ar); 6.87 (d, 2H ar, J = 8.4 Hz); 6.10 (br s, 1H, NH); 4.80–4.65 (m, 3H, CH_2N and C*H*-*i*-PrN); 3.80 (s, 3H); 2.91 (br t, 2H, CH_2 a); 1.78 (sext, 2H, CH_2 b, J = 7.4 Hz); 1.58 (d, 6H, 2CH_3-*i*-Pr, J = 6.7 Hz); 1.01 (t, 3H, CH_3 c, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 174.7 (CO); 159.0 (Cq ar); 154.7 (C4); 152.7 (C2); 150.0 (C6); 136.8 (CH, C8); 130.5 (Cq ar); 129.0 (2CH ar); 116.9 (C5); 114.0 (2CH ar OMe); 55.3 (CH_3O); 47.1 (*C*H-*i*-PrN); 42.6 (CH_2N); 39.0 (CH_2 a); 22.5 (2*C*H_3-*i*-Pr); 18.4 (CH_2 b); 13.9 (CH_3 c). MS (electrospray): *m*/*z* 384 (24%) [M+2H]; 383 (100%) [M+H]. HRMS calcd for $C_{20}H_{26}N_6O_2$: *m*/*z* [M+H] 383.2195. Found: 383.2190. Anal. Calcd for $C_{20}H_{26}N_6O_2$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.55; H, 6.64; N, 21.53.

4.13. *N*-[9-Isopropyl-6-(4-methoxy-benzylamino)-9*H*-purin-2-yl]-3-methyl-butyramide (18b)

A mixture of 2-iodopurine derivative **14** (100 mg, 0.24 mmol), Cs_2CO_3 (3 equiv, 0.72 mmol, 234 mg), isovaleramide (2 equiv, 0.48 mmol, 48 mg), $Pd_2(dba)_3$ (0.02 equiv, 0.005 mmol, 4.4 mg), and XantPhos (0.03 equiv, 0.007 mmol, 4 mg) in THF (12 mL) was stirred at 80 °C for 4 h. After concentration, the residue was dissolved in CH_2Cl_2 and washed twice with an aqueous saturated solution of $NaHCO_3$. The organic layers were combined, dried ($MgSO_4$), and evaporated in vacuo. The red oil was purified by silica gel column chromatography (CH_2Cl_2/EtOH 100:0–98:2) to afford the expected product (**18b**) as a yellow solid: 65 mg, 70%. R_f: 0.46 (CH_2Cl_2/EtOH 98:2). Mp: 145 °C. ^{1}H NMR ($CDCl_3$) δ: 8.32 (br s, 1H, NHCO); 7.53 (s, 1H, H8); 7.27 (d, 2H ar, J = 8.7 Hz); 7.06 (br s, 1H, NH); 6.84 (d, 2H ar, J = 8.6 Hz); 4.73–4.62 (m, 3H, PhCH_2N and C*H*-*i*-PrN); 3.79 (s, 3H, OCH_3); 2.82 (br d, 2H, CH_2CO, J = 5.2 Hz); 2.28 (sept, 1H, C*H*-*i*-Pr, J = 6.7 Hz); 1.54 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 1.00 (d, 6H, 2CH_3-*i*-Pr, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 173.6 (CO); 158.8 (Cq ar-OMe); 154.8 (C4); 152.7 (C2); 149.6 (C6); 136.7 (CH, C8); 130.7 (Cq ar); 128.8 (2CH ar); 116.7 (C5); 113.8 (2CH ar OMe); 55.1 (CH_3O); 46.8 (CH-*i*-PrN); 45.8 (CH_2 a); 43.7 (CH_2N); 25.2 (*C*H-*i*-Pr); 22.6 (2*C*H_3-*i*-PrN); 22.4 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 419 (18%) [M+Na]; 397 (100%) [M+H]. HRMS calcd for $C_{21}H_{28}N_6O_2$: *m*/*z* 397.2349 [M+H]. Found 397.2347. Anal. Calcd for $C_{21}H_{28}N_6O_2$: C, 63.62; H, 7.12; N, 21.20. Found: C, 63.71; H, 7.14; N, 21.13.

4.14. *N*-[9-Isopropyl-6-(4-methoxy-benzylamino)-9*H*-purin-2-yl]-isobutyramide (18c)

Compound **18c** was prepared from 2-iodopurine derivative **14** (200 mg, 0.47 mmol), and isobutyramide (2 equiv, 0.94 mmol 82 mg). See preparation of **18b** for details. After stirring at 80 °C for 3 h and work up, a yellow solid was obtained, 140 mg, 77%. R_f: 0.26 (CH_2Cl_2/EtOH 98:2). Mp: 104 °C. ^{1}H NMR ($CDCl_3$) δ: 8.18 (br s, 1H, NHCO); 7.52 (s, 1H, H8); 7.27 (d, 2H ar, J = 8.7 Hz); 6.93 (br s, 1H, NH); 6.84 (d, 2H ar, J = 8.7 Hz); 4.74–4.65 (m, 3H, PhCH_2N and C*H*-*i*-PrN); 3.79 (s, 3H, OCH_3); 3.45 (br s, 1H, CHCO); 1.54 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 1.25 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 177.6 (CO); 158.8 (Cq ar OMe); 154.8 (C4); 152.6 (C2); 149.7 (C6); 136.8 (CH, C8); 129.8 (Cq ar); 128.8 (2CH ar); 116.8 (C5); 113.9 (2CH ar OMe); 58.0 (CH_3O); 46.8 (*C*H-*i*-PrN); 43.8 (CH_2N); 34.5 (CH, CHCO); 22.5 (2*C*H_3-*i*-PrN); 19.2 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 405 (22%) [M+Na]; 383 (100%) [M+H]. HRMS calcd for $C_{20}H_{26}N_6O_2$: *m*/*z* 383.2202 [M+Na]. Found 383.2190. Anal. Calcd for $C_{20}H_{26}N_6O_2$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.43; H, 6.67; N, 21.41.

4.15. *N*-[9-Isopropyl-6-(4-methoxy-benzylamino)-9*H*-purin-2-yl]-3-oxo-butyramide (18d)

Compound **18d** was prepared from 2-iodopurine derivative **14** (200 mg, 0.47 mmol) and acetoacetamide (2 equiv, 0.94 mmol, 95 mg). See preparation of **18b** for details. After the usual work up, the red oil was purified by silica gel column chromatography (CH_2Cl_2/EtOH 1:0–98:2) to afford the expected product as a yellow solid: 106 mg, 57%. R_f: 0.28 (CH_2Cl_2/EtOH 98:2). Mp: 158 °C. ^{1}H NMR ($CDCl_3$) δ: 8.38 (br s, 1H, NHCO); 7.72 (s, 1H, H8); 6.26 (br s, 1H, NH); 4.67 (sept, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 4.11 (s, 2H, CH_2CO); 3.75 (br s, 2H, CH_2N); 3.59 (t, 2H, CH_2O, J = 5.1 Hz); 3.38 (s, 3H, CH_3O); 2.30 (s, 3H, CH_3CO); 1.55 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 205.0 (CO); 171.9 (CONH); 155.0 (C4); 152.0 (C2); 136.8 (CH, C8); 117.1 (C5); 71.0 (CH_2O); 58.8 (CH_3O); 52.5 (CH_2CO); 46.8 (*C*H-*i*-Pr); 40.5 (CH_2N); 30.1 (CH_3CO); 22.6 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 357 (42%) [M+Na]; 335 (100%) [M+H]. HRMS calcd for $C_{15}H_{22}N_6O_3$: *m*/*z* 335.1838 [M+H]. Found: 335.1826.

Anal. Calcd for $C_{15}H_{22}N_6O_3$: C, 53.88; H, 6.63; N, 25.13. Found: C, 54.14; H, 6.62; N, 24.96.

4.16. *N*-[9-Isopropyl-6-(4-methoxy-benzylamino)-9*H*-purin-2-yl]-4-methoxy-benzamide (18e)

Compound **18e** was prepared from 2-iodopurine derivative **14** (300 mg, 0.709 mmol), and *p*-methoxybenzamide (2 equiv, 1.42 mmol 214 mg). See preparation of **18b** for details. After the usual work up, the red oil was purified by silica gel column chromatography (CH_2Cl_2/EtOH 100:0–98:2) to afford **18e** as a white solid: 259.5 mg, 82%. R_f: 0.36 (CH_2Cl_2/EtOH 98:2). Mp: 123 °C. ^{1}H NMR ($CDCl_3$) δ: 8.56 (s, 1H, NHCO); 7.90 (d, 2H ar, J = 8.7 Hz); 7.56 (s, 1H, H8); 7.30 (d, 2H′ ar, J = 8.5 Hz); 6.94 (d, 2H ar, J = 8.8 Hz); 6.85 (d, 2H′ar, J = 8.5 Hz); 6.10 (br s, 1H, NH); 4.86–4.68 (m, 3H, CH_2N and CH-*i*-PrN); 3.86 (s, 3H, CH_3O); 3.78 (s, 3H, CH_3O); 1.55 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 162.6 (CO); 159.0 (Cq ar OMe); 154.8 (C4); 152.8 (C2); 151.0 (C6); 136.9 (CH, C8); 130.6 (Cq ar); 129.4 (2CH ar); 129.2 (2CH ar); 117.2 (C5); 114.0 (2CH ar); 113.8 (2CH ar); 55.4 (OMe); 55.3 (OMe); 46.7 (*C*H-*i*-PrN); 22.8 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 469 (100%) [M+Na]; 447 (34%) [M+H]. HRMS calcd for $C_{24}H_{26}N_6O_3$: *m*/*z* 469.1967 [M+Na]. Found 469.1959. Anal. Calcd for $C_{24}H_{26}N_6O_3$: C, 64.56; H, 5.87; N, 18.82. Found: C, 64.31; H, 6.03; N, 18.61.

4.17. *N*-[6-(4-Chlorobenzylamino)-9-isopropyl-9*H*-purin-2-yl]-butyramide (19a)

Compound **19a** was prepared from **17a** (see preparation of **18a** for conditions) (150 mg, 0.374 mmol) and 4-chlorobenzylamine (1.5 equiv, 0.560 mmol, 68 μL) in absolute ethanol (5 mL). Work up and purification by silica gel column chromatography (CH_2Cl_2/EtOH 100:0–95:5) gave the expected product (**19a**) as a white solid: 70 mg, 49%. R_f: 0.56 (CH_2Cl_2/EtOH 95:5). Mp: 167 °C. ^{1}H NMR ($CDCl_3$) δ: 8.48 (br s, 1H, NHCO); 7.60 (s, 1H, H8); 7.30 (s, 4H ar); 4.75 (br s, 1H, NH); 4.68 (sept, 1H, CH-*i*-PrN, J = 6.8 Hz); 3.84 (br s, 2H, CH_2N); 2.87 (t, 2H, CH_2 a, J = 7.2 Hz); 1.75 (sext, 2H, CH_2 b, J = 7.4 Hz); 1.56 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz); 0.99 (t, 3H, CH_3 c, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 174.2 (CO); 154.7 (C4); 152.6 (C2); 137.0 (CH, C8); 133.2 (Cq ar); 128.9 (2CH ar); 128.8 (2CH ar); 128.6 (Cq ar); 117.4 (C5); 47.1 (*C*H-*i*-PrN); 43.7 (CH_2N); 39.0 (CH_2 a); 22.5 (2*C*H_3-*i*-Pr); 18.4 (CH_2 b); 13.9 (CH_3 c). MS (electrospray): *m*/*z* 409 (13%) [M+Na]; 387 (100%) [M+H] HRMS calcd for $C_{19}H_{23}ClN_6O$: *m*/*z* 387.1705 [M+H]. Found: 387.1695. Anal. Calcd for $C_{19}H_{23}ClN_6O$: C, 58.99; H, 5.99; N, 21.72. Found: C, 58.81; H, 6.09; N, 21.45.

4.18. *N*-[6-(4-Chloro-benzylamino)-9-isopropyl-9*H*-purin-2-yl]-3-methyl-butyramide (19b)

Compound **19b** was prepared from **17b** which was oxidized to the 6-benzylsulfone-purine derivative in 66% yield (573 mg) in the same conditions as **19a**. R_f: 0.28 (CH_2Cl_2/EtOH 98:2). ^{1}H NMR ($CDCl_3$) δ: 8.68 (br s, 1H, NHCO); 8.27 (s, 1H, H8); 7.37–7.22 (m, 5H ar); 4.98–4.88 (m, 1H, CH-*i*-PrN); 4.93 (s, 2H, CH_2S); 2.57 (d, 2H, CH_2CO, J = 7.1 Hz); 2.26 (sept, 1H, CH-*i*-Pr, J = 6.7 Hz); 1.65 (d, 6H, CH_3-*i*-PrN, J = 6.8 Hz); 1.03 (d, 6H, 2CH_3-*i*-Pr, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 176.2 (CO); 153.3 (C2); 149.4 (C4); 147.5 (CH, C8); 130.0 (2CH ar); 129.7 (CH ar); 129.0 (2CH ar); 127.9 (C6); 126.3 (C5); 69.6 (CH_2S); 49.6 (*C*H-*i*-PrN); 45.8 (CH_2CO); 25.8 (*C*H-*i*-Pr); 22.3 (2*C*H_3-*i*-PrN); 22.1 (2*C*H_3-*i*-Pr). It was used without further purification in the next step. Substitution of the 6-benzylsulfonyl group was achieved on 130 mg (0.313 mmol) with 4-chlorobenzylamine (1.5 equiv, 0.469 mmol, 57 μL) in absolute ethanol (3 mL). See the preparation of **18a** for details. Work up and purification by silica gel column chromatography (CH_2Cl_2) gave the expected product (**19b**) as a beige solid: 100 mg, 80%. R_f: 0.30 (CH_2Cl_2/EtOH 98:2). Mp: 160 °C. ^{1}H NMR ($CDCl_3$) δ: 7.83 (br s, 1H, NHCO); 7.66 (s, 1H, H8); 7.29 (s, 4H ar); 6.30 (br s, 1H, NH); 4.76 (br s, 2H, CH_2N); 4.71 (sept, 1H, CH-*i*-PrN, J = 6.8 Hz); 2.77 (d, 2H, CH_2CO, J = 6.2 Hz); 2.26 (sept, 1H, CH-*i*-Pr, J = 6.7 Hz); 1.58 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 0.99 (d, 6H, 2CH_3-*i*-Pr, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 173.6 (CO); 154.8 (C4); 152.7 (C2); 149.6 (C6); 137.6 (Cq ar); 136.9 (CH, C8); 132.9 (Cq ar); 128.8 (2CH ar); 128.5 (2CH ar); 116.7 (C5); 46.9 (*C*H-*i*-PrN); 45.8 (CH_2 a); 43.5 (CH_2N); 25.1 (*C*H *i*-Pr); 22.5 (2*C*H_3-*i*-PrN); 22.4 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 423 (15%) [M+Na]; 401 (100%) [M+H]. HRMS calcd for $C_{20}H_{25}ClN_6O$: *m*/*z* 401.1856 [M+H]. Found: 401.1851. Anal. Calcd for $C_{20}H_{25}ClN_6O$: C, 59.92; H, 6.29; N, 20.96. Found: C, 59.71; H, 6.28; N, 20.66.

4.19. *N*-[6-(4-Chloro-benzylamino)-9-isopropyl-9*H*-purin-2-yl]-isobutyramide (19c)

Compound **19c** was prepared from **17c** which was oxidized to the 6-benzylsulfone derivative which was obtained as an oil in 98% yield (213 mg) in the same conditions as **19a**. R_f: 0.28 (CH_2Cl_2/EtOH 98:2). Mp: 64 °C. ^{1}H NMR ($CDCl_3$) δ: 8.80 (br s, 1H, NHCO); 8.32 (s, 1H, H8); 7.37–7.22 (m, 5H ar); 4.95 (br sept, 1H, CH-*i*-PrN, J = 6.8 Hz); 4.92 (s, 2H, CH_2S); 2.94 (quint, 1H, CHCO, J = 6.7 Hz); 1.64 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 1.28 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 176.1 (CO); 155.1 (C2); 151.7 (C4); 145.5 (CH, C8); 134.4 (C5); 131.5 (2CH ar); 130.4 (CH ar); 128.9 (2CH ar); 126.6 (C6); 126.2 (C5); 59.6 (CH_2S); 48.2 (*C*H-*i*-PrN); 35.9 (*C*H, CHCO); 22.3 (2*C*H_3-*i*-PrN); 18.8 (2*C*H_3-*i*-Pr). It was used without further purification in the next step.

Sulfonyl substitution was carried out on 200 mg (0.498 mmol) of the above sulfone and 4-chlorobenzylamine (1.5 equiv, 0.747 mmol, 91 μL) in absolute ethanol (5 mL). See the preparation of **18a** for details. Work up and purification by silica gel column chromatography (CH_2Cl_2/EtOH 100:0–95:5) gave the expected product (**19c**) as a white solid: 105 mg, 55%. R_f: 0.25 (CH_2Cl_2/EtOH 98:2). Mp: 158–159 °C. ^{1}H NMR ($CDCl_3$) δ: 8.13 (br s, 1H, NHCO); 7.61 (s, 1H, H8); 7.28 (s, 4H ar); 7.04 (br s, 1H, NH); 4.76 (br s, 2H,

CH_2N); 4.74 (sept, 1H, CH-*i*-PrN, J = 6.8 Hz); 3.70 (q, 1H, CHCO, J = 7.0 Hz); 1.55 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 1.23 (d, 6H, 2CH_3-*i*-Pr, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 177.4 (CO); 154.7 (C4); 152.6 (C2); 149.9 (C6); 137.2 (Cq ar); 136.9 (CH, C8); 133.1 (Cq ar); 128.9 (2CH ar); 128.7 (2CH ar); 116.8 (C5); 47.0 (*C*H-*i*-PrN); 43.8 (CH_2N); 34.7 (*C*H, CHCO); 22.6 (2*C*H_3-*i*-PrN); 22.3 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 409 (11%) [M+Na]; 387 (100%) [M+H]. HRMS calcd for $C_{19}H_{23}ClN_6O$: *m*/*z* 387.1706 [M+H]. Found: 387.1695. Anal. Calcd for $C_{19}H_{23}ClN_6O$: C, 58.99; H, 5.99; N, 21.72. Found: C, 59.22; H, 6.02; N, 21.29.

4.20. *N*-[6-(4-Chloro-benzylamino)-9-isopropyl-9*H*-purin-2-yl]-4- methoxy-benzamide (19e)

Compound **19e** was prepared from 2-iodopurine derivative **15e** (200 mg, 0.498 mmol) and *p*-methoxybenzamide (2 equiv, 0.996 mmol, 150 mg) in THF (8 mL). See the preparation of **18b** for details. Work up and purification by silica gel column chromatography (CH_2Cl_2/EtOH: 100:0–98:2) gave the expected product as a yellowish solid: 185 mg, 88%. R_f: 0.16 (CH_2Cl_2/EtOH 98:2). Mp: 102 °C. ^{1}H NMR ($CDCl_3$) δ: 8.45 (br s, 1H, NHCO); 7.88 (d, 2H ar, J = 8.7 Hz); 7.77 (d, 2H ar, J = 8.7 Hz); 7.64 (s, 1H, H8); 7.30 (d, 2H ar, J = 8.4 Hz); 6.89 (d, 2H ar, J = 8.9 Hz); 6.16 (br s, 1H, NH); 4.80 (m, 3H, PhCH_2N and C*H*-*i*-PrN); 3.83 (s, 3H, CH_3O); 1.54 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 162.5 (CO); 159.1 (Cq ar OMe); 154.6 (C4); 152.9 (C2); 136.6 (CH, C8); 129.5 (2CH ar); 129.3 (2*C*H ar OMe); 116.8 (C5); 55.3 (CH_3O); 46.8 (*C*H-*i*-PrN); 43.7 (CH_2N); 22.5 (2*C*H_3-*i*-PrN). MS (electrospray): *m*/*z* 451 (100%) [M+H]. HRMS calcd for $C_{23}H_{23}ClN_6O_2$: *m*/*z* 451.1648 [M+H]. Found: 451.1644.

4.21. *N*-[9-Isopropyl-6-(methoxy-ethylamino)-9*H*-purin-2-yl]- butyramide (20a)

Compound **20a** was prepared from purine **17a** which was oxidized as described previously to afford the sulfonyl intermediate, that was reacted (150 mg, 0.374 mmol) with 2-methoxyethylamine (1.5 equiv, 0.560 mmol, 50 μL) in absolute ethanol (5 mL). See the preparation of **18a** for details. Work up and purification by silica gel column chromatography (CH_2Cl_2/EtOH: 100:0–95:5) gave the expected product as a white solid: 63 mg, 53%. R_f: 0.52 (CH_2Cl_2/EtOH 95:5). Mp: 164 °C. ^{1}H NMR ($CDCl_3$) δ: 7.91 (br s, 1H, NHCO); 7.71 (s, 1H, H8); 6.21 (br s, 1H, NH); 4.70 (sept, 1H, C*H*-*i*-PrN, J = 6.7 Hz); 3.79 (br s, 2H, CH_2N); 3.60 (t, 2H, CH_2O, J = 4.8 Hz); 3.39 (s, 3H, CH_3O); 2.90 (br s, 2H, CH_2 a); 1.79 (sext, 2H, CH_2 b, J = 7.4 Hz); 1.58 (d, 6H, 2CH_3-*i*-Pr, J = 6.7 Hz); 1.02 (t, 3H, CH_3 c, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 174.1 (CO); 154.8 (C4); 152.5 (C2); 149.5 (C6); 136.8 (CH, C8); 116.9 (C5); 71.1 (CH_2O); 58.8 (CH_3O); 47.0 (*C*H-*i*-PrN); 39.1 (CH_2 a); 22.5 (2*C*H_3-*i*-Pr); 18.4 (CH_2 b); 13.9 (CH_3 c). MS (electrospray): *m*/*z* 343 (26%) [M+Na]; 321 (100%) [M+H]. HRMS calcd for $C_{15}H_{24}N_6O_2$: *m*/*z* 321.2037 [M+H]. Found: 321.2034. Anal. Calcd for $C_{15}H_{24}N_6O_2$: C, 56.23; H, 7.55; N, 26.23. Found: C, 56.57; H, 7.68; N, 26.20.

4.22. *N*-[9-Isopropyl-6-(methoxy-ethylamino)-9*H*-purin-2-yl]-3-methyl-butyramide (20b)

Compound **20b** was prepared from **17b** (100 mg, 0.240 mmol) which was oxidized to the 6-benzylsulfone-purine derivative and subsequently substituted with 2-methoxyethylamine (1.5 equiv, 0.361 mmol, 32 μL) in absolute ethanol (2 mL). See the preparation of **18a** for details. Work up and purification by silica gel column chromatography (CH_2Cl_2/EtOH 100:0–95:5) gave the expected product as a white solid: 73 mg, 90%. R_f: 0.09 (CH_2Cl_2/EtOH 98:2). Mp: 165 °C. ^{1}H NMR ($CDCl_3$) δ: 8.05 (br s, 1H, NHCO); 7.73 (s, 1H, H8); 6.47 (br s, 1H, NH); 4.70 (sept, 1H, C*H*-*i*-PrN, J = 6.7 Hz); 3.73 (br s, 2H, CH_2N); 3.59 (t, 2H, CH_2O, J = 5.0 Hz); 3.37 (s, 3H, CH_3O); 2.79 (br s, 2H, CH_2CO); 2.27 (sept, 1H, C*H*-*i*-Pr, J = 6.7 Hz); 1.57 (d, 6H, 2CH_3-*i*-PrN, J = 6.7 Hz); 1.01 (d, 6H, 2CH_3-*i*-Pr, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 173.3 (CO); 154.9 (C4); 152.5 (C2); 149.7 (C6); 136.8 (CH, C8); 116.9 (C5); 71.1 (CH_2O); 58.8 (CH_3O); 46.9 (*C*H-*i*-PrN); 45.9 (*C*H_2CO); 40.4 (CH_2N); 25.3 (*C*H-*i*-Pr); 22.6 (2*C*H_3-*i*-PrN); 22.4 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 357 [M+Na]; 335 [M+H]. Anal. Calcd for $C_{16}H_{26}N_6O_2$: C, 57.46; H, 7.84; N, 25.13. Found: C, 56.93; H, 7.87; N, 24.98.

4.23. *N*-[9-Isopropyl-6-(methoxy-ethylamino)-9*H*-purin-2-yl]-isobutyramide (20c)

Compound **20c** was prepared from **17c** (100 mg, 0.249 mmol) which was oxidized to its 6-benzylsulfone-purine derivative and subsequently substituted with 2-methoxyethylamine (1.5 equiv, 0.374 mmol, 33 μL) in absolute ethanol (2 mL). See the preparation of **18a** for details. Work up and purification by silica gel column chromatography (CH_2Cl_2/EtOH 100:0–95:5) gave the expected product as a white solid: 50 mg, 63%. R_f: 0.23 (CH_2Cl_2/EtOH 98:2). Mp: 128 °C. ^{1}H NMR ($CDCl_3$) δ: 8.09 (br s, 1H, NHCO); 7.71 (s, 1H, H8); 6.36 (br s, 1H, NH); 4.73 (sept, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 3.77 (br s, 2H, CH_2N); 3.58 (t, 2H, CH_2O, J = 5.2 Hz); 3.42 (br s, 1H, C*H*-*i*-Pr); 3.36 (s, 3H, CH_3O); 1.55 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 1.25 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 166.4 (CO); 154.9 (C4); 152.5 (C2); 136.8 (CH, C8); 117.2 (C5); 71.1 (CH_2O); 58.8 (CH_3O); 46.9 (CH-*i*-PrN); 40.5 (CH_2N); 22.5 (2*C*H_3-*i*-PrN); 19.3 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 343 (24%) [M+Na]; 321 (100%) [M+H]. HRMS calcd for $C_{15}H_{24}N_6O_2$: *m*/*z* 321.2034 [M+H]. Found: 321.2034. Anal. Calcd for $C_{15}H_{24}N_6O_2$: C, 56.23; H, 7.55; N, 26.23. Found: C, 55.79; H, 7.24; N, 25.84.

4.24. *N*-[9-Isopropyl-6-(methoxy-ethylamino)-9*H*-purin-2-yl]-3-oxo-butyramide (20d)

Compound **20d** was prepared from 2-iodopurine derivative **16** (200 mg, 0.498 mmol) and acetoacetamide (2 equiv, 1.11 mmol, 112 mg) in THF (8 mL). See the preparation of **18b** for details. Work up and purification by silica gel column chromatography (CH_2Cl_2/EtOH 100:0–98:2) gave the expected product as a yellow solid:

105 mg, 57%. R_f: 0.28 (CH_2Cl_2/EtOH 98:2). Mp: 158 °C. ^{1}H NMR ($CDCl_3$) δ: 8.38 (br s, 1H, NHCO); 7.72 (s, 1H, H8); 6.26 (br s, 1H, NH); 4.67 (sept, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 4.11 (s, 2H, CH_2CO); 3.75 (br s, 2H, CH_2N); 3.59 (t, 2H, CH_2O, J = 5.1 Hz); 3.38 (s, 3H, CH_3O); 2.30 (s, 3H, CH_3CO); 1.55 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 205.0 (CO); 171.9 (CONH); 155.0 (C4); 152.0 (C2); 136.8 (CH, C8); 117.1 (C5); 71.0 (CH_2O); 58.8 (CH_3O); 52.5 (*C*H_2CO); 46.8 (*C*H-*i*-Pr); 40.5 (CH_2N); 30.1 (*C*H_3CO); 22.6 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 357 (42%) [M+Na]; 335 (100%) [M+H]. HRMS calcd for $C_{15}H_{22}N_6O_3$: *m*/*z* 335.1838 [M+H]. Found: 335.1826. Anal. Calcd for $C_{15}H_{22}N_6O_3$: C, 53.88; H, 6.63; N, 25.13. Found: C, 54.14; H, 6.62; N, 24.96.

4.25. *N*-[9-Isopropyl-6-(methoxy-ethylamino)-9*H*-purin-2-yl]-4-methoxy-benzamide (20e)

Compound **20e** was prepared from 2-iodopurine derivative **16** (200 mg, 0.554 mmol) and *p*-methoxybenzamide (2 equiv, 1.11 mmol, 167 mg) in THF (8 mL). See the preparation of **18b** for details. Work up and purification by silica gel column chromatography (CH_2Cl_2) gave the expected product as a yellow solid: 110 mg, 51%. R_f: 0.41 (CH_2Cl_2/EtOH 95:5). Mp: 166 °C. ^{1}H NMR ($CDCl_3$) δ: 8.51 (br s, 1H, NHCO); 7.86 (d, 2H ar, J = 8.7 Hz); 7.72 (s, 1H, H8); 6.91 (d, 2H ar, J = 8.7 Hz); 6.38 (br s, 1H, NH); 4.78 (sept, 1H, C*H*-*i*-PrN, J = 6.7 Hz); 3.82 (s, 3H, CH_3OPh); 3.80 (br s, 2H, CH_2N); 3.57 (t, 2H, CH_2O, J = 5.0 Hz); 3.34 (s, 3H, CH_3O); 1.53 (d, 6H, 2CH_3-*i*-Pr, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 164.7 (CO); 162.4 (Cq ar OMe); 154.9 (C4); 152.7 (C2); 149.6 (C6); 136.8 (CH, C8); 129.3 (2CH ar); 127.2 (Cq ar); 117.2 (C5); 113.5 (2CH ar); 71.2 (CH_2O); 58.7 (CH_3O); 55.3 (*C*H_3OPh); 46.5 (*C*H-*i*-Pr); 40.3 (CH_2N); 22.7 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 385 (100%) [M+H]; 325 (90%) [M-methoxyethyl]. HRMS calcd for $C_{19}H_{24}N_6O_3$: *m*/*z* 385.1989 [M+H]. Found: 385.1983.

4.26. 9-Isopropyl-6-(4-methoxy-benzylamino)-9*H*-purine-2- carboxylic acid isobutylamide (21b)

A stirred mixture of 2-iodopurine derivative **14** (500 mg, 1.18 mmol) and $Pd(PPh_3)_4$ (0.05 equiv, 0.06 mmol, 68 mg) in dry THF (10 mL) was degassed with CO bubbling and maintained under CO atmosphere. Triethylamine (2 equiv, 2.36 mmol, 329 μL) and isobutylamine (3 equiv, 3.5 mmol, 352 μL) were then added, and the resulting mixture was stirred at 50 °C under CO atmosphere for 2 h 30 min. The volatile material was evaporated and the crude oil purified by silica gel column chromatography (CH_2Cl_2/EtOH 100:0–95:5) to afford the expected product as a white solid: 400 mg, 85%. R_f: 0.68 (CH_2Cl_2/EtOH 95:5). Mp: 154 °C. ^{1}H NMR ($CDCl_3$) δ: 8.08 (br s, 1H, NHCO); 7.90 (s, 1H, H8); 7.31 (d, 2H ar, J = 8.6 Hz); 6.87 (d, 2H ar, J = 8.6 Hz); 6.17 (br s, 1H, NH); 5.09 (sept, 1H, C*H*-*i*-PrN, J = 6.7 HZ); 4.80 (br s, 2H, CH_2NH); 3.79 (s, 3H, CH_3O); 3.30 (t, 2H, CH_2-*i*-Pr, J = 6.5 Hz); 1.91 (sept, 1H, C*H*-*i*-Pr, J = 6.7 Hz); 1.58 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 0.96 (d, 6H, 2CH_3-*i*-Pr, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 163.4 (CO); 159.1 (Cq ar); 156.4 (C2); 153.7 (C6); 152.1 (C4); 138.9 (CH, C8); 130.3 (Cq ar); 129.0 (2CH ar); 120.5 (C5); 114.1 (2CH ar); 55.3 (CH_3O); 47.0 (*C*H_2-*i*-Pr); 46.5 (*C*H-*i*-PrN); 44.3 (CH_2N); 28.6 (*C*H-*i*-Pr); 23.1 (2*C*H_3-*i*-PrN); 20.2 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 793 (2%) [2M+H]; 419 (7%) [M+Na]; 397 (100%) [M+H]. HRMS calcd for $C_{21}H_{28}N_6O_2$: *m*/*z* 397.2347 [M+H]. Found: 397.2349. Anal. Calcd for $C_{21}H_{28}N_6O_2$: C, 63.62; H, 7.12; N, 21.20. Found: C, 63.26; H, 7.18; N, 20.98.

4.27. 9-Isopropyl-6-(4-methoxy-benzylamino)-9*H*-purine-2-carboxylic acid isopropylamide (21c)

Following the same procedure as for **21b**, with 2-iodopurine derivative **14** (500 mg, 1.18 mmol) and isopropylamine (3 equiv, 3.5 mmol, 302 μL), a yellow solid was obtained: 350 mg, 77%. R_f: 0.43 (CH_2Cl_2/EtOH 95:5). Mp: 165 °C. ^{1}H NMR ($CDCl_3$) δ: 7.89 (s, 1H, H8); 7.81 (br d, 1H, NHCO, J = 8.0 Hz); 7.32 (d, 2H ar, J = 8.6 Hz); 6.87 (d, 2H ar, J = 8.6 Hz); 6.21 (br s, 1H, NH); 5.07 (sept, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 4.79 (br s, 2H, CH_2N); 4.24 (m, 1H, C*H*-*i*-PrNCO, J = 6.6 Hz); 3.80 (s, 3H, CH_3O); 1.57 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 1.27 (d, 6H, 2CH_3-*i*-Pr, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 162.5 (CO); 159.1 (Cq ar); 152.2 (C4); 138.9 (CH, C8); 130.4 (Cq ar); 129.0 (2CH ar); 114.1 (2CH ar); 55.3 (CH_3O); 46.4 (*C*H-*i*-PrN); 41.6 (*C*H-*i*-PrNH); 23.2 (2*C*H_3-*i*-PrN); 22.7 (2*C*H_3-*i*-PrNH). MS (electrospray): *m*/*z* 787 (24%) [2M+Na]; 383 (100%) [M+H]. HRMS calcd for $C_{20}H_{26}N_6O_2$: *m*/*z* 383.2190 [M+H]. Found: 383.2202. Anal. Calcd for $C_{20}H_{26}N_6O_2$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.81; H, 6.83; N, 21.93.

4.28. 6-(4-Chloro-benzylamino)-9-isopropyl-9*H*-purine-2-carboxylic acid isopropylamide (22c)

Following the same procedure as for **21b**, with 2-iodopurine derivative **15** (80 mg, 0.19 mmol) and isopropylamine (3 equiv, 0.56 mmol, 50 μL), a white solid was obtained: 55 mg, 76%. R_f: 0.43 (CH_2Cl_2/EtOH 95:5). Mp: 152 °C. ^{1}H NMR ($CDCl_3$) δ: 7.93 (s, 1H, H8); 7.69 (br s, 1H, NHCO); 7.33 (s, 4H ar); 6.22 (br s, 1H, NH); 5.09 (sept, 1H, NC*H*-*i*-Pr, J = 6.8 Hz); 4.86 (br s, 2H, CH_2N); 4.24 (m, 1H, C*H*-*i*-PrNH, J = 6.6 Hz); 1.59 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 1.25 (d, 6H, 2CH_3-*i*-PrNH, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 162.4 (CO); 153.8 (C2); 152.1 (C4); 148.9 (C6); 139.1 (CH, C8); 137.1 (Cq ar); 133.2 (Cq ar); 128.9 (2CH ar); 128.8 (2CH ar); 120.4 (C5); 46.5 (*C*H-*i*-PrN); 44.4 (CH_2N); 41.5 (*C*H-*i*-PrNH); 23.1 (2*C*H_3-*i*-Pr); 22.7 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 797 (34%) [2(M+H)+Na]; 795 (45%) [2M+Na]; 409 (30%) [M+Na]; 387 (100) [M+H]. HRMS calcd for $C_{19}H_{23}ClN_6O$: *m*/*z* 387.1695 [M+H]. Found: 383.1706. Anal. Calcd for $C_{19}H_{23}ClN_6O$: C, 58.99; H, 5.99; N, 21.72. Found: C, 58.88; H, 6.25; N, 21.57.

4.29. 9-Isopropyl-6-(2-methoxy-ethylamino)-9*H*-purine-2-carboxylic acid isobutylamide (23b)

Following the same procedure as for **21b**, with 2-iodopurine derivative **16** (500 mg, 1.18 mmol) and isobutyl-

amine (3 equiv, 3.5 mmol, 352 μL) a slightly yellow solid was obtained: 440 mg, 95%. R_f: 0.32 (CH_2Cl_2/EtOH 95:5). Mp: 112 °C. ^{1}H NMR ($CDCl_3$) δ: 8.09 (br s, 1H, NHCO); 7.91 (s, 1H, H8); 6.48 (br s, 1H, NH); 4.97 (sept, 1H, C*H*-*i*-PrN, J = 6.8 HZ); 3.83 (br s, 2H, CH_2NH); 3.57 (t, 2H, CH_2O, J = 5.2 Hz); 3.31 (s, 3H, CH_3O); 3.23 (t, 2H, CH_2-*i*-Pr, J = 6.5 Hz); 1.85 (sept, 1H, C*H*-*i*-Pr, J = 6.7 Hz); 1.50 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 0.90 (d, 6H, 2CH_3-*i*-Pr, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 163.3 (CO); 153.9 (C2); 151.8 (C4); 149.0 (C6); 138.8 (CH, C8); 120.3 (C5); 70.9 (CH_2O); 58.6 (CH_3O); 46.8 (*C*H_2-*i*-Pr); 46.3 (*C*H-*i*-PrN); 40.3 (*C*H_2NH); 28.4 (*C*H-*i*-Pr); 22.9 (2*C*H_3-*i*-PrN); 19.9 (2*C*H_3-*i*-Pr). MS (electrospray): *m*/*z* 691 (10%) [2M+Na]; 357 (33%) [M+Na]; 335 (100%) [M+H]. HRMS calcd for $C_{16}H_{26}N_6O_2$: *m*/*z* 335.2190 [M+H]. Found: 335.2199. Anal. Calcd for $C_{16}H_{26}N_6O_2$: C, 57.46; H, 7.84; N, 25.13. Found: C, 56.94; H, 7.87; N, 24.81.

4.30. 9-Isopropyl-6-(2-methoxy-ethylamino)-9*H*-purine-2-carboxylic acid isopropylamide (23c)

Following the same procedure as for **21b**, with 2-iodopurine derivative **16** (500 mg, 1.38 mmol) and isopropylamine (3 equiv, 3.5 mmol, 354 μL) a white solid was obtained: 400 mg, 90%. R_f: 0.35 (CH_2Cl_2/EtOH 95:5). Mp: 122 °C. ^{1}H NMR ($CDCl_3$) δ: 7.88 (s, 1H, H8); 7.80 (br d, 1H, NHCO, J = 7.9 Hz); 6.53 (br s, 1H, NH); 4.95 (sept, 1H, C*H*-*i*-PrN, J = 6.8 Hz); 4.14 (m, 1H, C*H*-*i*-PrNH, J = 6.6 Hz); 3.81 (br s, 2H, CH_2N); 3.55 (t, 2H, CH_2O, J = 5.3 Hz); 3.30 (s, 3H, CH_3O); 1.49 (d, 6H, 2CH_3-*i*-PrN, J = 6.8 Hz); 1.29 (d, 6H, 2CH_3-*i*-Pr, J = 6.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 162.5 (CO); 154.5 (C4); 152.5 (C2); 149.7 (C6); 139.3 (CH, C8); 120.8 (C5); 71.6 (CH_2O); 59.2 (CH_3O); 46.8 (*C*H-*i*-PrN); 41.9 (*C*H-*i*-PrNH); 40.9 (CH_2N); 23.5 (2*C*H_3 *i*-PrN); 23.1 (2*C*H_3-*i*-PrNH). MS (electrospray): *m*/*z* 663 (21%) [2M+Na]; 343 (70%) [M+Na]; 321 (100%) [M+H]. HRMS calcd for $C_{15}H_{24}N_6O_2$: *m*/*z* 321.2034 [M+H]. Found: 321.2046. Anal. Calcd for $C_{15}H_{24}N_6O_2$: C, 56.23; H, 7.55; N, 26.23. Found: C, 56.17; H, 7.72; N, 26.02.

Acknowledgments

The authors thank ARC (Association pour la Recherche sur le Cancer, France) for financial support (Contract No. 4660), the French Ministry of Research (MENRT fellowship for L.V.) and Institut Curie (Fellowship for S.K.). This research was also supported by a grant from the EEC (FP6-2002-Life Sciences & Health, PRO-KINASE Research Project) (L.M.), and the 'Cancéropole Grand-Ouest' (L.M.).

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