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Traceless solid-phase synthesis of 2,6,9-trisubstituted purines from resin bound 6-thiopurines

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Abstract—The preparation of 6-chloro-2-iodo-9-tetrahydropyranylpurine (**2**), was achieved in three high yield steps from 6-chloropurine. This derivative was then selectively substituted at C-6 by reaction with a benzylthiol to give **3**, a versatile intermediate for the synthesis of 2,6,9-trisubstituted purines. Reaction of **3** in palladium-catalyzed cross-coupling reactions, (including Sonogashira coupling at room temperature), as well as nucleophilic substitutions with amines occurred selectively at C-2. The 6-thiobenzyl substituent was activated through oxidation to the corresponding sulfone and replaced by various benzyl or phenyl amines. This strategy was subsequently adapted to solid support, wherein **23** is connected to Merrifield resin via a 6-thiovaleric ester linker. The presence of the linker, in combination with the use of palladacycle type catalysts improved the yield of palladium(0)-catalyzed Suzuki and Sonogashira cross-coupling reactions. This strategy opens a new route to combinatorial chemistry library synthesis of trisubstituted purines on the solid support. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Modified purines bearing substituents at the 2-, 6- and/or 9 positions have been associated with a wide variety of interesting biological properties. For instance, they find application as cyclin-dependent kinase inhibitors,[1–8] adenosine receptor antagonists,[9–11] modulators of multidrug resistance,[12] and as antiviral[13] and antineoplastic agents.[14]

2,6,9-Trisubstituted purines are generally obtained from the corresponding 2,6-dihalo-purines. These intermediates react with amine (alkyl, or aryl) and oxygen nucleophiles at C-6 prior substitution at the C-2 position.[15–18] Recently, palladium-catalyzed cross-coupling reactions between 2,6-dichloropurines have been explored, showing that in Stille couplings regioselective functionalization at the 6-position is achieved at 70–85°C, whereas at higher temperature (120°C) reaction occurs at both C-2 and C-6. Further, it has also been shown that the regioselectivity in Stille couplings is governed by the nature of the halogen leaving group, since for 2-bromo or 2-iodo-6-chloropurine selective coupling at the 2-position is achieved under mild conditions (40–60°C).[19] Similar C-2 regioselectivity was observed in Sonogashira cross-coupling reactions between 6-chloro-2-iodo purines and various acetylenic derivatives carried out at room temperature.[10,11]

In the course of our synthetic efforts toward the construction of purine libraries using solid support technology, we needed to introduce various amine, acetylenyl and aryl substituents selectively at the 2-position of the purine ring with the subsequent option to effect further nucleophilic substitution at the C-6 position. Keeping in mind that 2-iodo(or bromo- or chloro)-6-chloropurines always react initially at the 6-position with ammonia[15,16,20,21] and primary/secondary amines,[15,18,22,23] whereas the corresponding reactions of 2-fluoro-6-chloropurines produce either 6-mono-substituted-2-fluoropurines[24,25] or mixtures of 2 or 6-monosubstituted purines,[25–30] we chose to connect the purine ring to the resin via a sulfur atom at C-6. Indeed, it was predicted that the C6–S bond in such thiopurine derivatives would be stable to the conditions used to functionalize the 2 and 9-positions of the purine ring, as well as to a variety of acidic, basic, nucleophilic, mild electrophilic and oxophilic reaction conditions which are classically used in solid phase synthesis. Furthermore, the same sulfur atom would react as a good leaving group after activation through conversion to the corresponding sulfone.[31] This step serves also to liberate the fully functionalized purine from the polymer support.

In the present paper we present our results on the development of this strategy.[32–34] This involved initial optimization of the synthetic operations in solution using 2-iodo-6-thiobenzyl-purine derivatives to mimic the resin bound purine substrate. This chemistry, which includes Pd-catalyzed cross-coupling reactions to produce 2-alkynylated purine derivatives[11,35,36] was, subsequently adapted to the

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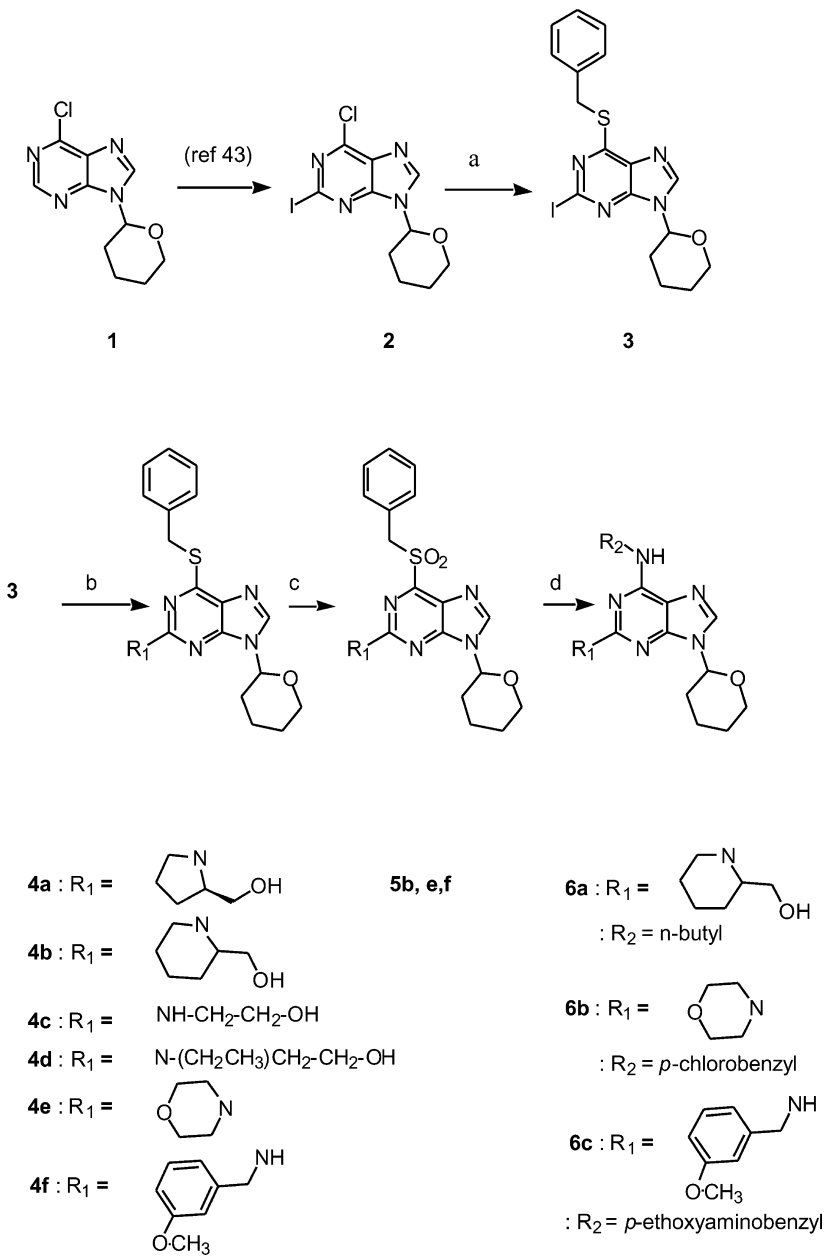
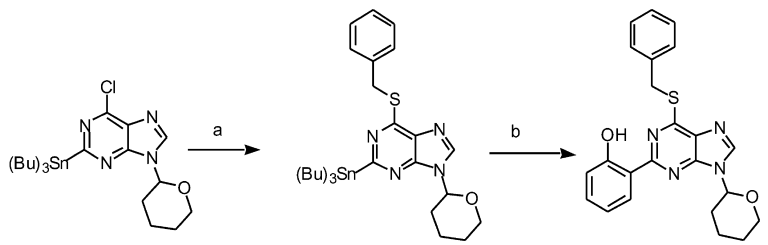


Scheme 1. (a) Benzyl thiol, ethanol, 60°C; (b) RNH_2, *N*,*N*-dimethylacetamide, $N(n-Pr)_3$, 100–120°C; (c) *m*-CPBA, CH_2Cl_2, 0°C, or rt, ≤10 min; (d) benzylamine, ethanol.

solid phase. The objective of this work was to propose a general method for the synthesis of 2,6,9-trisubstituted purines on solid support which is compatible with palladium-catalyzed cross-coupling reaction at C-2. As demonstrated, the key feature of our approach is the possibility to effect reaction at all three positions (2, 6 and 9) while the purine is on the solid support. Other reported methods to prepare trifunctionalized purines either require one step in the liquid phase,[37] or are limited by the necessity to make attachment of one of the amine components to the resin before connection of the purine.[38–41]

2. Results and discussion

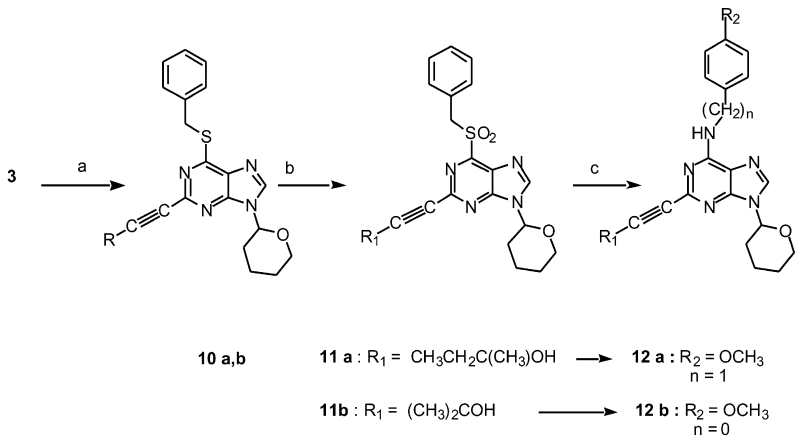
The 6-chloro-2-iodo-9-tetrahydropyranylpurine **2** (Scheme 1) was obtained from 6-chloro purine[42] **1** via a lithiation-mediated stannyl transfer process followed by 2-tributylstannyl–iodine exchange as described by Kato and colleagues.[43] We found that the presence of the 9-tetrahydropyran (THP) protecting group was required in order to obtain the 2-stannylated purine intermediate in high yield. Indeed, in our hands, the corresponding reaction of 9-alkyl purines did not proceed. Chelation of the 8-lithio intermediate by the THP oxygen might explain this result. A further interest for the use of tetrahydropyran group is that it is easily removed under mild acidic condition. In this way the 6-chloro-2-iodopurine derivative (**2**) was obtained in high yield from inexpensive 6-chloropurine (in contrast to 2,6-dichloropurine which although frequently employed in purine synthesis[3,29,44,45] is cost prohibitive). Selective substitution of the 6-chloro atom in **2** by benzylthiol was achieved upon simple heating (60°C), and led to **3** (Scheme 1) without any substitution of the 2-iodo atom.



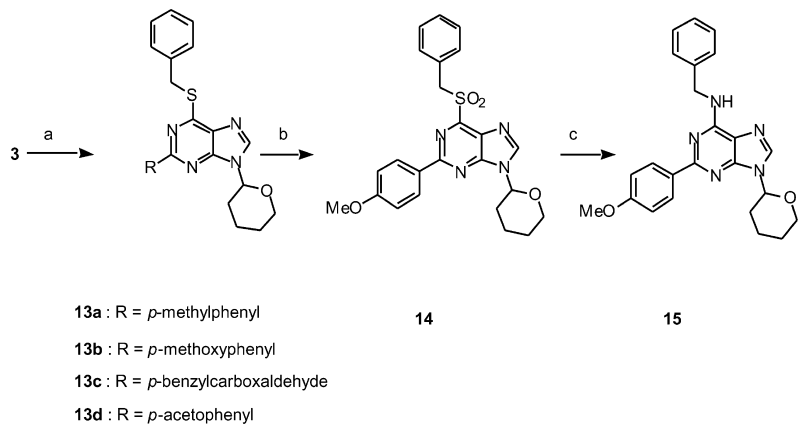
Scheme 2. (a) Benzyl thiol, *t*-BuOK, ethanol, rt; (b) *o*-iodo phenol, $Pd(PPh_3)_4$, CuI, THF.

In order to generate a small C-2 amine library, intermediate **3** was reacted with a series of primary/secondary amines to give compounds **4a**–**f**. (Scheme 1) The 6-benzylthio ether motif in compounds **4b**, **e** and **f** was then readily and cleanly converted to the corresponding sulfone. This oxidation reaction does not produce any 6-oxopurine or side chain oxidized side-products provided that the dichloromethane solution of *m*-CPBA was previously dried. Final reaction of compounds **5** with the appropriate amine provided the trisubstituted purine products **6a**–**c**.

By treating the stannylated intermediate **7** (precursor of **2**) with benzylthiol at room temperature the 6-benzylthio purine derivative **8** was obtained (Scheme 2). Stille cross-coupling reaction of **8** with *o*-iodophenol then afforded **9** in good yield, demonstrating that the presence of the 6-thiobenzyl susbstituent was not detrimental to this reaction. The conditions for this reaction are similar to those used for the Stille coupling of 6-chloro-2-stannylated purines.[43] The 2-iodo purine derivative **3** was in turn subjected to Sonogashira cross-coupling reactions with acetylene derivatives (Scheme 3). In this case, the 2-substituted acetylenic derivatives (**10a**, **b**) were obtained in good yield at room temperature. Thus, the reactivity of the 2-iodopurine **3** containing a 6-benzylthio substituent was comparable to the reactivity of 6-chloro-2-iodopurine.[11] Note that a Sonogashira cross-coupling at 2 would require higher temperatures in the presence of a 6-amino substituent.[46] Finally, Pd(0) catalyzed Suzuki cross-coupling reactions of iodopurine **3** with boronic acids provided a further means for introducing aromatic substituents at C-2 (**13a**–**d**) (Scheme 4).



Scheme 3. Alkyne, $(PPh_3)_2PdCl_2$, CuI, Et_3N/THF; *m*-CPBA, CH_2Cl_2, 0°C or rt, ≤10 min; (c) RNH_2, rt or 80°C.

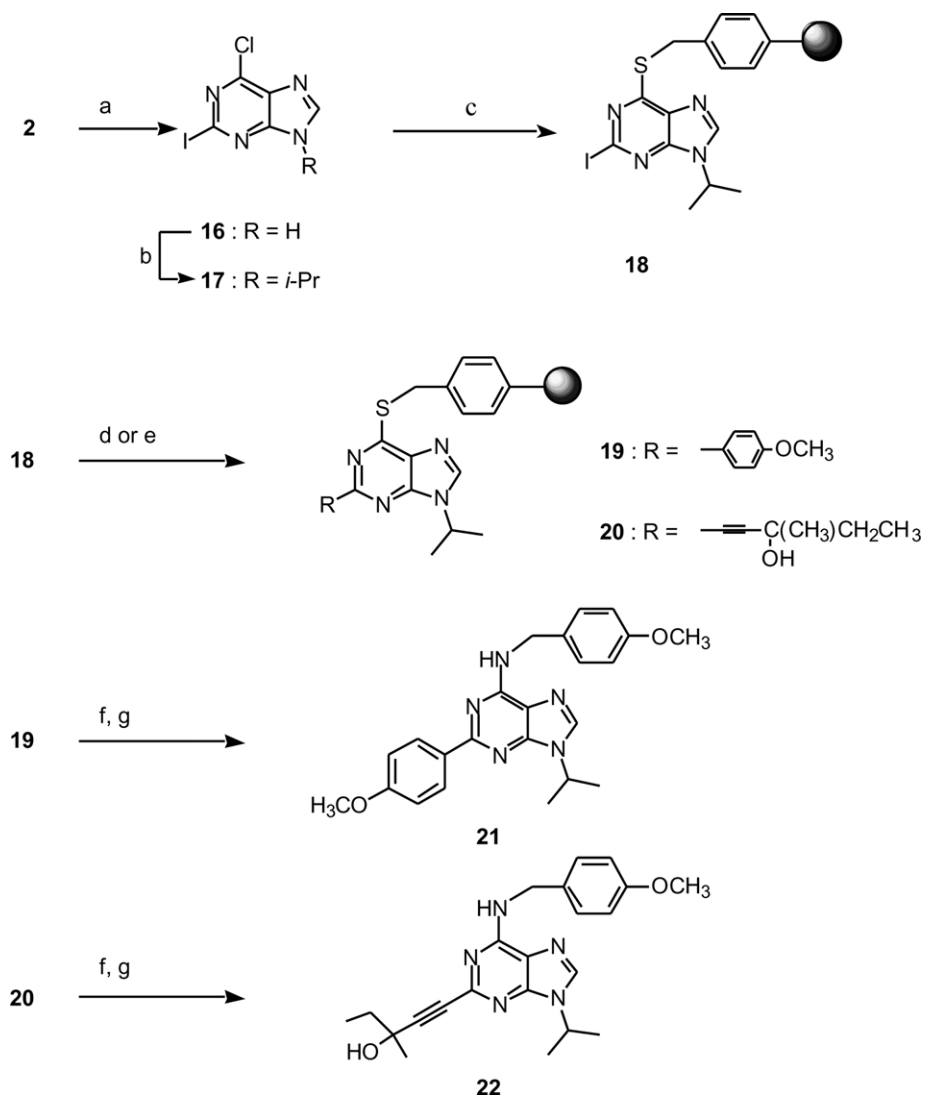


Scheme 4. $ArB(OH)_2$, $Pd(PPh_3)_4$ (3 mol%), Na_2CO_3, DMF, Δ, 24; (b) *m*-CPBA, CH_2Cl_2, rt; (c) $PhCH_2NH_2$, *tert*-BuOH, 60°C.

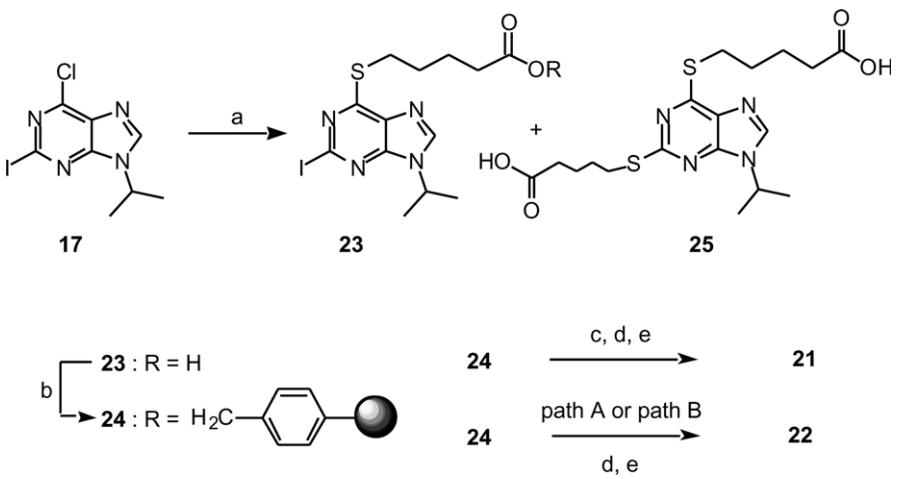
The strategy outlined in Schemes 2–4 therefore provides an efficient means for the creation of a C–C bond involving the purine C-2 position, while leaving the C-6 position unaffected. The subsequent displacement of the sulfur substituent at C-6 in compounds **10a**, **b** and **13a–d** by amines (aryl, benzyl,…) via the two-step oxidation SNAr reaction protocol again proved straightforward and high yielding. In this context it is pertinent to note that the 6-benzylthio substituent behaves as a temporary C-6 'protecting group', which is inert under a variety of reaction conditions including SNAr and particularly various palladium-catalyzed cross-coupling reactions (Sonogashira, Suzuki, Stille).

Having validated the 6-thiobenzylpurine approach to the synthesis of 2,6,9-trisubstituted purines in solution, the next step was to adapt this chemistry to the solid phase. The resin bound purine **18** was thus prepared (purine directly connected at **6** to a Merrifield-SH resin) and subjected to two palladium-catalyzed cross-coupling reactions (Scheme 5). Under conditions that led to alkynylated derivatives **10a**, **b** from **3** no reaction occurred on solid support, even by adding 1 equiv. of palladium reagent and a large excess of CuI and acetylene. In all cases, the resin rapidly turned black, indicating that the palladium metal was precipitating onto the resin surface. In addition, no purine could be recovered after performing the two-step procedure (S-oxidation and reaction with a benzylamine) used for product release. However, employing the more coordinating bidentate phosphine ligand 'dppe', the resin remained only slightly colored, and the alkynylated derivative **22** was obtained in 25% yield. This reaction was further improved in terms of the amount of palladium reagent, CuI and acetylene required through use of Herrmann's catalyst[47] (catalytic quantities). In a Suzuki reaction involving resin **18**, 0.5 equiv. of palladium tetrakis, an excess of base (3 equiv.) and boronate (3 equiv.), the yield of **19** remained low as judged by the yield (10%) of the cleaved compound (**21**).

To decrease the effect of steric crowding and its probable influence on catalyst destruction (and hence reaction yield)



Scheme 5. (a) TFA 20 equiv. dropwise in DCM then 5 min, rt; (b) $P(Ph)_3$ 1 equiv., DIAD 1 equiv., THF, −50°C, 10 min, *i*-PrOH 1 equiv., 10 min, then rt 2 days; (c) merrifield resin-SH 1 mmol/g 3 g in DMF, *tert*-BuOK 1 equiv., stirring 15 min under Ar then **17** 3 equiv., 80°C, 24 h; (d) resin **18**~1 mmol 200 mg, DMF, Pd(0) 0.5 equiv., DIEA 3 equiv., 4-methoxyphenylboronic acid 3 equiv., 100°C 3 days; (e) resin **18**~1 mmol 200 mg, DMF, $PdCl_2$(dppe) 1.1 equiv., CuI 2.2 equiv., ~DIEA 30 equiv., 3-methyl-pentyn-3-ol 20 equiv., 80°C, 36 h; (f) *m*-CPBA, CH_2Cl_2, rt, 24 h; (g) RNH_2, 70°C.



Scheme 6. (a) 5-Mercaptovaleric acid 1.2 equiv., DMF, NaH 1.2 equiv., stirring 15 min, rt, then **17** 1 equiv. 2 h; (b) merrifield resin 1 mmol/g, 1 g, DMF, cesium carbonate 3 equiv., KI 0.5 equiv., **17** 1.5 mmol; (c) resin **24**~1 mmol 200 mg, DMF, Pd(0) 0.5 equiv., DIEA 3 equiv., 4-methoxyphenylboronic acid 3 equiv., 100°C 3 days. (Path A) resin **24**~1 mmol 200 mg, DMF, $PdCl_2$(dppe) 1.1 equiv., CuI 2.2 equiv., DIEA 30 equiv., 3-methyl-pentyn-3-ol 20 equiv., 80°C, 36 h. (Path B) resin **24** 1 mmol/g 200 mg, NMP, Herrmann's catalyst 20 mol%, CuI 5 mol%, DIEA 3.6 equiv., 3-methyl-pentyn-3-ol 3.9 equiv., 80°C, 36 h; (d) *m*-CPBA, CH_2Cl_2, rt, 24 h; (e) RNH_2, 70°C.

through 'irreversible' coordination of Pd metal to the purine N7 and the sulfur atom at 6, the 6-chloro-2-iodopurine substrate **17** was connected to the Merrifield-Cl resin (35–75 μm; 1 mmol/g) via a 5-thiovaleric acid linker (Scheme 6). Indeed, Waldmann et al.[48] have recently shown that a wide range of Pd(0) coupling reactions are highly efficient when the substrate and polymer support are separated by a linker. Interestingly, the formation of compound **23** was always accompanied by small quantities (up to 15%) of the 2,6-disubstituted compound **25**. After condensation of intermediate **23** to the resin via $CsCO_3$ promoted ester formation, the resin bound substrate **24** was reacted with 3-methyl-1-pentyn-3-ol using the stoechiometric Pd(dppe)Cl_2–CuI system (Scheme 6). After cleavage of the coupling product from the resin via S-oxidation with *m*-CPBA and reaction of the derived sulfone with *p*-methoxybenzylamine, the trisubstituted purine derivative **22** was isolated in 64% overall yield (three steps from **24**). More pertinent, conducting the same reaction using a catalytic amount of Herrmann's catalyst (20 mol%) provided compound **22** in 50% isolated yield after the three-step sequence. The conditions previously used for the Suzuki cross-coupling on resin **18**, were then applied to resin **24** (($Pd(PPhe_3)_4$ (0.5 equiv.); DIEA 3 equiv.; boronic acid 3 equiv.). Although not optimized with respect to the catalyst, the presence of the linker led to significant improvement in the yield of product **21** (10% without linker to 35% with the linker). These experiments demonstrate the advantage of incorporating a linker between the resin and the purine substrate.

In summary, we have demonstrated the versatility of our strategy to build 2,6,9-trisubstituted purines in liquid as well as in solid phase synthesis. This methodology should open the route to the construction of more diverse purine libraries. Although ignored in the present work, the potential of the Mitsunobu reaction for introduction of diversity at the N-9 position of the purine ring has been clearly demonstrated by several groups in both solution[49–54] and solid phase synthesis.[55] Our method permits independent substitutions at the purine 2, 6 and 9 positions on solid support, and is compatible with a variety of Pd(0) coupling protocols for functionalization at C-2. In a recent article, Schultz et al.[56] reported a closely related strategy using a 2-fluoro-6-mercapto-polystyrene resin for the preparation of 2,6-diamino substituted purine libraries. However, in its present form their approach, where the purine is directly linked to the resin, may be limited with respect to the diversity of the chemistry that can be carried out at C-2.

3. Experimental

3.1. Material and methods

Melting points are uncorrected. NMR spectra were recorded on either 200 (Varian, AC200) or 300 (Bruker, Avance 300) MHz spectrometers. (Prime numbers refer to numbering of THP protons.) MS were measured by chemical ionization (CI, NH_3), or by electrospray. Microanalyses were performed by the Service de microanalyses, ICSN, CNRS, Gif sur Yvette. Anhydrous solvents were freshly distilled before use: tetrahydrofuran (THF) from sodium /benzophenone under argon, *N*,*N*-dimethylacetamide and *N*,*N*-dimethylformamide from P_2O_5. Flash chromatographies were performed on silica gel 60 (SDS, 35–70 μm) columns under pressure (5–10 bars).

3.1.1. 6-Chloro-9-(tetrahydro-pyran-2-yl)-2-tributyl-stannanyl-9*H*-purine (7). The 6-chloro-9-(tetrahydro-pyran-2-yl)-9*H*-purine (**1**) (7.5 g, 31 mmol, 1 equiv.) in THF (30 mL),was added dropwise to a THF (200 mL) solution of LTMP (lithium tetramethylpiperidine) (1.4 mol, 4.7 equiv.) under inert atmosphere (Argon), while maintaining the reaction temperature below −70°C. The mixture was stirred for 1 h, Bu_3SnCl (25 mL, 93 mmol, 3 equiv.) was added slowly, and stirring was continued for 0.5 h at −78°C. The reaction was quenched by adding aqueous NH_4Cl. The aqueous layer was extracted with dichloromethane, the organic layers (THF, CH_2Cl_2) were washed

with brine, dried ($MgSO_4$), evaporated and chromatographed on a silica gel column (heptane/EtOAc=9/1–7/3). This afforded the desired compound (**7**) as a colorless oil (15.7 g, 95%). MS (CI/NH_3): *m/z* 527 $(M)^+$; *m/z* 528 $(MH)^+$; *m/z* 445 $(M-THP)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.8–0.86 (t, *J*=7.31 Hz, 9H, CH_2CH_3); 1.1–1.40 (2m, 12H, 3×$CH_2CH_2CH_3$); 1.52–1.7 and 2.0–2.15 (2m, 12H, 3×CH_2Sn and $H_{2',3',4'}$); 3.65–3.78 (td, *J*=2.82, 10.97 Hz, 1H, $H_{5'}$); 4.09–4.15 (m, 1H, $H_{5'}$); 5.70–5.76 (dd, *J*=2.81, 9.9 Hz, 1H, $H_{1'}$); 8.02 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 8.9 (CH_3); 14.1 (CH_3CH_2); 23.0 ($C_{3'}$); 25.2 ($C_{4'}$); 27.6 ($CH_3CH_2CH_2$); 29.4 (CH_2Sn); 32.1 ($C_{2'}$); 69.1 ($C_{5'}$); 82.9 ($C_{1'}$); 130.6 (C_5); 141.9 (C_8); 149.5 (C_4); 150.4 (C_6); 181.1 (C_2). Anal. calcd for $C_{22}H_{37}N_4OClSn$: C, 50.07; H, 7.06; N, 10.61. Found: C, 50.6; H, 6.7; N, 10.2.

3.1.2. 6-Chloro-2-iodo-9-(tetrahydro-pyran-2-yl)-9*H*-purine (2). A solution of 6-chloro-9-(tetrahydro-pyran-2-yl)-2-tributylstannanyl-9*H*-purine (**7**) (12.2 g, 23.1 mmol) in THF (220 mL) containing iodine (7.4 g, 27.7 mmol, 1.2 equiv.) was stirred at room temperature until disappearance of the stannanyl-purine (as judged by TLC heptane/EtOAc 1/1). The reaction was quenched by adding a saturated solution of NaS_2O_3. The aqueous layer was extracted with dichloromethane, the organic layers were washed with brine, dried ($MgSO_4$) and evaporated. Silica gel chromatography column (heptane/EtOAc=8/2) of the residue gave compound (**2**) as a white solid, which was recrystallized from heptane in 79% yield; MS (CI/NH_3): *m/z* 365 $(MH)^+$; *m/z* 364 $(M)^+$; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.55–2.2 (m, 6H, $H_{2',3',4'}$); 3.6–3.85 (dt, *J*=3.61, 10.29 Hz, 1H, $H_{5'}$); 4.05–4.2 (m, 1H, $1H_{5'}$); 5.6–5.8 (dd, *J*=2.06, 9.81 Hz, $1H_{1'}$); 8.21 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.5 ($C_{3'}$); 24.7 ($C_{4'}$); 32.1 ($C_{2'}$); 68.9 ($C_{5'}$); 82.3 ($C_{1'}$); 116.6 (C_2); 131.6 (C_5); 143.0 (C_8); 150.3 (C_4); 151.6 (C_6). Anal. calcd for $C_{10}H_{10}ClIN_4O$: C, 32.95; H, 2.76; N, 15.37; I, 34.81. Found: C, 33.14; H, 2.76; N, 15.12; I, 35.05.

3.1.3. 6-Benzylsulfanyl-2-iodo-9-(tetrahydro-pyran-2-yl)-9*H*-purine (3). A solution of 6-chloro-2-iodo-9*H*-9-tetrahydropyranylpurine (**2**) in ethanol (15 mL) containing triethylamine (2 equiv.) and benzylmercaptan (2 equiv.) was stirred under inert atmosphere (Ar) at 60°C for 4 h. The mixture was cooled to room temperature, filtered. The solid compound was washed with ethanol and recrystallised from ethanol. The filtrate was evaporated to dryness before purification by column chromatography eluting with heptane/ethylacetate (4/6) to give a further amount of pure **3**. Desired compound was obtained in 93% yield; mp 186–187°C; MS (CI/NH_3): *m/z* 452 $(M)^+$; *m/z* 453 $(MH)^+$; ^1H NMR ($CDCl_3$; 200 MHz): δ 1.55–2.25 (2m, 6H, $H_{2',3',4'}$); 3.65–3.9 (td, *J*=2.85, 11.1 Hz, 1H, $H_{5'}$); 4.05–4.3 (m, 1H, $H_{5'}$); 4.55 (s, 2H, CH_2Ph); 5.6–5.8 (dd, 1H, *J*=1.9, 8.0 Hz, $H_{1'}$); 7.15–7.4 and 7.4–7.6 (2m, 5H, Ph); 8.04 (s, 1H, H_8); ^{13}C NMR: δ 22.6 ($C_{3'}$); 24.8 ($C_{4'}$); 32.1 ($C_{2'}$); 33.3 (CH_2Ph); 68.8 ($C_{5'}$); 81.8 ($C_{1'}$); 118.4 (C_2); 127.4, 128.4, 129.4, 137.2 (Ph); 131.1 (C_5); 140.3 (C_8); 148.4 (C_4); 161.6 (C_6). 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.

3.1.4. 6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-2-tributylstannanyl-9*H*-purine (8). A solution of benzylmercaptan (2 equiv.) in ethanol (25 mL) containing sodium terbutoxide was stirred under inert atmosphere (Ar) at room temperature for 10 min. A solution of 6-chloro-9-(tetrahydro-pyran-2-yl)-2-tributylstannanyl-9*H*-purine (**7**) in ethanol (5 mL) was then added and the mixture was stirred at room temperature for 2 h. After evaporation of the volatile material in vacuo, workup (CH_2Cl_2 extraction, water washing and $MgSO_4$ drying of the organic phase) was followed by column chromatography (SiO_2) which provided pure material as a colorless oil in 85% yield: MS (CI/NH_3): *m/z* 615 $(M)^+$; *m/z* 616 $(MH)^+$; ^1H NMR: ($CDCl_3$, 200 MHz): δ 0.7–1 (t, 9H, *J*=7.2 Hz, CH_3); 1–1.5 (2m, 12H, 3×$CH_2CH_2CH_3$); 1.5–2.15 (m, 12H, 3×CH_2Sn and $H_{2'3'4'}$); 3.6–3.8 (m, 1H, $H_{5'}$); 4.05–4.2 (m, 1H, $H_{5''}$); 4.67 (s, 2H, CH_2Ph); 5.65–5.85 (m, 1H, $H_{1'}$); 7.1–7.5 (2m, 2+3H, Ph); 8.06 (s, 1H, H_8); ^{13}C NMR: ($CDCl_3$, 75.47 MHz) δ 7.1 (CH_3); 13.6 (CH_2CH_3); 22.6 ($C_{3'}$); 24.7 ($C_{4'}$); 27.7 ($CH_2CH_2CH_3$); 28.9 (CH_2Sn); 31.5 ($C_{2'}$); 31.9 (CH_2Ph); 68.4 (C_5); 81.2 ($C_{4'}$); 126.8, 128.2, 128.8, 138.2 (Ph); 129.8 (C_5); 139.2 (C_8); 146.9 (C_4); 157.2 (C_6); 179.7 (C_2). Anal. calcd for $C_{23}H_{29}N_5O_2S$: C, 56.59; H, 7.20; N, 9.10; S, 5.2. Found: C, 56.66; H, 7.41; N, 9.11; S, 5.04.

3.1.5. 6-Chloro-2-iodo-(9*H*)-purine (16). To a solution of **2** (2.5 g, 6.8 mmol) in 100 mL of CH_2Cl_2, were added slowly 20 equiv. (10.5 mL) of a 50% solution of TFA in CH_2Cl_2 at room temperature. The mixture turned rapidly red, and the reaction was complete in a few min. The solvent was evaporated and the residue solubilized in AcOEt and washed with an aqueous solution of $NaHCO_3$. After silica gel chromatography (heptane/AcOEt: 1/1–3/7) pure **16** was obtained after crystallization from CH_2Cl_2/heptane in 84% yield. Mp 254°C; ^1H NMR (DMSO-d_6): δ 8.63 (s, 1H, H_8); 14.01 (broad s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 117.6 (C_2); 129.5 (C_5); 147.0 (C_8); 147.3 (C_4); 155.9 (C_6). Anal. calcd for $C_5H_2N_4ClI$: C, 21.41; H, 0.72; N, 19.98; Cl, 12.64; I, 45.25. Found: C, 21.41; H, 0.48; N, 20.11; Cl, 12.70; I, 45.49.

3.2. Preparation of resin bound 2-iodo-9-isopropyl-(9*H*)-purine (18)

A suspension of Merrifield-SH resin[57] (1 mmol/g; 2 g) in DMF under argon was treated with 1 equiv. of Potassium *tert*-butoxide. The yellowish-orange suspension was stirred mechanically and slowly for 15 min at room temperature. The purine **17**[5] (3 equiv.) was then added and the suspension was stirred for 24 h at 80°C under argon. The resin **18** was filtrated and washed successively with THF, CH_2Cl_2, water, EtOH, THF, acetone, CH_2Cl_2 and dried in vacuo.

3.3. Preparation of resin bound 2-iodo-9-isopropyl-(9*H*)-purine (24)

A suspension of Merrifield resin (1 mmol/g; 1 g) in DMF under argon was treated with 3 equiv. of cesium carbonate (977 mg), KI (0.5 equiv., and purine **23** (630 mg, 1.5 equiv.). The suspension was stirred for 24 h at 80°C under argon. The resin **23** was filtrated and washed successively with DMF, THF, EtOH, water, EtOH, THF, CH_2Cl_2 and dried in vacuo. Quantitative yield according to elemental analysis (Anal. calcd for: N, 4.04; S, 2.30. Found: N, 4.23; S, 2.42).

3.3.1. 5-(2-Iodo-9-isopropyl-9*H*-purin-6-yl sulfanyl)-pentanoic acid (23) and 5-[2-(4-carboxy-butylsulfanyl)-9-isopropyl-9*H*-purin-6-yl sulfanyl)-pentanoic acid (25). NaH (60%) (721 mg, 8.5 mmol) in DMF (10 mL) was added to a solution of 5-mercaptovaleric acid[58,59] (1.4 g, 8.5 mmol) in DMF (20 mL). The mixture was stirred for 15 min at room temperature and 6-chloro-2-iodo-9-isopropyl (9*H*)-purine (**17**)[5] (2.3 g, 7.13 mmol) in DMF (20 mL) was added. After 2 h at room temperature, solvent was evaporated, the residue was solubilized in water (50 mL) and acidified (pH 1). After extraction of the aqueous phase with AcOEt (5×20 mL) the combined organic phases were washed with water and dried over $MgSO_4$ before evaporation. Silica gel chromatography led to **23** after crystallization from a mixture of CH_2Cl_2/heptane in 62% yield. Mp 189–190°C; MS (CI/NH_3): *m/z* 419 $(M-1)^+$; ^1H NMR: ($CDCl_3$): δ 1.56–1.58 (d, *J*=6.8 Hz, 6H, $2CH_3$); 1.81–1.84 (m, 4H, $CH_2CH_2CH_2CH_2$); 2.41–2.46 (t, *J*=6.79 Hz, 2H, CH_2COOH); 3.31–3.36 (t, *J*=6.77 Hz, 2H, CH_2S); 4.79–4.88 (sept, *J*=6.8 Hz, 1H, $CH(CH_3)_2$); 7.93 (s, 1H, H_8); ^{13}C NMR: (DMSO) δ 22.3 ($CH(CH_3)_2$); 23.9 (CH_2CH_2S); 28.3 (CH_2CH_2COOH); 28.9 (CH_2S); 33.5 (CH_2COOH); 47.5 ($CH(CH_3)_2$); 119.1 (C_2); 131.2 (C_5); 143.0 (C_8); 149.2 (C_4); 161.1 (C_6); 174.6 (*C*OOH). Anal. calcd for $C_{13}H_{17}N_4IO_2S$: C, 37.15; H, 4.08; N, 13.33; S, 7.66. Found: C, 36.91; H, 4.05; N, 13.02; Cl, 12.70; S, 7.66.

A minor compound was then eluted from the column in 15% yield which was identified as the bis-2,6-substituted purine **25**. Mp 152–153°C. MS (CI/NH_3): *m/z* 427 $(M)^+$; *m/z* 449 $(M+2+Na)^+$; *m/z* 471 $(M+2Na)^+$ ^1H NMR: (DMSO): δ 1.52–1.54 (d, *J*=6.76 Hz, 6H, $2CH_3$); 1.61–1.77 (m, 8H, $2\times CH_2CH_2CH_2CH_2$); 2.21–2.28 (t, *J*=6.97 Hz, 4H, CH_2-COOH); 3.15–3.20 (t, *J*=6.87 Hz, 2H, CH_2S); 3.28–3.33 (t, *J*=6.76 Hz, 2H, CH_2S); 4.70–4.79 (sept, *J*=6.76 Hz, 1H, $CH(CH_3)_2$); 8.38 (s, 1H, H_8); 12.03 (broad s, 2H, 2×COOH); ^{13}C NMR: (DMSO) δ 22.3 ($CH(CH_3)_2$); 24.0–24.21 ($2\times CH_2CH_2S$); 27.9–29.0 ($2\times CH_2$ CH_2-COOH); 30.7–31 ($2\times CH_2S$); 33.5–33.6 ($2\times CH_2COOH$); 47.5 ($CH(CH_3)_2$); 128.9 (C_5); 142.0 (C_8); 149.2 (C_4); 159.9 (C_6); 162.2 (C_2); 74.6 (*C*OOH). Anal. calcd for $C_{18}H_{26}N_4O_4S_2$: C, 50.68; H, 6.14; N, 13.13; S, 15.03. Found: C, 50.41; H, 6.23; N, 13.41; S, 15.02.

3.4. General procedure for the preparation of compounds 4a–f (SNAr). Method A

A mixture of 6-benzylsulfanyl-2-iodo-9-(tetrahydro-pyran-2-yl)-9*H*-purine (**3**) (1.1 mmol) in *N*,*N*-dimethylacetamide (8 mL) containing tripropylamine (3 equiv.) and 3 equiv. of the appropriate amine was stirred under inert atmosphere (Ar) at 120°C for 12–20 h. After evaporation of the volatile material in vacuo, workup (CH_2Cl_2 extraction, water washing and $MgSO_4$ drying of the organic phase) was followed by column chromatography (SiO_2) which provided pure material after crystallisation from heptane or cyclohexane.

3.4.1. {(*R*)-1-[6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-pyrrolidin-2-yl}-methanol (4a). Compound **3** was treated with 2-piperidinemethanol according to method A to afford compound **4a** in 68% yield: mp 106–107°C; MS (CI/NH_3): *m/z* 426 $(MH)^+$; *m/z* 425 $(M)^+$; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.5–1.85 and 1.85–2.35 (m, 5H+m, 5H, $H_{2'3'4'}$ and $2\times CH_2CH_2N$); 3.6–3.95 (m, 5H, CH_2OH, CH_2N, $H_{5'}$); 4.05–4.2 (m, 1H, $H_{5''}$); 4.2–4.35 (m, 1H, $CHCH_2OH$); 4.5–4.65 (d, *J*=7.32 Hz, 2H, CH_2Ph); 5.4–5.5 (m, 1H, $H_{5'}$); 7.15–7.35 and 7.35–7.5 (2m, 5H, Ph); 7.76–7.78 (d, 1H, $1H_8$). (2 diastereoisomers); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 23.2 ($C_{3'}$); 24.4 ($C_{4'}$); 25.2 (CH_2CH_2N); 30.2 (CH_2CHN); 31.1 ($C_{2'}$); 31.6 (CH_2Ph); 33 (CH_2N); 49.5 (CH_2OH); 61.6 (*C*HN); 69.0 ($C_{5'}$); 82.5 ($C_{1'}$); 124.7 (C_5); 127.5, 128.8, 129.3, 137.6 (Ph); 138.1 (C_8); 150.3 (C_4); 158.0 (C_2); 162.5 (C_6). Anal. calcd for $C_{22}H_{27}N_5O_2S$: C, 62.09; H, 6.4; N, 16.46; S, 7.54. Found: C, 62.11; H, 6.49; N, 16.45; S, 7.39.

3.4.2. {1-[6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-piperidin-2-yl}-methanol (4b). Compound **3** was treated with 2-piperidinemethanol according to method A to afford compound **4b** in 68% yield: mp 71°C; MS (electrospray): *m/z* 440 $(MH)^+$; *m/z* 462 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.45–1.75 (m, 8H) and 1.95–2.1 (m, 4H) ($H_{2',3',4'}$ and $3\times CH_{2\ \text{piperidine}}$); 2.95–3.05 (m, 1H, CH_2N); 3.63–3.76 (m, 2H, $H_{5'}$ and 1H, CH_2OH); 3.90–3.97 (m, 1H, CH_2OH); 4.0–4.15 (m, 1H, $H_{5'}$); 4.4–4.56 (m, 2H, CH_2Ph); 4.65–4.80 (m, 1H, *CH*N); 4.93–5.01 (m, 1H, *CH*N); 5.47–5.52 (m, 1H, $H_{1'}$); 7.2–7.29 and 7.39–7.45 (2m, 5H, *Ph*); 7.78 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 20.2 ($CH_{2\ \text{piperidine}}$); 23.2 ($C_{4'}$); 25.3 ($CH_{2\ \text{piperidine}}$); 26.1 ($C_{3'}$); 31.6 ($C_{2'}$); 33.0 ($CH_2Ph$); 35.5 ($CH_{2\ \text{piperidine}}$); 40.4 ($CH_2N$); 53.4 (*C*HN); 63.2 ($CH_2OH$); 68.9 ($C_{5'}$); 81.8 ($C_{1'}$); 124.6 ($C_5$); 127.5, 128.8, 129.8, 138.1 (Ph); 137.8 (C_8); 150.3 (C_4); 159.6 (C_2); 160.5 (C_6). Anal. calcd for $C_{23}H_{29}N_5O_2S$: C, 62.84; H, 6.65; N, 15.93; S, 7.29. Found: C, 62.53; H, 6.93; N, 15.55; S, 7.11.

3.4.3. 2-[6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-ylamino]ethanol (4c). Compound **3** was treated with ethanolamine according to method A to afford compound **4c** in 68% yield: mp 50–58°C (decomposition); MS (electrospray): *m/z* 386 $(MH)^+$; *m/z* 408.2 $(M+Na)^+$; *m/z* 793.4 $(2M+Na)^+$; ^1H NMR ($CDCl_3$): δ 1.4–1.75 and 1.90–1.98 (m, 3H, and m, 3H, $H_{2',3',4'}$); 3.5–3.7 (2m, 2H+1H, CH_2N, $H_{5'}$); 3.7–3.8 (t, *J*=5.16 Hz, 2H, CH_2OH); 4.0–4.1 (m, 1H, $H_{5'}$); 4.44 (s, 2H, CH_2Ph); 5.35–5.45 (m, 1H, $H_{1'}$); 5.6 (s broad, 1H, NH); 7.1–7.4 (2m, 5H, Ph); 7.72 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$): δ 22.7 ($C_{3'}$); 25.2 ($C_{4'}$); 31.6 ($C_{2'}$); 32.9 (CH_2Ph); 45.3 (CH_2N); 63.5 (CH_2OH); 68.9 ($C_{5'}$); 81.9 ($C_{1'}$); 125.1 (C_5); 127.5, 128.5, 129.3, 137.7 (Ph); 138.0 (C_8); 150.1 (C_4); 159.4 (C_2); 161.5 (C_6). Anal. calcd for $C_{19}H_{23}N_5O_2S$: C, 59.20; H, 6.01; N, 18.17; S, 8.32. Found: C, 58.91; H, 6.08; N, 18.23; S, 8.12.

3.4.4. 2-{[6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-ethyl-amino}ethanol (4d). Compound **3** was treated with 2-(ethylamino)ethanol according to the method A, to afford compound **4d** in 70% yield: mp 122°C (white crystals); MS (electrospray): *m/z* 414 $(MH)^+$; *m/z* 436 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.04–1.09 (t, *J*=6.9 Hz, 3H, CH_3); 1.45–1.63 and 1.80–1.95 (m, 3H and m, 3H, $H_{2',3',4'}$); 3.53–3.69 (m, 5H, $H_{5'}$, $2\times CH_2N$); 3.74–3.80 (t, *J*=4.7 Hz, 2H, CH_2OH); 3.85–4.05 (m, 1H, $H_{5'}$); 4.45 (s, 2H, CH_2Ph); 5.35–5.40 (dd, *J*=3.5, 9 Hz, 1H, $H_{1'}$); 7.10–7.2 and 7.25–7.35 (2m, 5H, Ph); 7.67

(s, 1H, H_8); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 13.3 (CH_3); 23.1 ($C_{3'}$); 25.2 ($C_{4'}$); 31.4 ($C_{2'}$); 32.9 (CH_2Ph); 44.9 (CH_2CH_2N); 51.7 (CH_2OH); 64.0 (CH_3CH_2N); 68.9 ($C_{5'}$); 82.1 ($C_{1'}$); 124.6 (C_5); 127.5, 128.8, 129.1, 137.5 (Ph); 138.0 (C_8); 150.1 (C_4); 158.9 (C_2); 161.0 (C_6). Anal. calcd for $C_{21}H_{27}N_5O_2S$: C, 60.99; H, 6.58; N, 16.93; S, 7.75. Found: C, 60.91; H, 6.67; N, 17.21; S, 7.81.

3.4.5. 6-Benzylsulfanyl-2-morpholin-4-yl-9-(tetrahydropyran-2-yl)-9*H*-purine (4e). Compound **3** was treated with morpholine according to method A to afford compound **4e** in 91% yield: mp 128°C; MS (electrospray): *m/z* 412 $(MH)^+$; *m/z* 434 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.50–1.75 and 1.79–1.99 (2×m, 3H+3H, $H_{2'3'4'}$); 3.60–3.75 (m, 1H, $H_{5'}$); 3.65–3.73 and 3.75–3.79 (2×m, 4H+4H, $2CH_2N$, $2CH_2O$); 4.04–4.1 (m, 1H, $H_{5'}$); 4.49 (s, 2H, CH_2Ph); 5.47–5.52 (m, 1H, $H_{1'}$); 7.15–7.24 and 7.34–7.37 (2×m, 5H, Ph); 7.79 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 23.2 ($C_{3'}$); 25.2 ($C_{4'}$); 31.7 ($C_{2'}$); 32.9 (CH_2Ph); 45.3 ($2CH_2N$); 67.1 ($2CH_2O$); 68.9 ($C_{5'}$); 81.7 ($C_{1'}$); 124.9 (C_5); 127.4, 128.7, 129.1, 138.2 (Ph); 138.1 (C_8); 150.4 (C_4); 158.4 (C_2); 160.3 (C_6). Anal. calcd for $C_{21}H_{25}N_5O_2S$: C, 61.29; H, 6.12; N, 17.02; S, 7.79. Found: C, 61.02; H, 6.17; N, 16.96; S, 7.61.

3.4.6. 6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-9*H*purin-2-yl]-(3-methoxybenzyl)-amine (4f). Compound **3** was treated with 3-methoxybenzylamine according to method A to afford compound **4f** in 52% yield: mp 113°C; MS (electrospray): *m/z* 484 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.50–1.65 and 1.88–1.99 (2×m, 6H, $H_{2',3',4'}$); 3.65–3.76 (m, 1H, $H_{5'}$) and (s, 3H, OMe); 4.10–4.18 (m, 1H, $H_{5'}$); 4.51 (s, 2H, CH_2Ph); 4.65–4.67 (d, 3H, *J*=5.7 Hz, 1H, CH_2Ar); 5.50–5.56 (m, 2H, $H_{1'}$+*NH*); 6.78–6.82 (m, 1H) and 6.91–6.96 (m, 2H) (Ar); 7.17–7.30 (m, 4H) and 7.35–7.38 (m, 2H) (Ar); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 22.9 ($C_{3'}$); 25.0 ($C_{4'}$); 31.5 ($C_{2'}$); 32.7 (CH_2Ph); 46.2 (NCH_2Ar); 55.3 (OCH_3); 68.7 ($C_{5'}$); 81.6 ($C_{1'}$); 112.6, 113.2, 119.9 (Ar); 125.2 (C_5); 127.2, 128.5, 129.1, 129.7 (Ar); 137.7 (C_8); 137.9–141.3 (Ar); 150.1 (C_4); 158.4 (C_2); 159.9 (*C*–OMe); 160.7 (C_6). Anal. calcd for $C_{25}H_{27}N_5O_2S$: C, 65.05; H, 5.90; N, 15.17; S, 6.95. Found: C, 64.79; H, 5.91; N, 15.17; S, 6.71.

3.5. General procedure for the preparation of compounds 10a,b (Sonogashira coupling). Method B

A solution of 6-benzylsulfanyl-2-iodo-9-(tetrahydro-pyran-2-yl)-9*H*-purine (**3**) (1.1 mmol), CuI (1/20 equiv. mol), bistriphenylphosphine palladium dichloride (1/5 equiv. mol), triethylamine (1.2 equiv.) and the appropriate alkyne (1.2 equiv.) in dried tetrahydrofuran (20 mL) was stirred under inert atmosphere (Ar) at room temperature in the dark for 8–20 h (until disappearance of the iodopurine as judged by TLC in heptane/ethylacetate to dryness and subjected to silica gel column chromatography (heptane/ethylacetate 9/1–7/3). Compounds were obtained as pure solids after crystallization from heptane.

3.5.1. [6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-3-methyl-pent-1-yn-3-ol (10a). 2-Iodo derivative **3** was treated with 3-methyl-1-pentyn-3-ol according to Method B to afford compound **10a** in 80% yield: mp 113–115°C; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.06–1.27 (t, 3H, *J*=7.40 Hz, CH_3CH_2); 1.64 (s, 3H, CH_3); 1.52–2.28 (m, 8H, $H_{2',3',4'}$ and CH_2CH_3); 3.66–3.82 (td, *J*=3.74, 11.82 Hz, 1H, $H_{5'}$). 4.06–4.18 (dd, *J*=3.84, 10.29 Hz, 1H, $H_{5'}$); 4.62 (s, 2H, CH_2Ph); 5.71–5.80 (dd, *J*=2.18, 10.30 Hz, 1H, $H_{1'}$); 7.14–7.33 and 7.41–7.53 (5H, m, Ph); 8.17 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 9.0 (CH_3CH_2); 22.6 ($C_{4'}$); 24.8 ($C_{3'}$); 28.9 (CH_2CH_3); 32.2 ($C_{2'}$); 33.0 (CH_2Ph); 36.4 (CH_3); 68.7 ($C_{5'}$); 69.9 (*C*–OH); 81.6 ($C_{1'}$); 82.8 (C_2–*C*); 89.8 (*C*–C–OH); 129.3, 128.4, 127.2 (Ph); 130.1 (C_5); 137.4 (Ph); 141.2 (C_8); 145.2 (C_2); 147.7 (C_4); 160.6 (C_6). Anal. calcd for $C_{23}H_{26}N_4O_2S$: C, 65.38; H, 6.20; N, 13.26; S, 7.59. Found: C, 65.08; H, 6.31; N, 13.09; S, 7.43.

3.5.2. 4-[6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-2-methyl-but-3-yn-2-ol (10b). Treatment of **3** with 2-methyl-3-butyn-2-ol according to method B afforded compound **10b** in 74% yield: mp 65–72°C (decomposition); MS (electrospray): *m/z* 409.1 $(MH)^+$; *m/z* 431.1 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.55–1.80 and 2.02–2.20 (2×m, 3H+3H, $H_{2',3',4'}$); 1.71 (s, 6H, $2CH_3$); 2.42 (s broad, 1H, OH); 3.65–3.85 (td, *J*=2.83, 11.1 Hz, 1H, $H_{5'}$); 4.10–4.23 (m, 1H, $H_{5'}$); 4.65 (s, 2H, CH_2Ph); 5.73–5.81 (dd, *J*=2.15, 10.3 Hz, 1H, $H_{1'}$); 7.20–7.35 and 7.45–7.52 (2m, 5H, Ph); 8.21 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 23.1 ($C_{4'}$); 25.2 ($C_{3'}$); 31.5 (CH_3); 32.6 ($C_{2'}$); 33.6 (CH_2Ph); 65.80 (C–OH); 69.2 ($C_{5'}$); 82.0 (C_2–*C*); 82.1 ($C_{1'}$); 91.3 (*C*–C–OH); 127.7, 128.9, 129.8 (Ph); 130.4 (C_5); 137.6 (Ph); 141.7 (C_8); 145.6 (C_2); 148.13 (C_4); 161.2 (C_6). Anal. calcd for $C_{22}H_{24}N_4O_2S$: C, 64.68; H, 5.92; N, 13.71; S, 7.85. Found: C, 64.76; H, 6.09; N, 13.53; S, 7.89.

3.6. General procedure for the preparation of compounds 13a–d (Suzuki coupling). Method C

Dimethylformamide (5 mL) was added to an argon purged flask containing 6-benzylsulfanyl-2-iodo-9-(tetrahydro-pyran-2-yl)-9*H*-purine (**3**) (0.33 mmol), K_2CO_3 (1.5 equiv.), appropriate substituted phenylboronic acid (1.5 equiv.) and tetrakis(triphenylphosphine) palladium (5 mol%). The mixture was stirred under argon at 100°C for 48 h. After cooling to ambient temperature, the mixture was evaporated in vacuo and the residue was chomatographed on a silica gel column (heptane/ethylacetate 9/1–7/3). Pure compounds were obtained after recrystallisation from heptane or cyclohexane.

3.6.1. 6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-2-*p*-tolyl-9*H*-purine (13a). *p*-Tolyl derivative **13a** was obtained from **3**, according to method C, in 40% yield as white needles after crystallization from cyclohexane and a few drops of heptane: mp 148–149°C; MS (electrospray): *m/z* 417.2 $(MH)^+$; *m/z* 439.1 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.4–1.7 and 1.8–2.0 (2×m, 6H, $H_{2',3',4'}$); 2.23 (s, 3H, CH_3); 3.65–3.75 (td, *J*=2.7, 11.3 Hz, 1H, $H_{5'}$); 4.0–4.1 (m, 1H, $H_{5'}$); 4.67 (s, 2H, CH_2Ph); 5.71–5.75 (dd, *J*=2.9, 10.00 Hz, 1H, $H_{1'}$); 7.05–7.30 and 7.35–7.41 (2×m, 5H+2H, SCH_2Ph, $2CH_{Ar}$); 8.03 (s, 1H, H_8); 8.30–8.35 (d, *J*=8.21 Hz, 2H, $2CH_{Ar}$); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 21.9 (CH_3); 23.2 ($C_{3'}$); 25.3 ($C_{4'}$); 32.3 ($C_{2'}$); 33.1 (CH_2Ph); 69.1 ($C_{5'}$); 82.3 ($C_{1'}$); 127.6, 128.7, 128.9, 129.4, 129.6 (Ph, Ar); 129.9 (C_5); 135.7 (C_2); 138.3–140.8 (Ar); 140.9 (C_8);

149.3 (C_4); 158.8 (Ph); 160.2 (C6). Anal. calcd for $C_{24}H_{24}N_4OS$: C, 69.20; H, 5.81; N, 13.45; S, 7.70. Found: C, 68.99; H, 5.98; N, 12.98; S, 7.33.

3.6.2. 6-Benzylsulfanyl-2-(4-methoxyphenyl)-9-(tetrahydro-pyran-2-yl)-9*H*-purine (13b). *p*-Methoxyphenyl derivative **13b** was obtained from compound **3**, according to method C, in 93% yield: mp 117°C; MS (electrospray): *m/z* 433 $(MH)^+$; *m/z* 455.1 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.50–1.65 and 1.85–1.99 (2×m, 3H+3H, $H_{2',3',4'}$); 3.70–3.87 (m, 1H, $H_{5'}$); 3.87 (s, 3H, OCH_3); 4.11–4.22 (m, 1H, $H_{5'}$); 4.76 (s, 2H, CH_2Ph); 5.76–5.87 (dd, J=2.9, 9.8 Hz, $1H_{1'}$); 6.93–7.04 (d, J=8.9 Hz, 2H, $2CH_{Ar}$); 7.16–7.34 (m, 3H, Ph) and 7.41–7.53 (m, 2H, Ph); 8.12 (s, 1H, H_8); 8.42–8.56 (d, J=8.9 Hz, $2CH_{Ar}$); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 22.8 ($C_{3'}$); 24.9 ($C_{4'}$); 31.8 ($C_{2'}$); 35.4 (CH_2Ph); 55.4 (OCH_3); 68.7 ($C_{5'}$); 81.8 ($C_{1'}$); 113.7, 127.2, 128.5, 128.9 (Ph); 129.3 (C5); 129.9 (Ar); 130.7 (C_2); 137.9 (Ar); 140.4 (C_8); 148.9 (C_4); 158.2 (Ar); 159.7 (C_6); 161.5 (Ar). Anal. calcd for $C_{24}H_{24}N_4O_2S$: C, 66.64; H, 5.59; N, 12.95; S, 7.41. Found: C, 66.46; H, 5.69; N, 12.86; S, 7.41.

3.6.3. 4-[6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]benzaldehyde (13c). According to method C, this compound was obtained in 70% yield: mp 176°C; MS (electrospray): *m/z* 453 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.4–1.9 and 1.9–2.2 (2×m, 3H+3H, $H_{2',3',4'}$); 3.75–3.85 (td, J=2.8, 11.3 Hz, 1H, $H_{5'}$); 4.15–4.22 (m, 1H, $H_{5'}$); 4.76 (s, 2H, CH_2Ph); 5.82–5.87 (dd, J=2.8, 10.02 Hz, 1H, $H_{1'}$); 7.1–7.35 (m, 3H) and 7.46–7.50 (m, 2H) (Ph); 7.95–7.98 (d, J=8.3 Hz, 2H, 2CH_{Ar}); 8.19 (s, 1H, H_8); 8.65–8.68 (d, J=8.3 Hz, 2H, 2CH_{Ar}); 10.09 (s, 1H, C*H*O); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 22.3 ($C_{3'}$); 24.9 ($C_{4'}$); 31.9 ($C_{2'}$); 32.9 (*C*H_2Ph); 68.8 ($C_{5'}$); 82.0 ($C_{1'}$); 127.3, 128.6, 128.8, 128.0, 129.7 (Ar); 130.2 (C_5); 137.2 (Ar); 137.5 (*C*–CO); 141.4 (C_8); 143.4 (C_2); 148.7 (C_4); 156.8 (*C*–C_2); 160.4 (C_6); 192.1 (*C*O). Anal. calcd for $C_{24}H_{22}N_4O_2S$: C, 66.96; H, 5.15; N, 13.01; S, 7.45. Found: C, 66.81; H, 5.19; N, 13.04; S, 7.35.

3.6.4. 1-{4-[6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]phenyl}-ethanone (13d). According to method C, this compound was obtained from **3** in 73% yield: mp: 154°C; MS (electrospray): *m/z* 467 $(M+Na)^+$; *m/z* 468 $(MH+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.60–1.90 and 1.92–2.20 (2×m, 6H, $H_{2',3',4'}$); 2.65 (s, 3H, CH_3); 3.75–3.85 (td, J=2.81, 11.3 Hz, 1H, $H_{5'}$); 4.15–4.25 (m, 1H, $H_{5'}$); 4.76 (s, 2H, *C*H_2Ph); 5.82–5.86 (dd, J=2.8, 10.05 Hz, 1H, $H_{1'}$); 7.19–7.35 and 7.45–7.50 (2×m, 3H+2H, Ph); 8.02–8.07 (d, J=8.6 Hz, 2H, $2CH_{Ar}$); 8.19 (s, 1H, H_8); 8.57–8.62 (d, J=8.6 Hz, 2H, $2CH_{Ar}$); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 23.2 ($C_{3'}$); 25.3 ($C_{4'}$); 27.2 (CH_3); 32.2 ($C_{2'}$); 35.8 (CH_2Ph); 69.2 ($C_{5'}$); 82.5 ($C_{1'}$); 127.7, 128.83, 128.85, 128.9, 129.31 (Ar); 130.5 (C5); 137.9 (Ph); 138.5 (C2); 141.6 (C8); 142.5 (C–C=O); 148.9, 157.8 (Ar); 198.3 (C=O). Anal. calcd for $C_{24}H_{22}N_4O_2S$: C, 67.54; H, 5.44; N, 12.60; S, 7.21. Found: C, 67.49; H, 5.41; N, 12.42; S, 7.12.

3.6.5. 2-[6-Benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-phenol (9) (Stille). Dried tetrahydrofuran (12 mL) was added to an argon purged flask containing 6-benzylsulfanyl-9-(tetrahydro-pyran-2-yl)-2-tributylstannanyl-9*H*-purine (**8**) (0.81 mmol), CuI (20 mol%), tetrakistriphenylphosphine palladium (5 mol%) and 2-iodophenol (3 equiv.). The mixture was stirred under argon at 80°C in the dark for 16 h. After cooling to room temperature, the mixture was evaporated in vacuo. After workup (CH_2Cl_2 extraction, water washing and $MgSO_4$ drying of the organic phase), the residue was purified on silica gel column (heptane/ethylacetate 9/1–7/3). The compound was recrystallized from heptane to give white pure crystals in 70% yield: mp 149°C; MS (CI/NH_3): *m/z* 419 $(M)^+$; *m/z* 420 $(MH)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.56–1.84 (m, 3H) and 1.92–2.20 (m, 3H) ($H_{2'3'4'}$); 3.64–3.81 (td, J=3.08, 11.09 Hz, 1H, $H_{5'}$); 4.03–4.21 (m, 1H, $H_{5'}$); 4.65 (s, 2H, CH_2Ph); 5.59–5.73 (dd, J=2.78, 9.81 Hz, 1H, $H_{1'}$); 6.83–7.02 (m, 2H, H_{phenol}); 7.11–7.49 (m, 6H, Ph+$1H_{phenol}$); 8.09 (s, 1H, H_8); 8.43–8.57 (m, 1H, H_{phenol}); ^{13}C NMR: δ 23.2 ($C_{3'}$); 25.3 ($C_{4'}$); 32.1 ($C_{2'}$); 34.0 (*C*H_2Ph); 69.2 ($C_{5'}$); 82.9 ($C_{1'}$); 118.1, 119.6, 119.7 (C_{phenol}); 128.0, 129.1, 129.4 (Ph); 129.9–133.1 (C_{phenol}); 136.6 (C_5); 141.3 (C_8); 147.2 (C_2); 159.3 (C_4); 160.16 (*C*–OH); 161.2 (C_6). Anal. calcd for $C_{23}H_{22}N_4O_2S$: C, 66.01; H, 5.30; N, 13.39; S, 7.66. Found: C, 66.19; H, 5.39; N, 13.31; S, 7.61.

3.7. General procedure for the oxidation of sulfur to the sulfone derivative. Method D

A solution of *m*-CPBA (2.2 equiv.) in CH_2Cl_2 was dried ($MgSO_4$) and added to the purine in CH_2Cl_2 (5 mL) at room temperature. The mixture was stirred until disappearance of the sulfur as judged by TLC on silica gel in CH_2Cl_2/EtOH 99/1 (2–10 min). Water was added and after workup (CH_2Cl_2 extraction, water washing and $MgSO_4$ drying of the organic phase), the residue was chromatographed on a silica gel column (heptane/ethylacetate 1/1–3/7). Compounds could be recrystallized from heptane but were sufficiently pure after chromatography to be used directly in the next step.

3.7.1. {1-[6-Benzylsulfonyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-piperidin-2-yl}-methanol (5b). According to method D, this compound was obtained from **4b** in 74% yield: mp: 75–85°C (decomposition); MS (electrospray): *m/z* 494.1 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.50–2.03 (2m, 12H, $H_{2'3'4'}$ and $3CH_{2\ piperidine}$); 2.96–3.1 (m, 1H, *C*H_2N); 3.66–3.82 (m, 3H, $H_{5'}$+*C*H_2OH); 4.05–4.15 m, 1H, $H_{5'}$); 4.67–4.79 (m, 1H, $1CH_2N$); 4.79 (s, 2H, *C*H_2Ph); 4.99 (m, 1H, *C*HCH_2OH); 5.56–5.61 (m, 1H, $H_{1'}$); 7.22–7.35 (m, 5H, *Ph*); 8.06 (s, 1H, H_8). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 19.5 ($CH_{2\ piperidine}$); 22.7 ($C_{4'}$); 24.8 ($CH_{2\ piperidine}$); 25.2 ($CH_{2\ piperidine}$); 25.4 ($C_{3'}$); 31.4 ($C_{2'}$); 40.4 (*C*H_2N); 52.9 (*C*HCH_2OH); 59.4 (*C*H_2Ph); 61.7 (*C*H_2OH); 68.7 ($C_{5'}$); 81.7 ($C_{1'}$); 122.4 (C_5); 126.9, 128.7, 128.8, 131.2 (Ph); 142.1 (C_8); 153.2 (C_2); 155.6 (C_4); 158.8 (C_6).

3.7.2. 6-Benzylsulfonyl-2-morpholin-4-yl-9-(tetrahydro-pyran-2-yl)-9*H*-purine (5e). Compound **4e** was treated with *m*-CPBA according to method D to afford compound **5e** with 63% yield: mp: 177°C; MS (electrospray): *m/z* 466.1 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.54–1.67 and 1.90–1.98 (2m, 6H, $H_{2',3',4'}$); 3.61–3.78 (2m, 5H, $H_{5'}$+2*CH*N, 2*CH*O); 4.01–4.07 (m, 1H, $H_{5'}$); 4.73 (s, 2H,

CH_2Ph); 5.49–5.54 (dd, J=9.07, 2.29 Hz, 1H, $H_{1'}$); 8.06 (s, 1H, H_8). ^{13}C NMR ($CDCl_3$): δ 22.7 ($C_{3'}$); 24.8 ($C_{4'}$); 31.5 ($C_{2'}$); 44.8 (*C*HN); 59.2 (*C*H_2Ph); 66.8 (*C*HO); 68.8 ($C_{5'}$); 81.7 ($C_{1'}$); 122.9 (C_5); 126.8, 128.7, 128.8, 131.2 (Ph); 142.5 (C_8); 153.6 (C_2); 155.6 (C_4);157.8 (C_6).

3.7.3. 6-Benzylsulfonyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-(3-methoxy-benzyl)-amine (5f). According to method D, this compound was obtained from **4f** with 74% yield as an oil: MS (electrospray): *m/z* 516 $(M+Na)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41–1.68 and 1.69–1.98 (2m, 6H, $H_{2'3'4'}$); 3.94 (s, 3H, O*Me*); 3.71–3.93 (m, 1H, $H_{5'}$); 4.08–4.13 (m, 1H, $H_{5'}$); 4.61 (s, 2H, SO_2CH_2Ph); 4.80 (s broad, 2H, NH*C*H_2Ph); 5.55–5.58 (m, 1H, $H_{1'}$); 6.0 (s broad, 1H, *NH*); 6.73–6.83 (m, 1H); 6.85–7.0 (m, 2H); 7.12–7.46 (m, 5H) (Ar); 8.10 (s, 1H, H_8). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 22.6 ($C_{3'}$); 24.8 ($C_{4'}$); 31.3 ($C_{2'}$); 46.1 ($SO_2C$$H_2$Ph); 55.2 (O*C*$H_3$); 59.3 (*C*$H_2$NH); 68.7 ($C_{5'}$); 81.9 ($C_{1'}$); 112.6, 113.3, 119.83 (Ar); 123.5 (C_5); 126.7, 128.6, 128.7, 129.6, 131.2, 140.3 (Ar); 142.2 (C_8); 153.7 (C_4); 155.6 (C_2); 158.8 (C_6); 159.8 (Ar).

3.7.4. 2-[6-Benzylsulfonyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]3-methyl-pent-1-yn-3-ol (11a). Compound **10a** was treated with *m*-CPBA according to method D to afford compound **11a** with 63% yield: mp: 100°C; MS (CI/NH_3): *m/z* 355 (M-THP); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.05–1.25 (t, J=7.40 Hz, 3H, *C*$H_3$$CH_2$); 1.65 (s, 3H, CH_3); 1.55–2.25 (8H, m, $H_{2'3'4'}$ and q, J=7.40 Hz, CH_2CH_3); 3.65–3.9 (m, 1H, $H_{5'}$); 4.1–4.3 (m, 1H, $H_{5'}$); 4.92 (s, 2H, *C*H_2Ph); 5.75–5.95 (m, 1H, $H_{1'}$); 7.2–7.5 (m, 5H, Ph); 8.48 (s, 1H_8). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 8.9 (*C*$H_3$$CH_2$); 22.4 ($C_{4'}$); 24.6 ($C_{3'}$); 28.7 ($CH_3$); 32.1 ($C_{2'}$); 36.2 (*C*$H_2$$CH_3$); 59.04 (*C*$H_2$Ph); 68.9 ($C_{5'}$+*C*–OH); 81.7 ($C_2$–*C*); 82.3 ($C_{1'}$); 92.6 (*C*–C–OH); 126.0, 126.03, 126.3, 131.1 (Ph); 131.4 (C_5);145 (C_2); 146.5 (C_8); 153.4 (C_4); 153.5 (C_6).

3.7.5. 4-[6-Benzylsulfonyl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-2-methyl-but-3-yn-2-ol (11b). Compound **10b** was treated with *m*-CPBA according to method D to afford compound **11b** with 78% yield: mp: 96–100°C (decomposition); MS (electrospray): *m/z* 463.1 $(M+Na)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.69 (s, 6H, 2CH_3); 1.67–2.13 (2m, 6H, $H_{2'3'4'}$); 3.5–3.80 (m, 1H, $H_{5'}$); 4.15–4.22 (m, 1H, $H_{5'}$); 4.91 (s, 2H, *C*H_2Ph); 5.82–5.86 (dd, J=2.33, 10.4 Hz, 1H, $H_{1'}$); 7.25–7.30 and 7.36–7.41 (2m, 5H, Ph); 8.51 (s, 1H, H_8). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 22.9 ($C_{3'}$); 25.0 ($C_{4'}$); 31.3 (2CH_3); 32.5 ($C_{2'}$); 59.5 (*C*H_2Ph); 65.8 (*C*–OH); 69.3 ($C_{5'}$); 81.0 (C_2–*C*); 82.7 ($C_{1'}$); 93.7 (*C*–C–OH); 126.7 (C_5); 129.1, 129.3, 131.7 (Ph); 145.4 (C_2); 146.9 (C_8); 153.6 (C_6); 153.9 (C_4).

3.7.6. 6-Benzylsulfonyl-2-(4-methoxy-phenyl)-9-(tetrahydro-pyran-2-yl)-9*H*-purine (14). This compound was obtained from **13b**, according to method D, in 94% yield: mp 153–155°C; MS (electrospray) *m/z* 487.1 $(M+Na)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.5–1.9 and 2.0–2.25 (2×m, 6H, $H_{2',3',4'}$); 3.72–3.82 (td, J=2.83, 11.19 Hz, 1H, $H_{5'}$); 3.86 (s, 3H, O*Me*); 4.12–4.21 (m, 1H, $H_{5'}$); 4.92 (s, 2H, *C*H_2Ph); 5.81–5.86 (dd, J=2.46 Hz, 10.21 Hz, 1H, $H_{1'}$); 6.95–7.15 (d, J=9.09 Hz, 2H, 2CH_{Ar}); 7.19–7.23 and 7.31–7.37 (2×m, 3H+2H, Ph); 8.35 (s, 1H, H_8); 8.44–8.48 (d, J=9.09 Hz, 2H, 2CH_{Ar}). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 20.7 ($C_{3'}$); 23.0 ($C_{4'}$); 32.3 ($C_{2'}$); 55.8 (O*C*H_3); 60.8 (*C*H_2Ph); 69.3 ($C_{5'}$); 82.7 ($C_{1'}$); 114.4 (*C*H_{Ar}); 127.1 (Ph); 128.4 (C_5); 129.1–129.2 (Ph); 129.3 (C_2); 130.7 (*C*H_{Ar}); 132.4 (Ph);145.9 (C_8); 153.5 (C_2–*C*); 154.9 (C_4); 159.1 (C_6); 162.6 (*C*–OMe).

3.8. General procedure for sulfone substitution by various amines. Method E

A mixture of the sulfone in ethanol or *t*-BuOH containing 1.2–2.5 equiv. of the appropriate amine was stirred at 25–80°C for 0.5–20 h. After evaporation of the volatile material in vacuo, workup (CH_2Cl_2 extraction, water washing and $MgSO_4$ drying of the organic layer) was followed by column chromatography (SiO_2) which provided pure material after crystallisation from heptane, cyclohexane or heptane/CH_2Cl_2.

3.8.1. {1-[6-Butylamino-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-piperidin-2-yl}-methanol (6a). According to method E, compound **5b** was treated with butylamine (2.5 equiv.) at room temperature for 5 h to afford compound **6a** with 89% yield: mp: 50–60°C (decomposition); MS (electrospray): *m/z* 411.1 $(M+Na)^+$; *m/z* 389 $(MH)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86–0.96 (t, J=7.20 Hz, 3H, CH_3); 1.36–1.48 (hex, J=7.2 Hz, 2H, *C*$H_2$$CH_3$); 1.49–2.15 (m, 14H, $CH_3CH_2CH_2$, 3$CH_{2\ piperidine}$ and $H_{2'3'4'}$); 3.04–3.13 (m, 1H, N*C*H_2); 3.40–3.60 (m, 2H, *C*H_2NH); 3.66–3.77 (m, 2H, $H_{5'}$ and CH_2OH); 4.04–4.15 (m, 2H, $H_{5'}$ and CH_2OH); 4.71–4.77 (m, 1H, N*C*H_2); 4.96–5.01 (m, 1H, *C*HCH_2OH); 5.46–5.51 (m, 1H, $H_{1'}$); 6.8 (s large, 1H, NH); 7.63 (s, 1H, H_8). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 13.8 (*C*H_3); 20.08 (*C*H_2CH_3); 20.1 (*C*$H_{2\ piperidine}$); 23.0 ($C_{3'}$); 25.2–25.0 (2*C*$H_{2\ piperidine}$); 26.5 ($C_{4'}$); 31.4 ($C_{2'}$); 31.8 ($CH_3CH_2C$$H_2$); 40.08 (N*C*$H_2$); 40.12 (*C*$H_2$NH); 53.3 (*C*HC$H_2$OH); 60.40 (*C*$H_2$OH); 68.5 ($C_{5'}$); 81.3 ($C_{1'}$); 113.4 ($C_5$); 134.5 ($C_8$); 150.2 ($C_4$); 154.6 ($C_2$); 160.6 ($C_6$). Anal. calcd for $C_{20}H_{32}N_6O_2$: C, 61.83; H, 8.30; N, 21.63. Found: C, 61.61; H, 8.53; N, 21.43.

3.8.2. (4-Chloro-benzyl)-[2-morpholin-4-yl-9-(tetrahydro-pyran-2-yl)-9*H*-purin-6-yl]-amine (6b). According to method E, treatment of **5e** with 2 equiv. of *p*-chlorobenzylamine in *t*-BuOH at 80°C for 16 h afford compound **6b** with 67% yield: mp: 205°C; MS (electrospray): *m/z* 429.2 $(MH)^+$; *m/z* 451.1 $(M+Na)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.59–1.77 (m, 3H) and 1.99–2.10 (m, 3H) ($H_{2',3',4'}$); 3.74 (s, 8H, 2*C*H_2N and 2*C*H_2O); 3.69–3.75 (m, 1H, $H_{5'}$); 4.11–4.16 (m, 1H, $H_{5'}$); 4.91 (s, 2H, *C*H_2Ph); 5.50–5.56 (m, 1H, $H_{1'}$); 6.16 (s broad, 1H, NH); 7.26 (s, 4H, Ph); 7.62 (s, 1H, H_8). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 23.4 ($C_{3'}$); 25.3 ($C_{4'}$); 31.8 ($C_{2'}$); 44.1 (*C*H_2Ph); 45.3 (*C*H_2N); 67.3 (*C*H_2O); 68.9 ($C_{5'}$); 81.6 ($C_{1'}$); 114.1 (C_5); 128.9, 129.2, 133.2 (Ph); 135.5 (C_8); 138.2 (*C*–Cl); 151.2 (C_4); 154.6 (C_6); 159.6 (C_2). Anal. calcd for $C_{21}H_{25}N_6O_2Cl$: C, 58.81; H, 5.87; N, 19.59; O, 7.46; Cl, 8.27. Found: C, 58.86; H, 5.92; N, 19.36; Cl, 8.31.

3.8.3. *N*6-(4-Ethoxy-benzyl)-N_2-(3-methoxy-benzyl)-9-(tetrahydro-pyran-2-yl)-9*H*-purine-2,6-diamine (6c). According to method E, treatment of **5f** in ethanol with 2 equiv. of *p*-ethoxybenzylamine at 55°C for 8 h afford **6c** as

an oil with 74% yield: MS (electrospray): *m/z* 489.2 $(MH)^+$; *m/z* 511.1 $(M+Na)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20–1.25 (t, *J*=6.9 Hz, 3H, CH_3CH_2); 1.40–1.57 (m, 3H) and 1.77–1.82 (m, 3H, $H_{2'3'4'}$); 3.50–3.60 (m, 1H, $H_{5'}$); 3.58 (s, 3H, O*Me*); 3.78–3.85 (q, *J*=6.9 Hz, 2H, CH_2CH_3); 3.91–3.93 (m, 1H, $H_{5'}$); 4.43–4.46 (d, *J*=5.9 Hz, 2H, HNCH_2-ArOEt); 4.49 (s broad, 2H, HNCH_2ArOMe); 5.20–5.24 (t, *J*=5.9 Hz, 1H, *NH*CH_2ArOEt); 5.32–5.37 (m, 1H, $H_{1'}$); 6.21 (s broad, 1H, *NH*CH_2ArOMe); 6.58–6.64 (m, 3H); 6.76–6.79 (m, 2H); 7.00–7.06 (m, 3H) (Ar); 7.38 (s, 1H, H_8). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 15.2 (CH_2CH_3); 23.3 ($C_{3'}$); 27.3 ($C_{4'}$); 31.8 ($C_{2'}$); 44.2 (CH_2Ar); 46.4 (CH_2Ar); 55.5 (OCH_3); 63.7 (OCH_2CH_3); 68.9 ($C_{5'}$); 81.6 ($C_{1'}$); 112.7, 113.8, 114.8, 120.3, 129.4, 129.7, 131.5, 142.4, 155.2, 160.1 (Ar); 114.5 (C_5); 135.0 (C_8); 151.1 (C_4); 158.5 (C6); 160.0 (C2). Anal. calcd for $C_{27}H_{32}N_6O_3 \cdot 1/2H_2O$: C, 65.17; H, 6.68; N, 16.89; O, 11.25. Found: C, 65.25; H, 6.65; N, 16.84; O, 11.24.

3.8.4. (3*R*,*S*)-1-[6-(4-Methoxy-benzylamino)-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-3-methyl-pent-1-yn-3-ol (12a). According to method E, treatment of **11a** in ethanol with *p*-methoxybenzylamine at room temperature for 25 min afford compound **12a** in quantitative yield: mp: 154°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.05–1.15 (t, *J*=7.3 Hz, 3H, CH_2CH_3); 1.6 (s, 3H, CH_3); 1.55–2.25 (m, 8H, $H_{2'3'4'}$+CH_2CH_3); 2.68 (s broad, 1H, OH); 3.79 (s, 3H, OMe); 3.65–3.85 (m, 1$H_{5'}$); 4.1–4.15 (m, 1$H_{5'}$); 4.82 (s, 2H, CH_2Ph); 5.65–5.75 (m, 1H, $H_{1'}$); 6.75–6.9 (d, *J*=8.35 Hz, 2H, 2CH, Ph); 7.2–7.35 (d, *J*=8.35 Hz, 2H, 2CH, Ph); 7.95 (s, 1H, H_8). ^{13}C ($CDCl_3$, 50 MHz): δ 9.0 (CH_2CH_3); 22.8 ($C_{4'}$); 24.9 ($C_{3'}$); 28.9 (CH_3); 32.2 ($C_{2'}$); 36.3 (CH_2CH_3); 44.3 (CH_2Ph); 55.2 (OCH_3); 68.7 ($C_{5'}$); 81.2 ($C_{1'}$); 83.3 (C_2–C); 88.4 (*C*–C–OH); 113.9 (Ph); 118.7 (C_5); 129.3 (Ph); 130.4 (C_8); 138.2 (Ph); 146.25 (C_6); 148.6 (C_2); 154.2 (C_4);158.9 (*C*–OMe). Anal. calcd for $C_{24}H_{29}N_5O_3$: C, 66.19; H, 6.71; N, 16.08. Found: C, 66.32; H, 6.72; N, 16.26.

3.8.5. (3*R*,*S*)-4-[6-(4-Methoxy-phenylamino)-9-(tetrahydro-pyran-2-yl)-9*H*-purin-2-yl]-2-methyl-but-3-yn-2-ol (12b). According to method E, treatment of **11b** in *t*-BuOH with 2.5 equiv. of *p*-ethoxyaniline at 80°C for 16 h afford compound **12b** (recrystallized from cyclohexane) with 67% yield: mp: 238°C; MS (electrospray): *m/z* 408.1 $(MH)^+$; *m/z* 430 $(M+Na)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.66 (s, 6H, $2CH_3$); 1.65–2.16 (m, 6H, $H_{2'3'4'}$); 3.71–3.82 (m, 1H, $H_{5'}$); 3.82 (s, 3H, O*Me*); 4.13–4.18 (m, 1H, $H_{5'}$); 5.76–5.80 (dd, *J*=2.26, 10.4 Hz, 1H, $H_{1'}$); 6.91–6.94 (d, *J*=9.0 Hz, 2H, $2CH_{Ar}$); 7.65–7.68 (d, *J*=9.0 Hz, 2H, $2CH_{Ar}$); 7.88 (s large, 1H, NH); 8.08 (s, 1H, H_8). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 22.7 ($C_{3'}$); 24.9 ($C_{4'}$); 31.1 ($2CH_3$); 32.3 ($C_{2'}$); 55.5 (OCH_3); 65.4 (C–OH); 68.9 ($C_{5'}$); 81.6 ($C_{1'}$); 82.3 (C_2–C); 90.9 (C–C–OH); 118.7 (C_5); 114.3, 122.3, 131.3 (Ar); 138.7 (C_8); 145.1 (C_2); 148.6 (C_4); 151.6 (C_6);156.4 (C–OMe). Anal. calcd for $C_{22}H_{25}N_5O_3$: C, 64.85; H, 6.18; N, 17.19; O, 11.78. Found: C, 64.90; H, 6.30; N, 16.87; O, 11.92.

3.8.6. Benzyl-[2-(4-methoxy-phenyl)-9-(tetrahydro-pyran-2-yl)-9*H*-purin-6-yl]-amine (15). According to method E, treatment of **14** in *t*-BuOH with benzylamine at 60°C for 10 h afforded compound **15** with 68% yield: mp: 194°C; MS (electrospray): *m/z* 416.2 $(MH)^+$; *m/z* 438.2 $(M+Na)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.60–1.90 and 1.93–2.14 (2m, 6H, $H_{2',3'4'}$); 3.70–3.84 (m, 1H, $H_{5'}$); 3.86 (s, 3H, OMe); 4.15–4.21 (m, 1H, $H_{5'}$); 4.99 (s broad, 2H, CH_2Ph); 5.78–5.83 (dd, *J*=2.76, 9.92 Hz, 1H, $H_{1'}$); 6.15 (s broad, 1H, NH); 6.94–6.97 (d, *J*=8.9 Hz, 2H, $2CH_{Ar}$); 7.25–7.44 (2m, 5H, Ph); 7.91 (s, 1H, H_8); 8.42–8.45 (d, *J*=8.9 Hz, 2H, $2CH_{Ar}$). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 22.9 ($C_{3'}$); 25.6 ($C_{4'}$); 31.9 ($C_{2'}$); 44.5 (CH_2Ph); 55.3 (OCH_3); 68.7 ($C_{5'}$); 81.6 ($C_{1'}$); 113.5 (CH_{Ar}); 118.1 (C_5); 127.3, 127.8, 128.6 (Ph); 129.7 (CH_{Ar}); 131.6 (C_2); 137.6 (C_8); 139.2 (Ph); 150.1 (C_4); 154.2 (C_2–*C*); 159.1 (C_6); 161.1 (*C*–OMe). Anal. calcd for $C_{24}H_{25}N_5O_2$: C, 69.38; H, 6.06; N, 16.86. Found: C, 69.24; H, 6.15; N, 17.03.

3.8.7. 4-Methoxybenzyl-[2-(4-methoxy-phenyl)-9-(isopropyl)-9*H*-purin-6-yl]-amine (21). To a suspension of resin **18** or resin **24** (~1 mmol) in dry DMF (6 mL) was added $Pd(PPh_3)_4$ (0.5 equiv.), DIEA (3 equiv.) and 4-methoxyphenylboronic acid (3 equiv.). The mixture was stirred mechanically for 3 days at 100°C. The resin was then filtrated and washed with THF, EtOH, water, THF, CH_2Cl_2 and finally dried under vacuo. The resin was treated with *m*-CPBA according to method D and cleavage of the product was carried out according to method E with 4-methoxybenzylamine (5 equiv.) in THF. The resin was filtrated and washed with THF and CH_2Cl_2. The filtrate and washing were evaporated, chromatographed on silica gel column (heptane/AcOEt: 9/1–3/7), and finally crystallized from heptane to yield 10% of **21** from resin **18** or 35% of **21** from resin **24**. Mp 130°C; MS (electrospray): *m/z* 404.1 $(MH)^+$; *m/z* 427.1 $(M+Na)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.61–1.63 (d, *J*=6.79 Hz, 6H, $2CH_3$); 3.76 (s, 3H, OMe); 3.83 (s, 3H, OMe); 4.85–4.93 (m, *J*=6.79 Hz, 1H, $CH(CH_3)_2$ and 4.85–5.05 (m, 2H, CH_2Ph); 6.82–6.85 (d, *J*=8.94 Hz, 2H, *m*-CH_{Ar}); 6.94–6.97 (d, *J*=8.9 Hz, 2H, *m*-CH_{Ar}); 7.34–7.37 (d, *J*=8.9 Hz, 2H, *o*-CH_{Ar}); 7.76 (s, 1H, H_8); 8.44–8.47 (d, *J*=8.94 Hz, 2H, *o*-CH_{Ar}); ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 23.1 (CH_3); 44.5 (CH_2Ph); 47.1 ($CH(CH_3)_2$); 55.6 (OMe); 56.0 (OMe); 113.9–114.4 (Ph); 119.1 (C_5); 129.6, 130.0, 131.8, 132.2 (Ph); 137.7 (C_8); 150.6 (C_4); 154.6 (C_2); 158.9 (C_6); 159.3 and 161.4 (2×*C*–OMe). Anal. calcd for $C_{23}H_{25}N_5O_2$: C, 68.47; H, 6.25; N, 17.36. Found: C, 68.34; H, 6.23; N, 17.38.

3.8.8. (3*R*,*S*)-1-[9-Isopropyl-6-(4-methoxy-benzylamino)-9*H*-purin-2-yl]-3-methyl-pent-1-yn-3-ol (22). To a suspension of resin **18** (~1 mmol) in dry DMF (6 mL) was added dichloro(1,2-bis(diphenylphosphino)ethane)-palladium(II) (Strem) (1.1 equiv.), DIEA (30 equiv.), CuI (2.2 equiv.) and 3-methyl-pent-1-yn-3-ol (20 equiv.). The mixture was stirred mechanically for 36 h at 80°C. The resin was then filtrated and washed with THF, EtOH, water, EtOH, THF, CH_2Cl_2 and finally dried under vacuo. The resin was treated with *m*-CPBA according to method D and cleavage of the product was carried out according to method E with 4-methoxybenzylamine (5 equiv.) in THF. The resin was filtrated and washed with THF and CH_2Cl_2. The filtrate and washing were evaporated, chromatographed on silica gel column (heptane/AcOEt: 9/1–3/7), and finally crystallized from heptane to yield 25% of **22** from resin **18**. From resin **24**, the yield was improved to 64% using the same conditions as above. The yield of **22** raised to 50% from

resin **24** when the catalyst used was trans-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyldipalladium] (20 mol%), CuI (20 mol%), DIEA (3.5 equiv.) and 3.9 equiv. of alcyne, in NMP as solvent, instead of DMF. Mp 134–136°C. ^{1}H NMR was identical to the spectrum previously reported for a sample synthesized in liquid phase.[6]

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