Synthesis of sulfonamide-based kinase inhibitors from sulfonates by exploiting the abrogated S_N2 reactivity of 2,2,2-trifluoroethoxysulfonates

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The attenuated S_N2 reactivity of the 2,2,2-trifluoroethyl group has been exploited for the synthesis of a series of 6-cyclohexylmethoxy-2-arylaminopurines in which a sulfonamide moiety was attached to the aryl ring *via* a methylene group. These were required as potential inhibitors of serine-threonine kinases of interest for the treatment of cancer. 3-Nitrophenylmethanesulfonyl chloride was converted into the corresponding 2,2,2-trifluoroethoxysulfonyl ester by reaction with 2,2,2-trifluoroethanol in the presence of triethylamine/4-dimethylaminopyridine. Catalytic hydrogenation of the nitro group employing 2,2,2-trifluoroethanol as solvent gave 2,2,2-trifluoroethyl 3-aminophenylmethanesulfonate, which was reacted with 6-cyclohexylmethoxy-2-fluoropurine in 2,2,2-trifluoroethanol/trifluoroacetic acid to afford 2,2,2-trifluoroethyl 3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonate. 3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonamides were synthesised by microwave heating of the trifluoroethoxysulfonate with an amine and 1,8-diazabicycloundec-7-ene in tetrahydrofuran. The mechanism of this process was shown to involve an intermediate sulfene by a deuterium-labelling experiment. 3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonamide derivatives were assayed as inhibitors of human cyclin-dependent kinase 2. Previous structure–activity studies demonstrated that relocating the sulfonamide group of O^6-cyclohexylmethoxy-2-(4′-sulfamoylanilino)purine from the 4- to the 3-position on the 2-arylamino ring resulted in a 40-fold reduction in potency against CDK2. In the present study, no further loss of activity was observed on introducing a methylene group between the sulfonamide and the aryl ring, 3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonamide proving equipotent with O^6-cyclohexylmethoxy-2-(3′-sulfamoylanilino)purine (IC_{50} = 0.21 μM). *N*-Alkylation of the sulfonamide reduced CDK-2 inhibitory activity, while a substituted benzyl or 3-phenylpropyl group on the sulfonamide resulted in a loss of potency compared with 3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonamide. The dimethylaminopropyl derivative, 1-[3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]-*N*-(3-dimethylaminopropyl)methanesulfonamide was only 2-fold less potent than 3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonamide, suggesting an interaction between the basic dimethylamino group and the kinase. The presence of alicyclic groups on the pendant sulfonamide showed IC_{50} values in the 0.5–1.5 μM range. *N*-(4-*tert*-Butylphenyl)-1-[3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]methanesulfonamide was markedly less active (IC_{50} = 34 μM), suggesting a steric effect within the ATP-binding domain.

Introduction

Hine and Ghirardelli[1] showed that progressive substitution of fluorine atoms at C-2 of iodoethane had a remarkable effect on the rate of S_N2 reaction with sodium thiophenoxide in methanol. 2,2,2-Trifluoro-1-iodoethane was shown to react some 2×10^4 times slower than iodoethane at 20 °C. Subsequently, Bordwell and Brannen[2] demonstrated that 2,2,2-trifluoroethanol *O*-*p*-toluenesulfonate is much less reactive (*ca.* 10^4-fold) in a S_N2 reaction with potassium iodide in acetone than 4,4,4-trifluorobutan-1-ol *O*-*p*-toluenesulfonate. This behaviour was ascribed to repulsive interactions in the transition state between the electronegative fluorine atoms and the entering and leaving groups.[2,3] An alternative explanation derives from the preference of an electron-withdrawing trifluoromethyl group to be attached to a carbon atom donating an orbital of relatively high *p* character and hence minimal *s* character. This raises the energy of the pentacoordinated transition state for S_N2 displacement because the methylene carbon donates an sp^2 hybrid orbital to the CF_3 group.[2] {A. Eschenmoser, personal communication}

We have exploited this unique, attenuated S_N2 reactivity for the synthesis of a series of purine derivatives (**1a–1l**) bearing benzylic sulfonamides from the 2,2,2-trifluoroethoxysulfonate **7** in which trifluoroethoxy acts solely as a leaving group (Scheme 1) and

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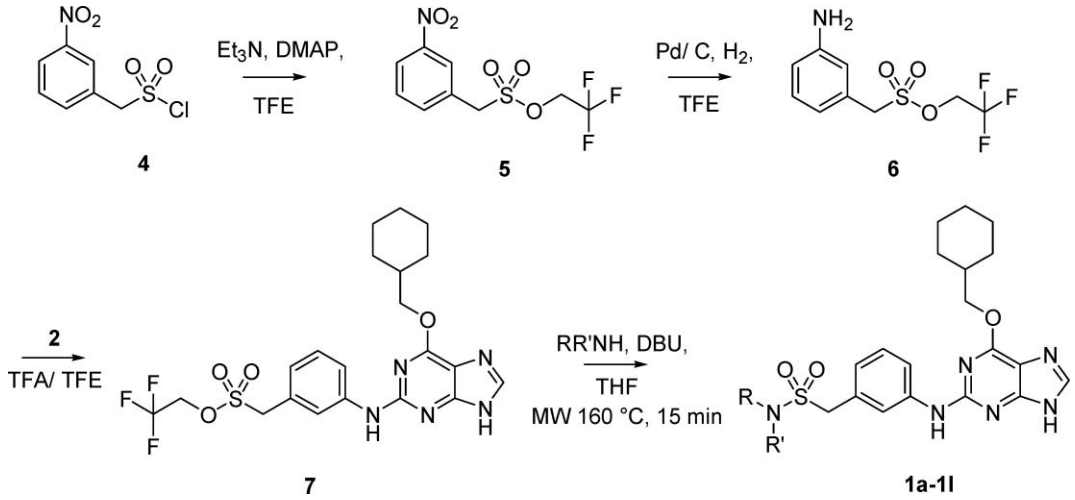
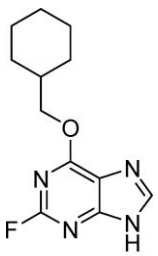


Scheme 1 Synthesis of 3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonamides.

is not subject to perceptible S_N2 attack. 6-Cyclohexylmethoxy-2-arylaminopurines (**1a–1l**) substituted with sulfonamide groups were required as potential inhibitors of serine-threonine kinases of interest as therapeutic targets for the treatment of cancer. Ordered progression of the cell cycle[4,5] is mediated by the CDKs, the abnormal functioning of which is implicated in the molecular pathology of cancer.[6] As a consequence, there is evidence to suggest that inhibition of CDKs may be therapeutically advantageous by inducing the apoptosis of tumour cells.[5,7] Although a large number of small molecule ATP-competitive CDK inhibitors have been reported to date, kinase selectivity remains a challenge.[8–10]



2

We have previously described O^6-cyclohexylmethoxy-2-(4′-sulfamoylanilino)purine (**NU6102**, **3**) and related compounds as potent inhibitors of cyclin-dependent kinase 2 (CDK2).[11,12] This and related compounds were readily prepared by reaction of 6-cyclohexylmethoxy-2-fluoropurine **2** with the appropriate aniline (*e.g.* sulfanilamide leading to **3**) in trifluoroacetic acid-2,2,2-trifluoroethanol.[13] As part of our continuing interest in purine-based kinase inhibitors derived from **3**, it was of interest to explore the effect, upon kinase-inhibitory activity, of inserting a methylene group between the sulfonamide and benzenoid moiety attached to the purine. To explore further the impact of the sulfonamide group on kinase inhibition we also wished to synthesise analogues of **3** in which the sulfonamide group was moved to the *meta*-position of the benzenoid ring, separated from this ring by a single methylene group and *N*-substituted with a range of functionalities. In addition to further delineating structure–activity relationships for CDK inhibition, an objective of these studies was to reduce or abolish CDK2 inhibitory activity, with a view to revealing other kinase targets for this chemotype. We have now found a synthetic strategy suitable for a multiple-parallel format that enables the generation of a library of novel kinase inhibitors containing the desired structural motif. As reported in this paper, we synthesised the 2,2,2-trifluoroethoxysulfonate **7** and studied its reactions with amines. In this way the sulfonamide derivatives **1a–1l** were obtained and shown to exhibit only modest inhibition of CDK2 compared with the parent purine **7** (see Table 1).

Results and discussion

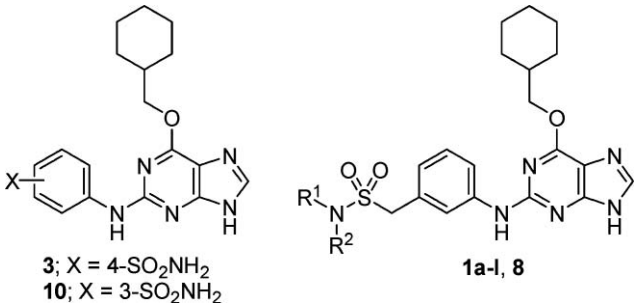
Synthesis

Commercially available 3-nitrophenylmethanesulfonyl chloride (**4**) was converted into the 2,2,2-trifluoroethyl ester **5** by reaction with neat 2,2,2-trifluoroethanol in the presence of triethylamine and 4-dimethylaminopyridine. Reduction of the nitro group of **5** to the corresponding aniline **6** was achieved by hydrogenation using palladium on carbon, employing 2,2,2-trifluoroethanol (TFE) as solvent. In agreement with Bailey *et al.* we have found TFE to be a useful alternative solvent to methanol and ethanol for catalytic hydrogenations.[14] The ability of the trifluoroethyl group to withstand conditions of catalytic hydrogenation contrasts with the trichloroethyl group. The latter was recently recommended as a protecting group for sulfonic acids with the trichloroethylsulfonates being deprotected by catalytic hydrogenation.[15]

Reaction of the aniline **6** with 6-cyclohexylmethoxy-2-fluoropurine **2** in a 2,2,2-trifluoroethanol/trifluoroacetic acid mixture afforded the 2,2,2-trifluoroethoxysulfonate **7**. Sulfonamides **1a–1l** (Table) were synthesised by heating **7** with an excess of the required amine and 1,8-diazabicycloundec-7-ene (DBU) in tetrahydrofuran (THF) under microwave conditions at 160 °C for 15 min. In most cases the yield of sulfonamide exceeded 70%. The transformations described are summarised in Scheme 1. Cleavage of the *p*-methoxybenzyl (PMB) group of **1d** in neat TFA proceeded smoothly to give **8** (Scheme 2).

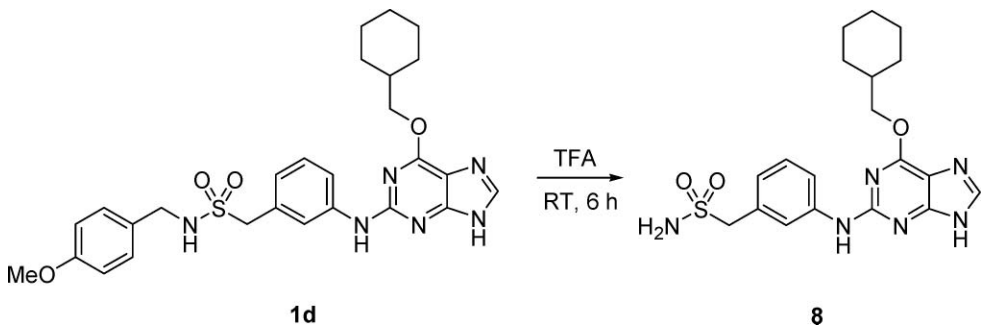
During the course of the study described herein, Caddick and coworkers reported an excellent method for synthesising alkylsulfonamides by treatment of the corresponding

Table 1 Structures, synthetic yields and activities for inhibitors of the kinase CDK2



Compound number	R^1 and R^2	Yield (%)	CDK2 Inhibition (IC_{50} μM)[a]
3 (NU6102)	—	—	0.005
10 (NU6176)	—	—	0.21[b]
8	$R^1 = R^2 = H$	85	0.24
1a	$R^1 = CH(CH_3)_2$, $R^2 = H$	70	1.1
1b	$R^1 = CH_2CH_2CH_2N(CH_3)_2$, $R^2 = H$	92	0.53
1c	$R^1 = CH_2CH_2N(CH_2CH_2)_2O$, $R^2 = H$	93	1.6
1d	$R^1 = CH_2$-*p*-$C_6H_4OCH_3$, $R^2 = H$	89	3.0
1e	$R^1 = CH_2$-*p*-$C_6H_4CH_3$, $R^2 = H$	72	36
1f	$R^1 = CH_2CH_2CH_2Ph$, $R^2 = H$	71	64
1g	$R^1, R^2 = (CH_2)_4$	91	1.1
1h	$R^1, R^2 = (CH_2)_5$	75	1.6
1i	$R^1, R^2 = (CH_2)_4NH$	75	0.45
1j	$R^1, R^2 = (CH_2)_4O$	72	0.82
1k	$R^1 = p$-$C_6H_4OCH_3$, $R^2 = H$	57	2.4
1l	$R^1 = p$-$C_6H_4CH(CH_3)_3$, $R^2 = H$	47	34

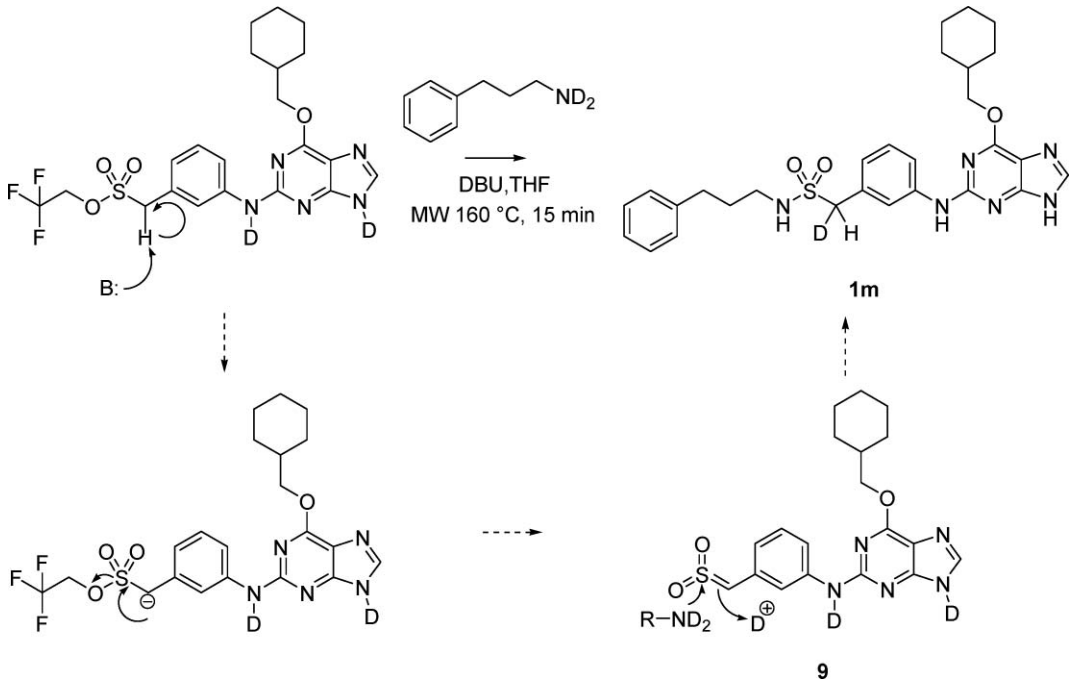
[a] Concentration of inhibitor required to reduce kinase activity by 50% of control. Values are the mean of at least three determinations. [b] Reference 12.



Scheme 2 Synthesis of [3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]methane-sulfonamide.

pentafluorophenylsulfonate with an amine.[16,17] For example, heating pentafluorophenyl 3-methylbutylsulfonate with 4-methylbenzylamine gave the required *N*-(4-methylbenzyl)-3-methylbutylsulfonamide in excellent yield. When the reaction between pentafluorophenyl 3-methylbutylsulfonate and 4-methylbenzylamine was carried out in a mixture of THF and D_2O the product contained one atom of deuterium in the methylene group attached to sulfonamide nitrogen.[17] This led to the proposal of a sulfene intermediate ($Me_2CHCH_2CH{=}SO_2$).[18–20] Caddick and his group reported similar preparations of sulfonamides from amines and 2,4,6-trichlorophenylsulfonates using microwave and conventional heating.[21]

To explore the mechanism of the synthesis of sulfonamides from **7**, the amino group of 3-phenylpropan-1-amine and NH groups of sulfonate ester **7** were initially deuterated by exchange in deuterated methanol (CD_3OD). The resulting mixture of deuterated starting materials with DBU was subjected to microwave heating to give **1m** labelled with deuterium. Mass spectrometric, ^1H and ^{13}C NMR analysis showed the dominant species in the methylene group adjacent to the sulfonamide to be CHD. In particular, the ^{13}C NMR showed a triplet (^{13}C-D 19 Hz) at δ 59.32 for *C*HD alongside a singlet for residual *C*H_2 at δ 59.60 in a ratio *ca.* 2 : 1. This was in agreement with the ratio of CHD to CH_2 of *ca.* 2 : 1 observed in the ^1H NMR spectrum. The results of this experiment are consistent with the intermediacy of sulfene **9** and hence a similar mechanism (Scheme 3) to that demonstrated by Caddick *et al.* in their studies (see above).[17] If it is assumed that during the experiment described for **7** that the proton abstracted from the benzylic methylene group exchanges with the deuterons (*N*-D) introduced into **7**, then the theoretical deuterium content of **1m** should be *ca.* 87% (note that 2.5 mol equiv. of 3-phenylpropan-1-amine was used), which compares with *ca.* 65–70% observed.



Scheme 3 Mechanism for incorporation of deuterium into 1-[3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]-*N*-(3-phenylpropyl)[$^2H_1$]methanesulfonamide *via* a sulfene intermediate.

Activity of sulfonamides against CDK2

Compounds **1a–1l** were assayed for the inhibition of human cyclin-dependent kinase 2, as described[22] and the results are summarised in Table 1. Previous structure–activity studies with this class of CDK inhibitor, demonstrated that relocating the sulfonamide group of NU6102 (**3**) from the 4- to the 3-position on the 2-arylamino ring (**10**) resulted in a 40-fold reduction in potency against CDK2.[12] In the present study, no further loss of activity was observed on introducing a methylene group between the sulfonamide and the aryl ring, the homosulfonamide **8** proving equipotent with **10**. *N*-Alkylation of the sulfonamide generally reduced CDK-2 inhibitory activity as observed for **1a** and **1c**, while a substituted benzyl (**1d**, **1e**) or 3-phenylpropyl (**1f**) group on the sulfonamide resulted in a marked loss of potency compared with the parent compound (**8**). Interestingly, the dimethylaminopropyl derivative (**1b**) was only some two-fold less potent than **8**, perhaps suggesting an interaction between the basic dimethylamino group and the kinase. 6-Cyclohexylmethoxy-2-arylaminopurines bearing alicyclic amines on the pendant sulfonamide (**1g**, **1h**, **1i**, **1j**) showed a less dramatic reduction in potency, with IC_{50} values in the 0.5–1.5 μM range, and although the *N*-4-methoxyphenylsulfonamide (**1k**) exhibited low micromolar activity against CDK2, the corresponding 4-*t*-butylphenyl derivative (**1l**) was markedly less active (IC_{50} = 34 μM), suggesting a steric effect within the ATP-binding domain.

Conclusion

Given the special importance of the sulfonamide group in medicinal chemistry, on account of its unique hydrogen bonding characteristics (see *e.g.* ref. 23), numerous methods have been reported for the synthesis of sulfonamides beyond the classical reaction of sulfonyl chlorides with amines.[24] Recent reports include the activation of sulfonic acids using either 2,4,6-trichloro-[1,3,5]-triazine[25] or triphenylphosphine ditriflate[26] followed by addition of an amine, and the reaction of sulfonic acids with an isocyanide.[27] In addition, methyl sulfinates have been reacted with a lithium amide, followed by oxidation to the corresponding sulfonamide using *m*-chloroperbenzoic acid.[28] Oxidation of sulfenamides to sulfonamides using either *m*-chloroperbenzoic acid, or a mixture of $KMnO_4$ and $CuSO_4$ have been reported in modest yields.[29,30] The method described in this paper starts with the relatively stable trifluoroethoxysulfonate **7**, avoids noxious or hazardous reagents and affords good yields of the target sulfonamides. The exploitation of trifluoroethyl as a leaving group because of its abrogated S_N2 reactivity is, to the best of our knowledge, a novelty. The evaluation of compounds **1a–1l** against kinase targets other than CDK2 is being pursued and will be reported elsewhere.

Experimental section

General procedures

Chemicals and solvents were obtained from reputable suppliers. THF was freshly distilled from sodium/benzophenone. Other dry solvents were obtained from commercial sources and used directly. Triethylamine was dried by distillation from calcium hydride and stored over potassium hydroxide, under nitrogen. Microwave irradiation was conducted in an Initiator(tm) Sixty Biotage reactor. Chromatography, spectroscopy and combustion analyses were performed as previously described.[31–34]

General procedure A

For the synthesis of the 2-arylaminopurine derivatives **1a–1m**, [3-(6-cyclohexylmethoxy-9*H*-purin-2-ylanilino]methane(2,2,2-trifluoroethyl)sulfonate ester **7**, 1,8-diazabicyclo[5.4.0]undec-7-ene, and the appropriate amine (quantities of reagents are given below for individual compounds) were heated under microwave conditions in anhydrous tetrahydrofuran (2 mL) for 15 min at 160 °C. After removal of the solvent, the white solid was extracted with ethyl acetate or THF and washed with aq. sodium bicarbonate and brine. The organic phase was concentrated to give a residue that was purified by medium pressure chromatography or by normal phase chromatography with a Biotage SP4 machine.

2,2,2-Trifluoroethyl 3-nitrophenylmethanesulfonate (5). To a stirred solution of DMAP (155 mg, 1.27 mmol) and Et_3N (5.37 mL, 38 mmol) in 2,2,2-trifluoroethanol (30 cm^3) was added 3-nitromethanesulfonyl chloride (3 g, 12.7 mmol). After stirring at room temperature for 3 h the solvent was removed. The brown residue was extracted into dichloromethane (250 mL) was washed with 0.05 M HCl soln. (1 × 250 mL) and water (1 × 250 mL). The organic layer was dried through a phase separator (Biotage ISOLUTE) and concentrated to give a colourless oil that was sonicated in water (50 mL) to give the title compound as a white crystalline solid that was collected by suction filtration (3.66 g, 96%). R_f 0.52 (6 : 4 v/v EtOAc-petrol), mp 84–85 °C; (Found: C, 36.2; H, 2.6; N, 4.5%. $C_9H_8F_3NO_5S$ requires C, 36.1; H, 2.7; N, 4.7%); δ_H (300 MHz, DMSO-d_6) 5.00 (2H, q, *J* 8.6 Hz, OCH_2CF_3), 5.18 (2H, s, $ArCH_2$), 7.76 (1H, dd, *J* 7.8, 8.0 Hz, Ar*H*), 7.91 (1H, d, *J* 7.8 Hz, Ar*H*), 8.29 (1H, d, *J* 8.2 Hz, Ar*H*), 8.37 (1H, s, Ar*H*). δ_C (125 MHz, DMSO) 53.86, 64.86 (q, $^2J_{C-F}$ 36 Hz), 122.50 (q, $^1J_{C-F}$ 276 Hz), 123.80, 125.52, 130.02, 130.25, 137.39, 147.76.

2,2,2-Trifluoroethyl 3-aminophenylmethanesulfonate (6). To **5** (3.5 g, 11.7 mmol) in 2,2,2-trifluoroethanol (35 mL) was added 10% palladium on carbon (1.05 g) and the reaction mixture was stirred under H_2 for 18 h. The resulting mixture was filtered through Celite and concentrated *in vacuo* to give the title compound **6** as a pale yellow solid (2.92 g, 93%). R_f 0.81 (6 : 4 v/v EtOAc-petrol), mp 77–78 °C; (Found: C, 40.2; H, 3.7; N, 5.15%. $C_9H_{10}F_3NO_3S$ requires C, 40.15; H, 3.7; N, 5.2%); δ_H (300 MHz, DMSO-d_6) 4.71 (2H, s, $ArNH_2$), 4.89 (2H, q, *J* 8.6 Hz, OCH_2CF_3), 5.22 (2H, s, $ArCH_2$), 6.52–6.62 (3H, m, 3 × Ar*H*), 7.03 (1H, dd, *J* 7.6, 7.8 Hz, Ar*H*).

2,2,2-Trifluoroethyl-3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonate (7). To **6** (2.8 g, 10.4 mmol) and 6-cyclohexylmethoxy-2-fluoropurine[12] (1.24 g, 5.0 mmol) in 2,2,2-trifluoroethanol (25 mL), was added trifluoroacetic acid (1.84 mL, 24.8 mmol). The mixture was boiled at reflux for 24 h and allowed to cool to room temperature. The solvent and TFA were removed *in vacuo* and the residue was extracted into EtOAc (100 mL). The resulting solution was washed with saturated aqueous $NaHCO_3$ solution (100 mL) and dried (Na_2SO_4). The solvents were removed to furnish the crude product, which was dry loaded onto silica (~50 mL) and purified by medium pressure chromatography using 60% ethyl acetate-petrol as eluent to give a viscous oil that was triturated with dichloromethane (~35 mL), giving the product **7** as a pale yellow powder (1.83 g, 74%). R_f 0.22 (6 : 4 v/v EtOAc-petrol), mp 199–200 °C; (Found: C, 50.8; H, 4.6; N, 13.9%. $C_{21}H_{24}F_3N_5O_4S$ requires C, 50.5; H, 4.8; N, 14.0%); UV λ_{max} 272, 292 nm (EtOH); ν_{max}(film)/cm^{-1} 3436, 3112, 2924, 2848, 1591, 1537, 1494, 1435, 1392, 1338, 1287, 1151, 1028, 950, 812; δ_H (300 MHz, DMSO-d_6) 1.0–1.9 (11H, m, cyclohexyl), 4.35 (2H, d, *J* 6.2 Hz, OCH_2), 4.84 (2H, s, $ArCH_2$), 4.94 (2H, q, *J* 8.6 Hz, CH_2CF_3), 6.99 (2H, d, *J* 7.6 Hz, 2 × Ar*H* overlap), 7.31 (1H, t, *J* 7.8, 8.1 Hz, Ar*H*), 7.86–7.88 (2H, m, 2 × Ar*H*), 8.03 (1H, s, H^8), 9.44 (1H, s, ArN*H*Ar), 12.86 (1H, br, N^9H). LCMS (MeOH) (ESI+) *m*/*z* 500 $(M + H)^+$.

1-[3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]-*N*-isopropylmethanesulfonamide (1a). Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonate (75 mg, 0.15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (68 µl, 0.45 mmol), and isopropylamine (32 µl, 0.38 mmol) was purified by medium pressure chromatography on Biotage KP-NH silica using 95% ethyl acetate–methanol to give the title compound as a white solid (48 mg, 70%). R_f 0.37 (9 : 1 v/v EtOAc–MeOH, KP-NH), mp 230–231 °C; UV λ_{max} 272 nm (EtOH); ν_{max}(film)/cm^{-1} 3435, 3254, 3088, 2928, 2851, 1734, 1598, 1530, 1487, 1447, 1393, 1348, 1300, 1241, 1115, 1026, 974, 938, 905, 858, 790, 691; δ_H (300 MHz, DMSO-d_6) 1.00–1.90 (11H, m, cyclohexyl), 1.08 (6H, d, *J* 6.4 Hz, $(CH_3)_2CH$), 3.35 (1H, m, overlap with H_2O, $CHMe_2$), 4.21 (2H, s, $ArCH_2$), 4.34 (2H, d, *J* 6.0 Hz, OCH_2), 6.92 (1H, d, *J* 7.3 Hz, Ar*H*), 7.00 (1H, d, *J* 7.3 Hz, Ar*H*), 7.25 (1H, dd, *J* 7.8, 7.9 Hz, Ar*H*), 7.83 (1H, s, Ar*H*), 7.84 (1H, s, H^8), 7.98 (1H, br, SO_2NH), 9.38 (1H, s, ArN*H*Ar), 12.77 (1H, s br, N^9H); LCMS (MeOH) (ESI+) *m*/*z* 459.42 $(M + H)^+$. HRMS (ESI+) $C_{22}H_{30}N_6O_3S$ + H requires 459.2173, found 459.2172. HPLC purity (as area %):98.

1-[3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]-*N*-(3-dimethylaminopropyl)methanesulfonamide (1b). Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonate (60 mg, 0.12 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (55 µl, 0.36 mmol), and *N*,*N*-dimethylpropane-1,3-diamine (38 µl, 0.30 mmol) was purified by medium pressure chromatography on KP-NH silica using 85% ethyl acetate–methanol to give the title compound as a white solid (55 mg, 92%). R_f 0.13 (9 : 1 v/v EtOAc–MeOH, KP-NH), mp 167–168 °C; (Found: C, 57.8; H, 7.15; N, 19.7%. $C_{24}H_{35}N_7O_3S$ requires C, 57.5; H, 7.0; N, 19.55%); UV λ_{max} 272, 293 nm (EtOH); ν_{max}(film)/cm^{-1} 2924, 2850, 1589, 1541, 1489, 1441, 1390, 1356, 1308, 1243, 1214, 1146, 1121, 973, 887, 789, 693; δ_H (300 MHz, DMSO-d_6) 1.00–1.90 (13H, m, cyclohexyl and $NCH_2CH_2CH_2NH$), 2.07 (6H, s, 2 × CH_3), 2.19 (2H, t, *J* 6.9 Hz, Me_2NCH_2), 2.95 (2H, t, *J* 6.7 Hz, CH_2CH_2NH), 4.23 (2H, s, $ArCH_2$), 4.35 (2H, d, *J* 5.8 Hz, OCH_2), 6.92 (1H, d, *J* 5.8 Hz, Ar*H*), 7.26 (1H, dd, *J* 7.8, 7.8 Hz, Ar*H*), 7.83 (1H, d, *J* 7.7 Hz, Ar*H*), 7.84 (1H, s, Ar*H*), 8.00 (1H, s, H^8), 9.35 (1H, s, ArN*H*Ar). LCMS (MeOH) (ESI+) *m*/*z* 502.36 $(M + H)^+$. HRMS (ESI+) $C_{24}H_{35}N_7O_3S$ + H requires 502.2595, found 502.2600. HPLC purity (as area %):99.

1-[3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]-*N*-(2-morpholin-4-ylethyl)methanesulfonamide (1c). Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonate (60 mg, 0.12 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (55 µl, 0.36 mmol), and 2-morpholinoethanamine (39 µl,

0.30 mmol) was purified by medium pressure chromatography on KP-NH silica using 85% ethyl acetate–methanol to give the title compound as a colourless solid (59 mg, 93%). R_f 0.23 (9 : 1 v/v EtOAc–MeOH, KP-NH), mp 136–137 °C; UV λ_{max} 272, 293 nm (EtOH); ν_{max}(film)/cm^{-1} 2924, 2852, 2158, 2021, 1973, 1588, 1542, 1491, 1443, 1393, 1356, 1304, 1243, 1214, 1115, 973, 787, 692; δ_H (300 MHz, DMSO-d_6) 1.00–1.86 (11H, m, cyclohexyl), 2.34 (6H, br m, 2 × NCH_2CH_2O and CH_2CH_2SO$_2$NH), 3.03 (2H, t, J 6.6 Hz, CH_2NH), 3.52 (4H, t, J 4.6 Hz, 2 × NCH$_2$CH_2O), 4.31 (2H, s, ArCH_2), 4.34 (2H, d, J 6.0 Hz, OCH_2), 6.93 (1H, d, J 7.4 Hz, ArH), 7.26 (1H, dd, J 7.6, 7.7 Hz, ArH), 7.81 (1H, s, ArH), 7.83 (1H, d, J 7.7 Hz, ArH), 8.00 (1H, s, H^8), 9.34 (1H, s, ArNHAr). LCMS (MeOH) (ESI+) m/z 530.43 (M + H)$^+$. HRMS (ESI+) $C_{25}H_{35}N_7O_4S$ + H requires 530.2544, found 530.2549. HPLC purity (as area %):95.

1-[3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]-*N*-(4-methoxybenzyl)methanesulfonamide (1d). Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonate (150 mg, 0.3 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (136 µl, 0.9 mmol), and 4-methoxybenzylamine (97 µl, 0.75 mmol) was purified by medium pressure chromatography on silica using 90% ethyl acetate-petrol to give the title compound as a white solid (143 mg, 89%). R_f 0.37 (EtOAc), mp 118–119 °C; UV λ_{max} 272 nm (EtOH); ν_{max}(film)/cm^{-1} 2922, 2850, 2361, 2338, 2026, 1589, 1541, 1506, 1444, 1395, 1354, 1303, 1244, 1121, 1030, 947, 887, 787, 730, 692; δ_H (300 MHz, DMSO-d_6) 1.00–1.90 (11H, m, cyclohexyl), 3.70 (3H, s, OCH_3), 4.05 (2H, d, J 9.0 Hz, ArCH_2NH), 4.22 (2H, s, ArCH_2SO$_2$NH), 4.35 (2H, d, J 6.1 Hz, OCH_2), 6.86–6.90 (3H, m, 3 × ArH), 7.23 (2H, d, J 7.0 Hz, ArH), 7.26 (1H, dd, J 7.6, 7.9 Hz, ArH), 7.57 (1H, t, J 6.0 Hz, SO$_2$NH), 7.81–7.85 (2H, m, 2 × ArH), 7.99 (1H, s, H^8), 9.37 (1H, s, ArNHAr), 12.77 (1H, s br, N^9H); LCMS (MeOH) (ESI+) m/z 537.40 (M + H)$^+$. HRMS (ESI$^-$) $C_{27}H_{32}N_6O_4S$ - H requires 535.2133, found 535.2143. HPLC purity (as area %):95.

1-[3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]-*N*-(4-methylbenzyl)methanesulfonamide (1e). Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonate (75 mg, 0.15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (68 µl, 0.45 mmol), and *p*-tolylmethanamine (48 µl, 0.38 mmol) was purified by medium pressure chromatography on silica using 75% ethyl acetate-petrol to give the title compound as a colourless solid (56 mg, 72%). R_f 0.46 (8 : 2 v/v EtOAc-Petrol), mp 147–148 °C; (Found: C, 62.2; H, 6.2; N, 16.0%. $C_{27}H_{32}N_6O_3S$ requires C, 62.3; H, 6.2; N, 16.15%); UV λ_{max} 272 nm (EtOH); ν_{max}(film)/cm^{-1} 2922, 2850, 2361, 2338, 1589, 1540, 1491, 1443, 1393, 1352, 1306, 1121, 1059, 974, 945, 887, 837, 787, 691; δ_H (300 MHz, DMSO-d_6) 1.00–1.86 (11H, m, cyclohexyl), 2.26 (3H, s, ArCH_3), 4.07 (2H, s, ArCH_2NH), 4.23 (2H, s, ArCH_2SO$_2$NH), 4.35 (2H, d, J 6.1 Hz, OCH_2), 6.90 (1H, d, J 7.5 Hz, ArH), 7.12 (2H, d, J 7.8 Hz, 2 × ArH), 7.20 (2H, d, J 7.9 Hz, 2 × ArH), 7.26 (1H, dd, J 7.8, 7.8 Hz, ArH), 7.81–7.85 (2H, m, 2 × ArH), 8.01 (1H, s, H^8), 9.35 (1H, s, ArNHAr), 12.79 (1H, s br, N^9H); LCMS (MeOH) (ESI+) m/z 521.39 (M + H)$^+$. HRMS (ESI+) $C_{27}H_{32}N_6O_3S$ + H requires 521.2329, found 521.2328. HPLC purity (as area %):97.

1-[3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]-*N*-(3-phenylpropyl)methanesulfonamide (1f). Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonate (75 mg, 0.15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (68 µl, 0.45 mmol), and 3-phenylpropan-1-amine (53 mg, 0.38 mmol) was purified by medium pressure chromatography on silica using 90% ethyl acetate-petrol to give the title compound as a white solid (57 mg, 71%). R_f 0.41 (EtOAc), mp 138–139 °C; UV λ_{max} 272 nm (EtOH); ν_{max}(film)/cm^{-1} 3277, 2923, 2850, 2444, 2361, 1586, 1551, 1510, 1447, 1395, 1352, 1310, 1126, 976, 951, 882, 787, 741, 695; δ_H (300 MHz, DMSO-d_6) 1.00–1.90 (11H, m, cyclohexyl), 1.70 (2H, m, CH$_2$CH_2CH$_2$NH), 2.56 (2H, t, J 7.7 Hz, PhCH_2), 2.92 (2H, m, CH$_2$CH_2NH), 4.24 (2H, s, ArCH_2), 4.35 (2H, d, J 6.0 Hz, OCH_2), 6.91 (1H, d, J 7.5 Hz, ArH), 7.10–7.28 (7H, m, 7 × ArH), 7.80–7.85 (2H, m, ArH and SO$_2$NH), 8.01 (1H, s, H^8), 9.36 (1H, s, ArNHAr), 12.69 (1H, s br, N^9H); δ_C (500 MHz, CD$_3$OD) 25.59, 26.25, 29.58, 31.98, 32.49, 37.45, 42.82, 58.29, 71.81, 118.62, 120.87, 123.57, 124.81, 125.47, 127.97, 128.03, 128.39, 137.84, 141.18, 141.48, 156.31; LCMS (MeOH) (ESI+) m/z 535.45 (M + H)$^+$. HRMS (ESI$^-$) $C_{28}H_{34}N_6O_3S$ - H requires 533.2340, found 533.2350. HPLC purity (as area %):95.

1-(3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonyl)pyrrolidine (1g). Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonate (75 mg, 0.15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (68 µl, 0.45 mmol), and pyrrolidine (32 µl, 0.38 mmol), was purified by medium pressure chromatography on silica using 80% ethyl acetate-petrol to give the title compound as a white solid (53 mg, 75%). R_f 0.74 (EtOAc), mp 120–121 °C; UV λ_{max} 272, 292 nm (EtOH); ν_{max}(film)/cm^{-1} 2926, 2852, 2159, 2031, 1590, 1540, 1492, 1445, 1394, 1317, 1122, 789; δ_H (300 MHz, DMSO-d_6) 1.0–1.9 (15H, m, cyclohexyl and 2 × pyrrolidine CH_2), 3.15 (4H, t, J 6.5 Hz, 2 × pyrrolidine CH_2), 4.35 (4H, s and d, J 5.8 Hz, OCH_2 and ArCH_2), 6.96 (1H, d, J 7.5 Hz, ArH), 7.26 (1H, dd, J 7.8, 7.9 Hz, ArH), 7.81 (1H, d, J 8.4 Hz, ArH), 7.89 (1H, s, ArH) 7.98 (1H, s, H^8), 9.41 (1H, s, ArNHAr), 12.78 (1H, br, N^9H); LCMS (MeOH) (ESI+) m/z 471 (M + H)$^+$. HRMS (ESI+) $C_{23}H_{30}N_6O_3S$ + H requires 471.2173, found 471.2172. HPLC purity (as area %):100.

1-(3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonyl)piperidine (1h). Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy - 9*H* - purin - 2 - ylamino) phenylmethanesulfonate (75 mg, 0.15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (68 µl, 0.45 mmol), and piperidine (37 µl, 0.38 mmol) was purified by medium pressure chromatography on silica using 95% ethyl acetate–methanol to give the title compound as a white solid (54 mg, 75%). R_f 0.26 (EtOAc), mp 217–218 °C; (Found: C, 59.2; H, 6.6; N, 17.2%. $C_{24}H_{32}N_6O_3S$ requires C, 59.5; H, 6.7; N, 17.3%); UV λ_{max} 272, 293 nm (EtOH); ν_{max}(film)/cm^{-1} 2922, 2853, 2362, 2338, 1589, 1541, 1437, 1396, 1350, 1310, 1242, 1152, 1121, 1067, 1045, 949, 888, 789, 694; δ_H (300 MHz, DMSO-d_6) 1.0–1.8 (11H, m, cyclohexyl), 1.47 (6H, m, piperidyl CH), 3.12 (4H, br m, 2 × piperidyl CH_2), 4.28 (2H, s, ArCH_2), 4.35 (2H, d, J 6.2 Hz, OCH_2), 6.94 (1H, d, J 7.5 Hz, ArH), 7.25 (1H, dd, J 7.9, 8.0 Hz, ArH), 7.81 (1H, d, J 8.5 Hz, ArH), 7.88 (1H, s, ArH), 8.02 (1H, s,

H^8), 9.42 (1H, s, ArN*H*Ar), 12.76 (1H, br, N^9H); LCMS (MeOH) (ESI+) *m/z* 485.18 $(M + H)^+$.

1-(3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonyl)piperazine (1i). Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy - 9*H* - purin - 2 - ylamino) phenylmethanesulfonate (75 mg, 0.15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (68 µl, 0.45 mmol), and piperazine (45 mg, 0.53 mmol) was purified using the Biotage SP4 with KP-NH silica and 95% ethyl acetate–methanol to give the title compound as a colourless solid (66 mg, 91%). R_f 0.73 (8 : 2 v/v EtOAc–MeOH, KP-NH), mp 127–128 °C; UV λ_{max} 272, 293 nm (EtOH); ν_{max}(film)/cm^{-1} 2922, 2853, 2362, 2338, 1589, 1541, 1437, 1396, 1350, 1310, 1242, 1152, 1121, 1067, 1045, 949, 888, 789, 694; δ_H (300 MHz, DMSO-d_6) 1.0–1.9 (11H, m, cyclohexyl), 3.11 (4H, br, 2 × piperazinyl CH_2), 3.16 (4H, br, 2 × piperazinyl CH_2), 4.33 (2H, s, ArCH_2), 4.35 (2H, d, *J* 6.7 Hz, OCH_2), 6.95 (1H, d, *J* 7.5 Hz, Ar*H*), 7.26 (1H, dd, *J* 7.8, 7.9 Hz, Ar*H*), 7.62 (1H, d, *J* 8.0 Hz, Ar*H*), 7.91 (1H, s, Ar*H*), 7.97 (1H, s, H^8), 9.34 (1H, s, ArN*H*Ar), 12.77 (1H, br, N^9H); LCMS (MeOH) (ESI+) *m/z* 486 $(M + H)^+$. HRMS (ESI+) $C_{23}H_{31}N_7O_3S$ + H requires 484.2136, found 484.2145. HPLC purity (as area %):95.

4-(3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonyl)morpholine (1j). Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy - 9*H* - purin - 2 - ylamino) phenylmethanesulfonate (46 mg, 0.09 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (42 µl, 0.18 mmol), and morpholine (16 µl, 0.18 mmol), was purified by medium pressure chromatography on silica using 80% ethyl acetate-petrol as eluent to give the title compound as a white solid (32 mg, 72%). R_f 0.64 (EtOAc), mp 140–141 °C; UV λ_{max} 216, 272, 292 nm (EtOH); ν_{max}(film)/cm^{-1} 3302, 2924, 2854, 1587, 1552, 1494, 1396, 1307, 1242, 1141, 943, 788; δ_H (300 MHz, DMSO-d_6) 1.0–1.9 (11H, m, cyclohexyl), 3.11 (4H, t, *J* 4.5 Hz, NCH_2CH_2O), 3.57 (4H, t, *J* 4.5 Hz, NCH$_2$CH_2O), 4.34 (2H, d, *J* 7.3 Hz, OCH_2), 4.35 (2H, s, ArCH_2), 6.96 (1H, d, *J* 7.6 Hz, Ar*H*), 7.27 (1H, dd, *J* 7.8, 8.1 Hz, Ar*H*), 7.83–7.85 (2H, m, 2 × Ar*H*), 7.98 (1H, s, H^8), 9.43 (1H, s, ArN*H*Ar), 12.77 (1H, br, N^9H); LCMS (MeOH) (ESI+) *m/z* 487 $(M + H)^+$. HRMS (ESI+) $C_{23}H_{30}N_6O_4S$ + H requires 487.2122, found 487.2116. HPLC purity (as area %):100.

1-[3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]-*N*-(4-methoxyphenyl)methanesulfonamide (1k). Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy - 9*H* - purin - 2 - ylamino) phenylmethanesulfonate (75 mg, 0.15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (68 µl, 0.45 mmol), and 4-aminoanisole (45 mg, 0.38 mmol) was purified by medium pressure chromatography on silica using 80% ethyl acetate-petrol to give the title compound as a white solid (45 mg, 57%). R_f 0.43 (8 : 2 EtOAc-Petrol), mp 220–221 °C; UV λ_{max} 273 nm (EtOH); ν_{max}(film)/cm^{-1} 3341, 2924, 2850, 2361, 2337, 1632, 1608, 1579, 1553, 1499, 1438, 1404, 1362, 1331, 1296, 1220, 1150, 1120, 1030, 934, 824, 791, 693; δ_H (300 MHz, DMSO-d_6) 1.00–1.83 (11H, m, cyclohexyl), 3.73 (3H, s, ArOCH_3), 4.24 (2H, s, ArCH_2SO$_2$NH), 4.27 (2H, d, *J* 6.2 Hz, OCH_2), 6.80 (1H, d, *J* 7.5 Hz, Ar*H*), 6.89 (2H, d, *J* 8.9 Hz, 2 × Ar*H*), 7.16 (2H, d, *J* 8.9 Hz, 2 × Ar*H*), 7.25 (1H, dd, *J* 7.9, 7.9 Hz, Ar*H*), 7.75–7.82 (2H, m, 2 × Ar*H*), 8.01 (1H, s, H^8), 9.39 (1H, s, ArN*H*Ar), 12.79 (1H, s br, N^9H); LCMS (MeOH) (ESI+) *m/z* 523.40 $(M + H)^+$. HRMS (ESI+) $C_{26}H_{30}N_6O_4S$ + H requires 523.2122, found 523.2122. HPLC purity (as area %):97.

***N*-(4-*tert*-Butylphenyl)-*C*-[3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]methanesulfonamide (1l).** Following the **general procedure A**, the reaction of 2,2,2-trifluoroethyl-3-(6-cyclohexylmethoxy - 9*H* - purin - 2 - ylamino) phenylmethanesulfonate (75 mg, 0.15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (68 µl, 0.45 mmol), and 4-*t*-butylaniline (60 µl, 0.38 mmol) was purified by medium pressure chromatography on silica using 75% ethyl acetate-petrol to give the title compound as a colourless powder (39 mg, 47%). R_f 0.54 (8 : 2 EtOAc-Petrol), mp 132–133 °C; UV λ_{max} 273 nm (EtOH); ν_{max}(film)/cm^{-1} 3356, 2923, 2851, 2361, 2338, 1707, 1591, 1499, 1442, 1398, 1356, 1300, 1147, 1125, 934, 835, 785, 691; δ_H (300 MHz, DMSO-d_6) 1.00–1.83 (11H, m, cyclohexyl), 1.25 (9H, br s, C(CH_3)$_3$), 4.29 (2H, d, *J* 6.2 Hz, OCH_2), 4.31 (2H, s, ArCH_2SO$_2$NH), 6.79 (1H, d, *J* 7.1 Hz, Ar*H*), 7.14 (2H, d, *J* 8.6 Hz, 2 × Ar*H*), 7.24 (1H, dd, *J* 7.7, 8.0 Hz, Ar*H*), 7.32 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.76 (1H, s, Ar*H*), 7.81 (1H, d, *J* 7.9 Hz, Ar*H*), 8.00 (1H, s, H^8), 9.37 (1H, s, ArN*H*Ar), 12.79 (1H, s br, N^9H); LCMS (MeOH) (ESI+) *m/z* 549.49 $(M + H)^+$. HRMS (ESI+) $C_{29}H_{36}N_6O_3S$ + H requires 549.2642, found 549.2647. HPLC purity (as area %):95.

1-[3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]-*N*-(3-phenylpropyl)[$^2H_1$]methanesulfonamide (1m). 2,2,2-Trifluoroethyl-3-(6-cyclohexylmethoxy-9*H*-purin-2-ylamino)phenylmethanesulfonate (75 mg, 0.15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (68 µl, 0.45 mmol) and 3-phenylpropan-1-amine (54 µl, 0.38 mmol) were dissolved in ethyl acetate (5 mL) and concentrated to a residue that was co-evaporated with CD_3OD (2 × 2 mL, after an initial incubation for 2 h each time) *in vacuo* followed by anhydrous THF (2 mL). The residual material was subjected to **general procedure A** (8 min microwave heating) and the crude product was purified by medium pressure chromatography on silica using 90% ethyl acetate-petrol as eluent to give the title compound as a white solid (48 mg, 60%). R_f 0.41 (EtOAc), mp 139–140 °C; UV λ_{max} 272, 294 nm (EtOH); ν_{max}(film)/cm^{-1} 3279, 2923, 2851, 2361, 2337, 1725, 1589, 1549, 1489, 1447, 1381, 1350, 1310, 1287, 1130, 1083, 974, 945, 889, 787, 743, 692; δ_H (300 MHz, DMSO-d_6) 1.00–1.87 (11H, m, cyclohexyl), 1.69 (2H, m, CH$_2$CH_2CH$_2$NH), 2.56 (2H, t, *J* 7.6 Hz, PhCH_2), 2.92 (2H, m, CH$_2$CH_2NH), 4.22 (*ca.* 0.6H, br s, ArC*H*DSO$_2$NH), 4.24 (*ca.* 0.3H, br s, ArCH_2SO$_2$NH), 4.35 (2H, d, *J* 6.1 Hz, OCH_2), 6.91 (1H, d, *J* 7.3 Hz, Ar*H*), 7.12–7.28 (7H, m, 7 × Ar*H*), 7.81–7.86 (2H, m, Ar*H* and SO$_2$N*H*), 8.01 (1H, s, H^8), 9.38 (1H, s, ArN*H*Ar), 12.79 (1H, s br, N^9H); δ_C (125 MHz, CD_3OD) 59.32 (t, $J_{C\text{-}D}$ 19 Hz), 59.60 (s) and other peaks as observed in the spectrum of **1f**; LCMS (MeOH) (ESI+) *m/z* 536.40 $(M + H)^+$. HRMS (ESI+) $C_{28}H_{33}DN_6O_3S$ + H requires 536.2540, found 536.2532. HPLC purity (as area %):95.

[3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]methanesulfonamide (8). [3-(6-Cyclohexylmethoxy-9*H*-purin-2-ylamino)phenyl]-*N*-(4-methoxybenzyl)methanesulfonamide (**1d**, 80 mg, 0.15 mmol) was stirred in neat TFA (2 mL) for 6 h. Upon completion of the reaction, the TFA was removed *in vacuo* and the residual solid was extracted into EtOAc (50 mL). The organic layer was washed with aqueous sodium bicarbonate (50 mL), dried (Na_2SO_4) and concentrated to give a white solid.

Purification by medium pressure chromatography on silica using ethyl acetate as eluent gave the title compound as a white powder (53 mg, 85%). R_f 0.50 (EtOAc), mp 134–135 °C; UV λ_{max} 272, 292 nm (EtOH); ν_{max}(film)/cm^{-1} 3344, 2924, 2852, 2361, 2338, 1719, 1599, 1542, 1488, 1449, 1393, 1336, 1256, 1156, 1123, 1046, 966, 951, 890, 856, 834, 789, 692; δ_H (300 MHz, DMSO-d_6) 1.0–1.9 (11H, m, cyclohexyl), 4.20 (2H, s, ArCH_2SO$_2$NH$_2$), 4.34 (2H, d, J 6.0 Hz, OCH_2), 6.85 (2H, s br, SO$_2$NH_2), 6.93 (1H, d, J 7.3 Hz, ArH), 7.26 (1H, dd, J 7.8, 7.9 Hz, ArH), 7.75 (1H, s, ArH), 7.85 (1H, d, J 8.3 Hz, ArH), 7.97 (1H, s, H^8), 9.37 (1H, s, ArNH), 12.77 (1H, br, N^9H); LCMS (MeOH) (ESI+) m/z 417 (M + H)$^+$. HRMS (ESI+) $C_{19}H_{24}N_6O_3S$ + H requires 417.1703, found 417.1702. HPLC purity (as area %):96.

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