Design and synthesis of 9-dialkylamino-6-[(1*H*-1,2,3-triazol-4-yl)methoxy]-9*H*-purines

Álvaro Lorente-Macías[a,b], Juan J. Díaz-Mochón[a], María José Pineda de las Infantas y Villatoro[a,*] and Asier Unciti-Broceta[b,*]

[a] Department of Medicinal & Organic Chemistry, Faculty of Pharmacy, University of Granada, Campus de Cartuja s/n, 18071, Granada, Spain

[b] Cancer Research UK Edinburgh Centre, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Crewe Road South, Edinburgh EH4 2XR, UK

ABSTRACT

The purine ring is a common structural component of a large variety of biomolecules with important roles in both physiological and pathological processes. The biological ubiquity and versatility of this heterocyclic scaffold makes it a privileged structure in drug design. Consequently, the development of novel purine analogs remains of great interest in the medicinal chemistry field. Here, we report the design and synthesis of a series of 9-dialkylamino-6-[(1*H*-1,2,3-triazol-4-yl)methoxy]-9*H*-purines and their intermediates. This series of compounds aims to diversify the chemical space around the purine scaffold in the search towards the discovery of new biologically active small molecules.

INTRODUCTION

The purine ring system is the most abundant nitrogen-based heterocycle in nature.[1] It is found in the nucleobases guanine and adenine, thus being an essential component of the coded structure of nucleic acids and of many different cofactors and second messengers.[2] Purines are present in natural ligands and substrates of key regulatory elements of signaling networks, such as protein kinases, polymerases and G proteins. It is therefore not surprising that purine analogs have demonstrated a wide range of pharmacological properties and are considered privileged structures in drug discovery,[3,4] with several examples currently approved for the treatment of different pathologies and many more in clinical trials, or widely used as chemical probes or molecular tools.[5–8] The pharmaceutical interest in purines and their nucleoside derivatives has led to a thorough exploration of this chemical structure,[9–11] making the development of novel purine analogs a challenging task.

Looking at the chemical space explored so far around the purine scaffold, we identified two moieties at C6 and N9 of the purine system which have not been properly investigated. The introduction of 1,2,3-triazole moieties at C6 and dialkylamino groups at N9 (giving rise to an endocyclic-exocyclic N-N bond), could produce purine libraries with novel physicochemical features. Following this goal, herein we report the design and synthesis of a novel series of 9-dialkylamino-6-[(1*H*-1,2,3-triazol-4-yl)methoxy]-9*H*-purines aiming to contribute to the discovery of new tool compounds and bioactive agents.

RESULTS AND DISCUSSION

Design of general scaffold. The starting point of this work was compound **1**, a purine derivative previously discovered by our group that demonstrated pro-apoptotic activity in Jurkat

cells while not being active in K562 cells.[12,13] Compound **1** contains a purine ring substituted at positions C6, C8 and N9 with a benzyloxy, phenyl and *tert*-butyl groups, respectively. Although these groups seem to be required for the biological activity of **1**, they also confer unfavorable physicochemical properties (cLogD = 5.17) that hamper its progress to more complex preclinical models.

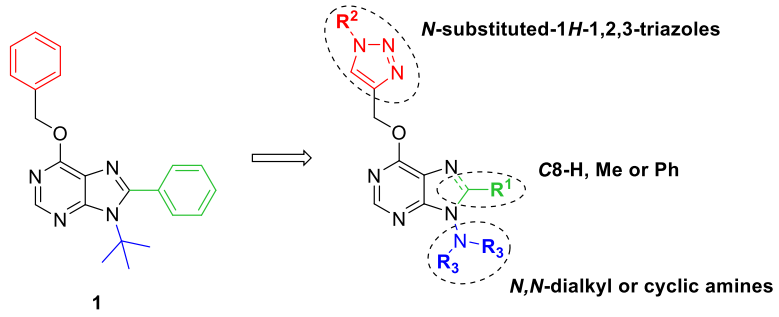
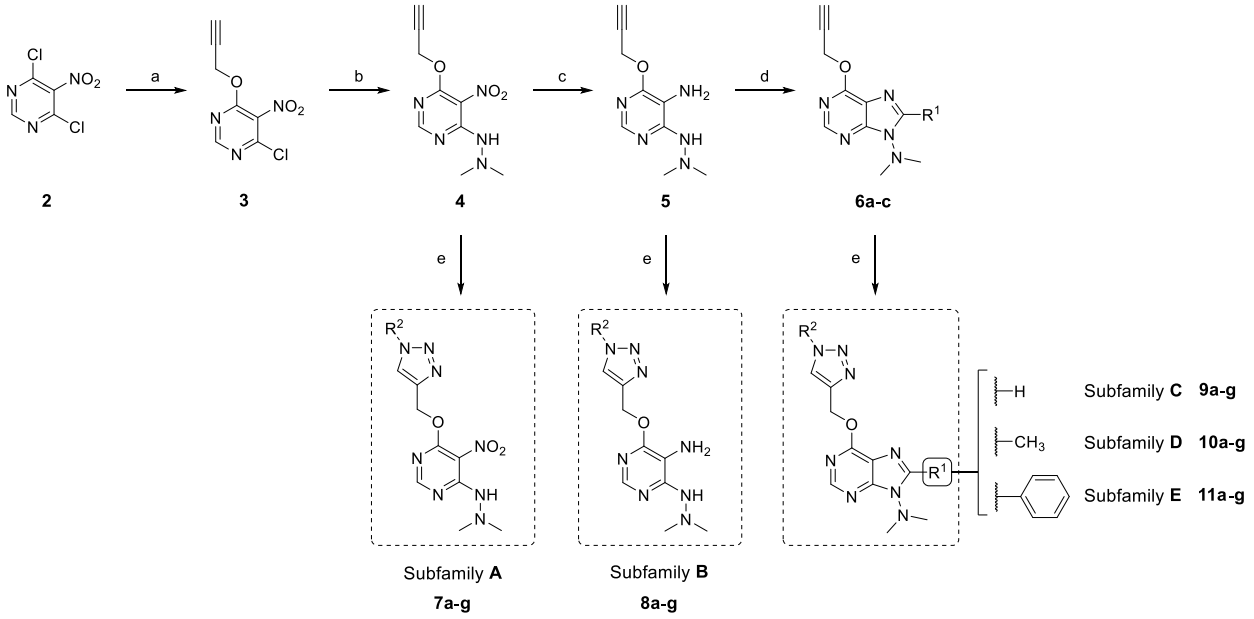


Figure 1. Design of the 9-dialkylamino-6-[(1*H*-1,2,3-triazol-4-yl)methoxy]-9*H*-purine scaffold explored in this work.

Inspired by the bioactivity of compound **1**[12,13] and related derivatives,[14,15] a new series of purine analogs was designed by introducing heteroatom-containing groups at the positions C6 and N9, aiming to explore uncharted chemical space with biological potential, to provide molecules with more favorable physicochemical properties and facilitate the combinatorial synthesis of novel derivatives (Figure 1). The main structural features introduced in the ring are: (i) *N*,*N*-dimethylamino or cyclic amino groups at N9 to replace the highly conserved alkyl groups (isopropyl or *tert*-butyl) presented at this position in many purine-based compounds; and (ii) bioisosteric replacement of the phenyl ring from the benzyloxy group at the C6 position of **1** by 1-substituted-1*H*-1,2,3-triazoles. Additionally, the synthetic route used for the preparation of the purine analogs (Scheme 1) facilitated the generation of a 24-member library of novel pyrimidines, thus increasing the number and chemical diversity of the compound collection.

Scheme 1. Synthesis of compounds 7a–g, 8a–g, 9a–g, 10a–g and 11a–g[a].



Compound library

Sub-library	R^2							
	A	7a	7b	7c	7d	7e	7f	7g
	B	8a	8b	8c	8d	8e	8f	8g
	C	9a	9b	9c	9d	9e	9f	9g
	D	10a	10b	10c	10d	10e	10f	10g
	E	11a	11b	11c	11d	11e	11f	11g

[a] Reagents and conditions: (a) Propargyl alcohol, DBU, THF, 0 °C, 2 h, 67%; (b) *N,N*-dimethylhydrazine, THF, rt, 18 h, 66%; (c) iron, NH_4Cl, $EtOH/H_2O$, reflux, 18 h, 45%; (d) $(CH_3O)_3C\text{-}R^1$, methanesulfonic acid, 100 °C, 18 h, 45% – 84%; (e) $N_3\text{-}R^2$, CuI, sodium ascorbate, TEA, 1,4-dioxane/H_2O or MeCN/H_2O, rt, 18 h, 7% – 79%.

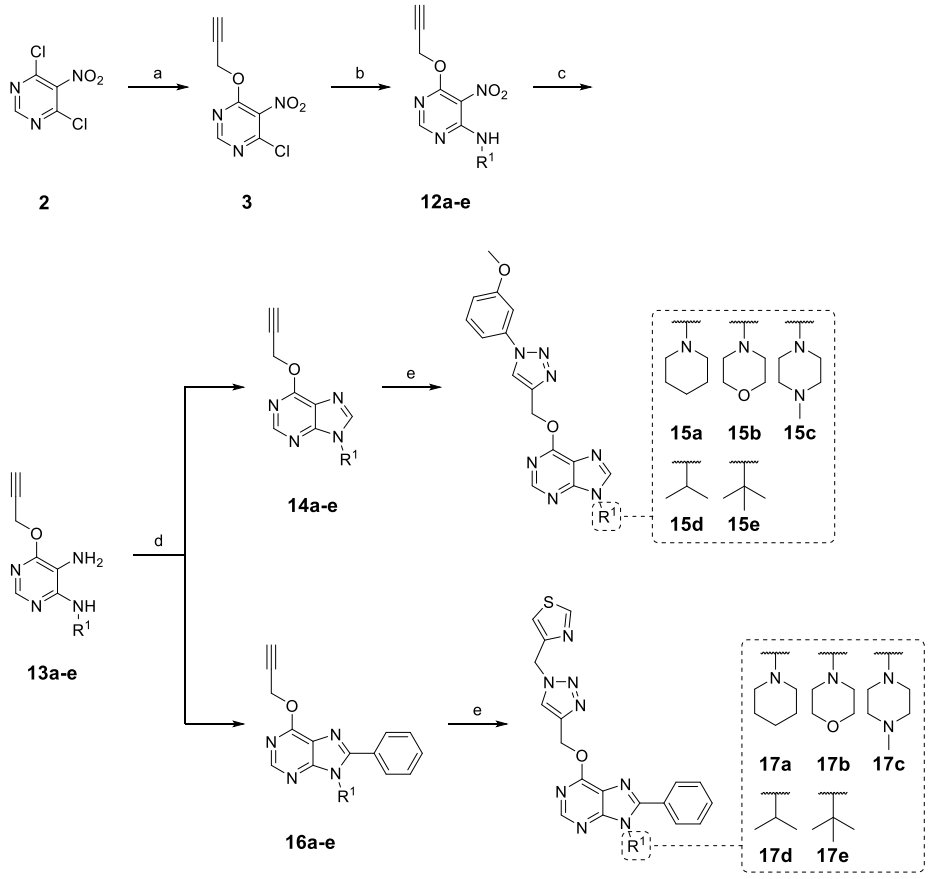
Synthesis. Compounds **7a**–**g**, **8a**–**g**, **9a**–**g**, **10a**–**g** and **11a**–**g** were synthesized according to Scheme 1. 4,6-dichloro-5-nitropyrimidine (**2**) was sequentially substituted with propargyl alcohol and *N,N*-dimethylhydrazine at the positions 4 and 6 of the pyrimidine ring, respectively, providing intermediate **4**. The iron(0)-catalyzed reduction of the nitro group under acidic conditions generated **5**, which was then treated with the appropriate orthoesther to provide

intermediates **6a**–**c**. Final compounds were generated by copper(I)-catalyzed alkyne-azide [3 + 2] cycloadditions (CuAAC) reactions between the alkynes **4** (to obtain **7a**–**g**), **5** (to obtain **8a**–**g**), **6a**–**c**, (to obtain **9a**–**g**, **10a**–**g** and **11a**–**g**) and seven different organic azides.

To further exploit the structural diversification offered by the synthetic route, the introduction of cyclic amino groups at the N9 position of the purine system was carried out by using a number of *N*,*N*-disubstituted hydrazines (piperidin-1-yl, morpholin-4-yl and 4-methylpiperazin-1-yl hydrazine) at the second step of the scheme. Isopropyl and *tert*-butyl amine were also used in this step to prepare derivatives that feature the most broadly used lipophilic moieties at N9. Compounds **9b** and **11f**, from the subfamilies **C** and **E**, respectively, were selected as representative molecules of the compound library to generate the new derivatives.

Novel derivatives **15a**–**e** and **17a**–**e** were prepared according to Scheme 2. Compound **2** was first reacted with propargyl alcohol and DBU to generate compound **3**. S_NAr of the Cl atom at C6 with the appropriate cycloalkyl hydrazine or alkylamine afforded 5-nitro derivatives **12a**–**e**, which were subsequently reduced to produce compounds **13a**–**e**. These intermediates underwent cyclocondensation reactions with both trimethyl orthoformate and trimethyl orthobenzoate to generate intermediates **14a**–**e** and **16a**–**e**, respectively. Finally, compounds **15a**–**e** and **17a**–**e** were prepared by CuAAC reactions of **14a**–**e** and **16a**–**e** with 3-methoxyphenyl azide and 4-(azidomethyl)thiazole, respectively.

Scheme 2. Synthesis of compounds **15a**–**e** and **17a**–**e**[a].

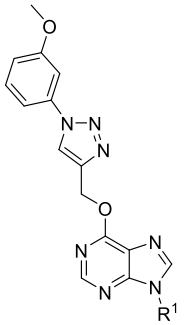


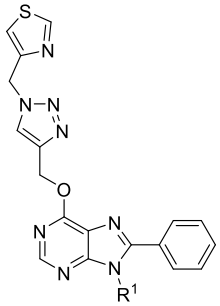
[a] Reagents and conditions: (a) Propargyl alcohol, DBU, THF, 0 °C, 2 h, 67%; (b) cycloheteroalkanyl hydrazine, THF, rt, 18 h, 46% – 75%; or alkylamine, TEA, DCM, rt, 18 h, 87 – 90%; (c) iron, NH_4Cl, EtOH/H_2O, reflux, 18 h, 31 – 76%; (d) trimethyl orthoformate or trimethyl orthobenzoate, methanesulfonic acid, 100 °C, 18 h, 34% – 94%; (e) 3-methoxyphenyl azide or 4-(azidomethyl)thiazole, CuI, sodium ascorbate, TEA, MeCN/H_2O, rt, 18 h, 53% – 86%.

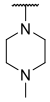
Finally, to understand the effect of the different moieties introduced at the position N9 of the purine ring in the physicochemical properties of the compounds, lipophilicity values (cLogD) were estimated for **9b**, **15a–e** and **11f**, **17a–e** using Chemicalize[16] (ChemAxon Ltd). As shown in Table 1, the modification of the N9 position enabled the generation of compounds with a broad range of lipophilicity values. Compounds derived from **9b** (**15a–e**) presented cLogD values between -0.05 and 2.77, while compounds originated from the modification of compound **11f** (**17a–e**) showed cLogD values between 0.79 and 3.76. As expected, in both compound series, the

lowest cLogD values were obtained for the analogs featuring a 4-methylpiperazin-1-yl group at position N9, while the highest values were presented by the N9-alkylated derivatives. It also is important to note that the presence of the nitrogen atom in the *N*,*N*-dimethylamino group of compounds **9b** and **11f** greatly decreased the lipophilic character of these molecules compared with their isopropyl analogs (**15d** and **17d**). Of note, cLogD are logarithmic values, hence the novel hydrazine-type moieties decreases lipophilicity of purine analogs by more than one order of magnitude, even when the number of C atoms is increased (e.g. in **15a** and **17a**). These results highlight the use of *N*,*N*-dimethylhydrazine as a novel and promising route to generate N9-substituted purines with improved physicochemical properties.

Table 1. Comparison of cLogD values of compounds 9b, 11f, 15a–e and 17a–e.





R^1	Compd.	clogD[a]	Compd.	clogD[a]
	**9b**	0.69	**11f**	1.68
	**15a**	1.54	**17a**	2.53
	**15b**	0.48	**17b**	1.46
	**15c**	-0.05	**17c**	0.79
	**15d**	2.49	**17d**	3.48
	**15e**	2.77	**17e**	3.76

[a]clogD values were calculated using Chemicalize by ChemAxon Ltd. at pH 7.4.

Conclusions. Herein, we have presented a novel synthetic pathway that allows the expansion of the chemical space of purine derivatives. This has been achieved by functionalizing the purine C6 position with CuAAC reactions and introducing *N*,*N*-dialkylamino groups at the N9 position. The synthetic route used in this work also allowed the generation of a 24-member library of novel pyrimidine intermediates. Of note, the installation of *N*,*N*-dialkylamino groups at N9, a strategy that has been poorly investigated in purine-based molecules,[17,18] has shown to favorably modulate the lipophilic character of these analogs. Finally, in addition to the presented chemical work, this compound library is currently undergoing biological screening across a panel of human cancer cell lines and parasites, in order to both elucidate the biological activity and to find out the structure-activity-relationships of these molecules. The results of these studies will be published as soon as they are completed.

EXPERIMENTAL SECTION

Chemistry. Reactions involving air sensitive reagents were performed using oven-dried reaction vessels and were carried out under a nitrogen atmosphere with dry solvents, unless otherwise stated. Yields refer to chromatographically and spectroscopically pure isolated yields. Reagents were purchased at the highest commercial quality and used without further purification. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60 F_{254}) using ultraviolet light visualization. Purifications were carried out by flash column chromatography using a silica gel 220 − 440 mesh (Sigma-Aldrich). ^{1}H NMR, ^{13}C NMR, DEPT 135º and DEPTQ 135º spectra were recorded on a BRUKER Nanobay Avance III HD (400 MHz) or BRUKER Avance NEO (400 or 500 MHz) spectrometers and were internally referenced using residual protic solvent ($CDCl_3$: ^{1}H NMR = 7.26, ^{13}C NMR = 77.16; DMSO-d_6: ^{1}H NMR = 2.50, 3.33, ^{13}C NMR = 39.52). Chemical shifts are reported in parts per million (ppm,

δ) downfield from tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hz. Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet) or combinations of these terms. High-resolution mass spectra (HRMS) were recorded on a Waters LCT Premier XE Spectrometer.

Synthesis of 4-chloro-5-nitro-6-(prop-2-yn-1-yloxy) pyrimidine (3). To a solution of propargyl alcohol (529.7 µL, 9.10 mmol, 1 equiv.) in dry THF (10 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (2.11 mL, 13.59 mmol, 1.5 equiv.) and the mixture stirred at 20 °C for 30 min. This solution was then added, dropwise over 45 min, into a stirring solution of 4,6-dichloronitropyrimidine (**2**) (1.76 g, 9.10 mmol, 1 equiv.) in dry THF (20 mL) at 0 °C. After the addition, the mixture was allowed to warm to room temperature over 1 h. Then the solvent was removed under reduced pressure and the resulting residue partitioned between DCM and H_2O. The layers were separated and the organic phase washed with saturated brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica (20% EtOAc in hexane) to provide the tittle compound as a white solid (1.30 g, 6.087 mmol, 67% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.68 (1H, s, CH), 5.15 (2H, d, J = 2.4 Hz, OCH_2), 2.58 (1H, t, J = 2.4 Hz, CH). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.39 (C), 157.48 (CH), 152.21 (C), 132.70 (C), 77.11 (C), 76.06 (CH), 56.72 (CH_2).

General procedure for the synthesis of compounds 4, 12a–c. To a 0.2 M solution of **3** (1 equiv.) in dry THF was added the corresponding hydrazine (2 equiv.) dropwise and the mixture stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure and the residue partitioned between DCM and H_2O. The layers were separated and the organic phase washed with saturated brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was

removed under reduced pressure and the crude product purified by flash chromatography on silica.

*4-(2,2-dimethylhydrazinyl)-5-nitro-6-(prop-2-yn-1-yloxy)-pyrimidine (**4**).* The crude product was purified by flash chromatography on silica (18 → 66% EtOAc in hexane) to provide the tittle compound as a yellow solid (1.04 g, 4.368 mmol, 66% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.72 (1H, bs, NH), 8.38 (1H, s, CH), 5.12 (2H, d, *J* = 2.4 Hz, OCH_2), 2.70 (6H, s, 2 x CH_3), 2.53 (1H, t, *J* = 2.4 Hz, CH). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 162.85 (C), 159.36 (CH), 156.10 (C), 129.89 (C), 77.49 (C), 75.86 (CH), 55.53 (CH_2), 48.00 (2 x CH_3). **HRMS** (ES + ve), $C_9H_{12}N_5O_3$ $(M + H)^+$: Calculated 238.0940. Obtained 238.0953.

*5-nitro-4-[(piperidin-1-yl)amino]-6-(prop-2-yn-1-yloxy)pyrimidine (**12a**).* The crude product was purified by flash chromatography on silica (15 → 75% EtOAc in hexane) to provide the tittle compound as a white solid (912.9 mg, 3.282 mmol, 69% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.90 (1H, bs, NH), 8.32 (1H, s, CH), 5.09 (2H, d, *J* = 2.5 Hz, OCH_2), 2.88 (4H, t, 2 x CH_2), 2.52 (1H, t, *J* = 2.4 Hz, CH), 1.86 – 1.63 (4H, m, 2 x CH_2), 1.62 – 1.31 (2H, m, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 162.47 (C), 159.12 (CH), 155.34 (C), 115.97 (C), 77.49 (C), 75.82 (CH), 57.36 (2 x CH_2), 55.34 (CH_2), 25.11 (2 x CH_2), 23.15 (CH_2). **HRMS** (ES + ve), $C_{12}H_{16}N_5O_3$ $(M + H)^+$: Calculated 278.1253. Obtained 278.1251.

*4-[(morpholin-4-yl)amino]-5-nitro-6-(prop-2-yn-1-yloxy)pyrimidine (**12b**).* The crude product was purified by flash chromatography on silica (25 → 75% EtOAc in hexane) to provide the tittle compound as an orange solid (1.49 g, 5.319 mmol, 56% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.35 (1H, s, CH), 5.11 (2H, d, *J* = 2.4 Hz, OCH_2), 3.82 (4H, t, 2 x CH_2), 2.89 (4H, t, 2 x CH_2), 2.53 (1H, t, *J* = 2.4 Hz, CH). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.66 (C), 154.37 (C),

144.18 (CH), 119.80 (C), 77.35 (C), 75.98 (CH), 66.29 (2 x CH_2), 56.33 (2 x CH_2), 55.53 (CH_2). **HRMS** (ES + ve), $C_{11}H_{14}N_5O_4$ $(M + H)^+$: Calculated 280.1046. Obtained 280.1036.

*4-[(4-methylpiperazin-1-yl)amino]-5-nitro-6-(prop-2-yn-1-yloxy)pyrimidine (**12c**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a yellow solid (1.27 g, 4.33 mmol, 46% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.32 (1H, s, CH), 5.29 (1H, bs, NH), 5.09 (2H, d, *J* = 2.4 Hz, OCH_2), 2.91 (4H, t, 2 x CH_2), 2.61 (4H, t, 2 x CH_2), 2.52 (1H, t, *J* = 2.4 Hz, CH), 2.32 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.23 (C), 155.45 (C), 145.26 (CH), 113.79 (C), 77.36 (C), 75.87 (CH), 55.69 (2 x CH_2), 55.39 (CH_2), 54.09 (2 x CH_2), 45.75 (CH_3). **HRMS** (ES + ve), $C_{12}H_{17}N_6O_3$ $(M + H)^+$: Calculated 293.1362. Obtained 293.1356.

General procedure for the synthesis of compounds 5, 13a–e. To a 0.2 M solution of the corresponding nitro derivatives (**4**, **12a**–**e)** (1 equiv.) in a mixture of EtOH and H_2O (4:1 v/v) was added iron powder (5 equiv.) and NH_4Cl (5 equiv.). The mixture was refluxed for 18 h, then cooled to room temperature and filtered through a pad (2 cm) of Celite. The filtrate was diluted with H_2O and extracted with DCM. The combined organic layers were washed with H_2O and saturated brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica.

*5-amino-4-(2,2-dimethylhydrazinyl)-6-(prop-2-yn-1-yloxy)-pyrimidine (**5**).* The crude product was purified by flash chromatography on silica (50 → 66% EtOAc in hexane) to provide the tittle compound as a light yellow solid (357.9 mg, 1.72 mmol, 45% yield). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.69 (1H, s, CH), 7.09 (1H, bs, NH), 4.96 (2H, d, *J* = 2.4 Hz, OCH_2), 4.70 (2H, bs, NH_2), 3.47 (1H, t, *J* = 2.4 Hz, CH), 2.51 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, DMSO-d_6): δ

154.25 (C), 150.07 (C), 144.18 (CH), 112.93 (C), 79.81 (C), 77.15 (CH), 52.97 (CH_2), 47.18 (2 x CH_3). **HRMS** (ES + ve), $C_9H_{14}N_5O$ $(M + H)^+$: Calculated 208.1198. Obtained 208.1187.

*5-amino-4-[(piperidin-1-yl)amino]-6-(prop-2-yn-1-yloxy)pyrimidine (**13a**).* The crude product was purified by flash chromatography on silica (100% EtOAc) to provide the tittle compound as a white solid (281.8 mg, 1.135 mmol, 36% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.84 (1H, s, CH), 5.52 (1H, bs, NH), 5.01 (2H, d, J = 2.4 Hz, OCH_2), 4.27 (2H, bs, NH_2), 2.74 (4H, t, 2 x CH_2), 2.48 (1H, t, J = 2.4 Hz, CH), 1.70 – 1.62 (4H, m, 2 x CH_2), 1.46 – 1.38 (2H, m, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.24 (C), 149.78 (C), 145.31 (CH), 114.20 (C), 79.06 (C), 74.68 (CH), 58.22 (2 x CH_2), 53.91 (CH_2), 25.77 (2 x CH_2), 23.32 (CH_2). **HRMS** (ES + ve), $C_{12}H_{18}N_5O$ $(M + H)^+$: Calculated 248.1511. Obtained 248.1521.

*5-amino-4-[(morpholin-4-yl)amino]-6-(prop-2-yn-1-yloxy)pyrimidine (**13b**).* The crude product was purified by flash chromatography on silica (50 → 75% EtOAc in hexane) to provide the tittle compound as a light red solid (658 mg, 2.631 mmol, 50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88 (1H, s, CH), 5.53 (1H, bs, NH), 5.03 (2H, d, J = 2.4 Hz, OCH_2), 4.05 (2H, bs, NH_2), 3.78 (4H, t, J = 4.7 Hz, 2 x CH_2), 2.83 (4H, t, J = 4.7 Hz, 2 x CH_2), 2.49 (1H, t, J = 2.5 Hz, CH). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.49 (C), 149.35 (C), 145.57 (CH), 114.29 (C), 78.92 (C), 74.82 (CH), 66.65 (2 x CH_2), 57.25 (2 x CH_2), 54.05 (CH_2). **HRMS** (ES + ve), $C_{11}H_{16}N_5O_2$ $(M + H)^+$: Calculated 250.1304. Obtained 250.1302.

*5-amino-4-[(4-methylpiperazin-1-yl)amino]-6-(prop-2-yn-1-yloxy)pyrimidine (**13c**).* The crude product was purified by flash chromatography on silica (0 → 30% MeOH in EtOAc) to provide the tittle compound as an off-white solid (607.8 mg, 2.31 mmol, 53% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (1H, s, CH), 5.37 (1H, bs, NH), 5.01 (2H, d, J = 2.4 Hz, OCH_2), 4.48 (2H, bs, NH_2), 2.85 (4H, t, 2 x CH_2), 2.56 (4H, t, 2 x CH_2), 2.48 (1H, t, J = 2.4 Hz, CH), 2.31 (3H, s,

CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.43 (C), 149.74 (C), 145.73 (CH), 114.23 (C), 79.03 (C), 74.72 (CH), 56.51 (2 x CH_2), 54.68 (CH_2), 53.93 (2 x CH_2), 45.72 (CH_3). **HRMS** (ES + ve), $C_{12}H_{19}N_6O$ $(M + H)^+$: Calculated 263.1620. Obtained 263.1625.

*5-amino-4-(isopropylamino)-6-(prop-2-yn-1-yloxy)pyrimidine (**13d**).* The crude product was purified by flash chromatography on silica (33% EtOAc in hexane) to provide the tittle compound as a yellow solid (329.6 mg, 1.591 mmol, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.05 (1H, s, CH), 4.99 (2H, d, J = 2.4 Hz, OCH_2), 4.54 (1H, bs, NH), 4.31 – 4.20 (1H, m, CH), 2.88 (2H, bs, NH_2), 2.48 (1H, t, J = 2.4 Hz, CH), 1.23 (6H, d, J = 6.4 Hz, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.31 (C), 155.23 (C), 149.31 (CH), 108.69 (C), 79.18 (C), 74.68 (CH), 53.76 (CH_2), 42.98 (CH), 23.35 (2 x CH_3). **HRMS** (ES + ve), $C_{10}H_{15}N_4O$ $(M + H)^+$: Calculated 207.1246. Obtained 207.1237.

*5-amino-4-(tert-butylamino)-6-(prop-2-yn-1-yloxy)pyrimidine (**13e**).* The crude product was purified by flash chromatography on silica (20% EtOAc in hexane) to provide the tittle compound as a blue oil (589.7 mg, 2.667 mmol, 31% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (1H, s, CH), 4.98 (2H, d, J = 2.4 Hz, OCH_2), 4.59 (1H, bs, NH), 2.81 (2H, bs, NH_2), 2.47 (1H, t, J = 2.4 Hz, CH), 1.48 (9H, s, 3 x CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.35 (C), 156.09 (C), 149.01 (CH), 108.88 (C), 79.33 (C), 74.57 (CH), 53.62 (CH_2), 51.96 (C), 29.49 (3 x CH_3). **HRMS** (ES + ve), $C_{11}H_{17}N_4O$ $(M + H)^+$: Calculated 221.1402. Obtained 221.1425.

General procedure for the synthesis of compounds **6a**–**c**, **14a**–**e**, **16a**–**e**.

A reaction vial was charged with the corresponding diaminopyrimidine (**5**, **13a**–**e**) (1 equiv.), the appropriate orthoesther (3 equiv.) and methanesulfonic acid (0.2 equiv.). The vial was sealed, placed in a pre-heated oil bath at 100 °C and stirred at that temperature for 18 h. The reaction was cooled to room temperature, diluted with DCM, washed with saturated $NaHCO_3$ solution

and saturated brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica.

*9-(dimethylamino)-6-(prop-2-yn-1-yloxy)-9H-purine (**6a**).* The crude product was purified by flash chromatography on silica (30 → 60% EtOAc in hexane) to provide the tittle compound as a white solid (98.3 mg, 0.451 mmol, 84% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.55 (1H, s, CH), 8.01 (1H, s, CH), 5.23 (2H, d, *J* = 2.4 Hz, OCH_2), 3.16 (6H, s, 2 x CH_3), 2.49 (1H, t, *J* = 2.4 Hz, CH). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.78 (C), 151.44 (CH), 151.37 (C), 142.31 (CH), 120.70 (C), 78.23 (C), 75.25 (CH), 54.25 (CH_2), 47.02 (2 x CH_3). **HRMS** (ES + ve), $C_{10}H_{12}N_5O$ $(M + H)^+$: Calculated 218.1042. Obtained 218.1048.

*8-methyl-9-(dimethylamino)-6-(prop-2-yn-1-yloxy)-9H-purine (**6b**).* The crude product was purified by flash chromatography on silica (25 → 30% EtOAc in hexane) to provide the tittle compound as a white solid (78.2 mg, 0.337 mmol, 51% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.47 (1H, s, CH), 5.19 (2H, d, *J* = 2.4 Hz, OCH_2), 3.14 (6H, s, 2 x CH_3), 2.57 (3H, s, CH_3), 2.47 (1H, t, *J* = 2.4 Hz, CH). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 158.59 (C), 152.86 (C), 152.50 (C), 150.20 (CH), 119.25 (C), 78.39 (C), 75.08 (CH), 54.00 (CH_2), 45.78 (2 x CH_3), 13.62 (CH_3). **HRMS** (ES + ve), $C_{11}H_{14}N_5O$ $(M + H)^+$: Calculated 232.1198. Obtained 232.1204.

*9-(dimethylamino)-8-phenyl-6-(prop-2-yn-1-yloxy)-9H-purine (**6c**).* The crude product was purified by flash chromatography on silica (15 → 18% EtOAc in hexane) to provide the tittle compound as a white solid (141 mg, 0.479 mmol, 45% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.54 (1H, s, CH), 8.28 – 8.19 (2H, m, 2 x CH), 7.52 – 7.44 (3H, m, 3 x CH), 5.25 (2H, d, *J* = 2.5 Hz, OCH_2), 3.23 (6H, s, 2 x CH_3), 2.49 (1H, t, *J* = 2.4 Hz, CH). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.28 (C), 153.42 (C), 151.32 (C), 150.60 (CH), 130.56 (CH), 129.52 (2 x CH), 129.05 (C),

128.38 (2 x CH), 119.99 (C), 78.39 (C), 75.15 (CH), 54.11 (CH_2), 45.53 (2 x CH_3). **HRMS** (ES + ve), $C_{16}H_{16}N_5O$ $(M + H)^+$: Calculated 294.1355. Obtained 294.1338.

*9-(piperidin-1-yl)-6-(prop-2-yn-1-yloxy)-9H-purine (**14a**).* The crude product was purified by flash chromatography on silica (50% EtOAc in hexane) to provide the tittle compound as a white solid (87.6 mg, 0.339 mmol, 61% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.55 (1H, s, CH), 8.04 (1H, s, CH), 5.22 (2H, d, J = 2.4 Hz, OCH_2), 3.46 (4H, t, J = 5.4 Hz, 2 x CH_2), 2.49 (1H, t, J = 2.4 Hz, CH), 1.85 – 1.77 (4H, m, 2 x CH_2), 1.64 – 1.56 (2H, m, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.76 (C), 151.52 (C), 151.37 (CH), 142.56 (CH), 120.60 (C), 78.24 (C), 75.24 (CH), 56.07 (2 x CH_2), 54.24 (CH_2), 26.20 (2 x CH_2), 23.16 (CH_2). **HRMS** (ES + ve), $C_{13}H_{16}N_5O$ $(M + H)^+$: Calculated 258.1355. Obtained 258.1382.

*9-(morpholin-4-yl)-6-(prop-2-yn-1-yloxy)-9H-purine (**14b**).* The crude product was purified by flash chromatography on silica (100% EtOAc) to provide the tittle compound as a white solid (155 mg, 0.596 mmol, 69% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.56 (1H, s, CH), 8.06 (1H, s, CH), 5.23 (2H, d, J = 2.4 Hz, OCH_2), 3.91 (4H, t, J = 4.7 Hz, 2 x CH_2), 3.56 (4H, t, 2 x CH_2), 2.50 (1H, t, J = 2.4 Hz, CH). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.81 (C), 151.65 (CH), 151.34 (C), 142.21 (CH), 120.54 (C), 78.13 (C), 75.33 (CH), 67.00 (2 x CH_2), 55.03 (2 x CH_2), 54.33 (CH_2). **HRMS** (ES + ve), $C_{12}H_{14}N_5O_2$ $(M + H)^+$: Calculated 260.1147. Obtained 260.1139.

*9-(4-methylpiperazin-1-yl)-6-(prop-2-yn-1-yloxy)-9H-purine (**14c**).* The crude product was purified by flash chromatography on silica (30% MeOH in EtOAc) to provide the tittle compound as an off-white solid (209.8 mg, 0.768 mmol, 94% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.53 (1H, s, CH), 8.05 (1H, s, CH), 5.22 (2H, d, J = 2.4 Hz, OCH_2), 3.52 (4H, t, 2 x CH_2), 2.69 (4H, t, 2 x CH_2), 2.49 (1H, t, J = 2.4 Hz, CH), 2.38 (3H, s, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.76 (C), 151.65 (CH), 151.41 (C), 141.93 (CH), 120.49 (C), 78.20 (C), 75.27

(CH), 54.94 (2 x CH_2), 54.47 (2 x CH_2), 54.26 (CH_2), 45.81 (CH_3). **HRMS** (ES + ve), $C_{13}H_{17}N_6O$ $(M + H)^+$: Calculated 273.1464. Obtained 273.1463.

*9-isopropyl-6-(prop-2-yn-1-yloxy)-9H-purine (**14d**).* The crude product was purified by flash chromatography on silica (75% EtOAc in hexane) to provide the tittle compound as a light yellow solid (131.3 mg, 0.605 mmol, 49% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.55 (1H, s, CH), 8.01 (1H, s, CH), 5.22 (2H, d, *J* = 2.4 Hz, OCH_2), 4.93 – 4.83 (1H, m, CH), 2.48 (1H, t, *J* = 2.4 Hz, CH), 1.62 (6H, d, *J* = 6.9 Hz, 3 x CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.54 (C), 152.22 (C), 151.60 (CH), 140.32 (CH), 121.88 (C), 78.30 (C), 75.16 (CH), 54.20 (CH_2), 47.68 (CH), 22.72 (2 x CH_3). **HRMS** (ES + ve), $C_{11}H_{13}N_4O$ $(M + H)^+$: Calculated 217.1089. Obtained 217.1086.

*9-(tert-butyl)-6-(prop-2-yn-1-yloxy)-9H-purine (**14e**).* The crude product was purified by flash chromatography on silica (25 → 50% EtOAc in hexane) to provide the tittle compound as a light yellow oil (96.1 mg, 0.416 mmol, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.55 (1H, s, CH), 8.04 (1H, s, CH), 5.22 (2H, d, *J* = 2.4 Hz, OCH_2), 2.48 (1H, t, *J* = 2.4 Hz, CH), 1.81 (9H, s, 3 x CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.65 (C), 152.80 (C), 150.83 (CH), 140.36 (CH), 122.87 (C), 78.40 (C), 75.11 (CH), 57.91 (C), 54.09 (CH_2), 29.17 (3 x CH_3). **HRMS** (ES + ve), $C_{12}H_{15}N_4O$ $(M + H)^+$: Calculated 231.1246. Obtained 231.1237.

*8-phenyl-9-(piperidin-1-yl)-6-(prop-2-yn-1-yloxy)-9H-purine (**16a**).* The crude product was purified by flash chromatography on silica (15 → 17% EtOAc in hexane) to provide the tittle compound as a light yellow solid (174.8 mg, 0.532 mmol, 62% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.53 (1H, s, CH), 8.32 – 8.24 (2H, m, 2 x CH), 7.52 – 7.43 (3H, m, 3 x CH), 5.25 (2H, d, *J* = 2.4 Hz, OCH_2), 4.06 (2H, t, *J* = 10.3 Hz, CH_2), 3.20 (2H, t, *J* = 10.3 Hz, CH_2), 2.49 (1H, t, *J* = 2.4 Hz, CH), 1.89 – 1.67 (6H, m, 3 x CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.25 (C),

153.67 (C), 151.31 (C), 150.52 (CH), 130.52 (CH), 129.64 (2 x CH), 129.02 (C), 128.29 (2 x CH), 119.82 (C), 78.41 (C), 75.15 (CH), 54.26 (CH_2), 54.10 (2 x CH_2), 26.33 (2 x CH_2), 23.16 (CH_2). **HRMS** (ES + ve), $C_{19}H_{20}N_5O$ $(M + H)^+$: Calculated 334.1668. Obtained 334.1646.

*9-(morpholin-4-yl)-8-phenyl-6-(prop-2-yn-1-yloxy)-9H-purine (**16b**).* The crude product was purified by flash chromatography on silica (25 → 66% EtOAc in hexane) to provide the tittle compound as a white solid (219.5 mg, 0.653 mmol, 55% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.54 (1H, s, CH), 8.29 – 8.20 (2H, m, 2 x CH), 7.56 – 7.44 (3H, m, 3 x CH), 5.26 (2H, d, *J* = 2.4 Hz, OCH_2), 4.38 (2H, t, CH_2), 3.06 (4H, t, 2 x CH_2), 3.06 (2H, t, CH_2), 2.50 (1H, t, *J* = 2.4 Hz, CH). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.36 (C), 153.45 (C), 151.23 (C), 150.86 (CH), 130.72 (CH), 129.60 (2 x CH), 128.80 (C), 128.43 (2 x CH), 119.82 (C), 78.34 (C), 75.23 (CH), 67.17 (2 x CH_2), 54.22 (CH_2), 53.49 (2 x CH_2). **HRMS** (ES + ve), $C_{18}H_{18}N_5O_2$ $(M + H)^+$: Calculated 336.1461. Obtained 336.1449.

*9-(4-methylpiperazin-1-yl)-8-phenyl-6-(prop-2-yn-1-yloxy)-9H-purine (**16c**).* The crude product was purified by flash chromatography on silica (0 → 10% MeOH in EtOAc) to provide the tittle compound as an off-white solid (291.9 mg, 0.836 mmol, 77% yield). **^{1}H NMR** (400 MHz, CDCl3): δ 8.50 (1H, s, CH), 8.31 – 8.22 (2H, m, 2 x CH), 7.52 – 7.43 (3H, m, 3 x CH), 5.25 (2H, d, J = 2.4 Hz, OCH2), 4.41 (2H, t, CH2), 3.08 (2H, t, CH2) 2.93 (4H, t, 2 x CH2), 2.48 (1H, t, J = 2.4 Hz, CH), 2.39 (3H, s, CH3). **^{13}C NMR** (101 MHz, CDCl3): δ 159.28 (C), 153.66 (C), 151.17 (C), 150.74 (CH), 130.57 (CH), 129.58 (2 x CH), 128.98 (C), 128.35 (2 x CH), 119.88 (C), 78.42 (C), 75.14 (CH), 55.18 (2 x CH2), 54.12 (CH2), 52.61 (2 x CH2), 45.89 (CH3). **HRMS** (ES + ve), $C_{19}H_{21}N_6O$ (M + H)+: Calculated 349.1777. Obtained 349.1776.

*9-isopropyl-8-phenyl-6-(prop-2-yn-1-yloxy)-9H-purine (**16d**).* The crude product was purified by flash chromatography on silica (15 → 20% EtOAc in hexane) to provide the tittle compound

as a yellow solid (80.1 mg, 0.273 mmol, 34% yield). **^{1}H NMR** (400 MHz, CDCl3): δ 8.56 (1H, s, CH), 7.71 – 7.62 (2H, m, 2 x CH), 7.57 – 7.48 (3H, m, 3 x CH), 5.24 (2H, d, J = 2.5 Hz, OCH2), 4.84 – 4.73 (1H, m, CH), 2.48 (1H, t, J = 2.4 Hz, CH), 1.73 (6H, d, J = 6.8 Hz, 2 x CH3). **^{13}C NMR** (101 MHz, CDCl3): δ 159.29 (C), 153.89 (C), 153.38 (C), 150.75 (CH), 130.40 (CH), 130.08 (C), 129.67 (2 x CH), 128.88 (2 x CH), 121.94 (C), 78.48 (C), 75.06 (CH), 54.03 (CH2), 50.04 (CH), 21.39 (2 x CH3). **HRMS** (ES + ve), $C_{17}H_{17}N_4O$ (M + H)+: Calculated 293.1402. Obtained 293.1388.

*9-(tert-butyl)-8-phenyl-6-(prop-2-yn-1-yloxy)-9H-purine (**16e**).* The crude product was purified by flash chromatography on silica (10% EtOAc in hexane) to provide the tittle compound as a yellow oil (80.4 mg, 0.262 mmol, 46% yield). **^{1}H NMR** (400 MHz, CDCl3): δ 8.57 (1H, s, CH), 7.53 – 7.37 (5H, m, 5 x CH), 5.20 (2H, d, J = 2.4 Hz, OCH2), 2.46 (1H, t, J = 2.5 Hz, CH), 1.66 (9H, s, 3 x CH3). **^{13}C NMR** (101 MHz, CDCl3): δ 159.39 (C), 154.57 (C), 153.69 (C), 150.19 (CH), 134.75 (C), 129.93 (2 x CH), 129.67 (CH), 127.98 (2 x CH), 121.59 (C), 78.45 (C), 75.04 (CH), 61.05 (C), 53.99 (CH2), 31.02 (3 x CH3). **HRMS** (ES + ve), $C_{18}H_{19}N_4O$ (M + H)+: Calculated 307.1559. Obtained 307.1579.

General procedure for the synthesis of compounds **7a**–**g**, **8a**–**g**, **9a**–**g**, **10a**–**g**, **11a**–**g**, **15a**–**e**, **17a**–**e**.

The corresponding alkyne (**4**, **5**, **6a**–**c**, **14a**–**e**, **16a**–**e**) (1 equiv.) was dissolved in a mixture of 1,4-dioxane and H_2O (9:1 v/v, 2 mL). Then the corresponding azide (0.5 M in methyl tert-butyl ether, MTBE, 1 equiv.), sodium ascorbate (0.1 equiv.), copper (I) iodide (0.25 equiv.) and triethylamine (0.4 equiv.) were added. The vial was sealed, evacuated, backfilled with argon and the mixture allowed to stir at room temperature for 18 h. The mixture was partitioned between DCM and H_2O. The layers were separated and the organic phase washed with saturated brine,

dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica. For the preparation of compounds **8a**, **8b**, **8d**–**g**, **15a**–**e**, **17a**–**e**, 0.2 equiv. of sodium ascorbate, 0.1 equiv. of copper (I) iodide and a mixture of MeCN/H_2O (9:1 v/v, 2 mL) as a solvent were used.

*6-{[1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-4-(2,2-dimethylhydrazinyl)-5-nitropyrimidine (**7a**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a white solid (23.4 mg, 0.06 mmol, 29% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.40 (1H, s, CH), 8.04 (1H, s, CH), 7.62 (2H, d, *J* = 9.0 Hz, 2 x CH), 7.01 (2H, d, *J* = 9.0 Hz, 2 x CH), 5.74 (2H, s, OCH_2), 5.29 (1H, s, NH), 3.86 (3H, s, CH_3), 2.69 (6H, s, 2 x CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.26 (C), 160.10 (C), 159.47 (CH), 156.09 (C), 143.42 (C), 130.48 (C), 122.47 (2 x CH), 122.05 (CH), 119.26 (C), 114.93 (2 x CH), 61.80 (CH_2), 55.78 (CH_3), 47.99 (2 x CH_3). **HRMS** (ES + ve), $C_{16}H_{19}N_8O_4$ (M + H)$^+$: Calculated 387.1529. Obtained 387.1518.

*6-{[1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-4-(2,2-dimethylhydrazinyl)-5-nitropyrimidine (**7b**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a yellow solid (13.9 mg, 0.036 mmol, 42% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.40 (1H, s, CH), 8.11 (1H, s, CH), 7.45 – 7.21 (3H, m, 3 x CH), 7.01 – 6.93 (1H, m, 1 x CH), 5.74 (2H, s, OCH_2), 3.87 (3H, s, CH_3), 2.69 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.26 (C), 163.34 (C), 160.74 (C), 159.45 (CH), 156.09 (C), 143.58 (C), 138.02 (C), 130.66 (CH), 121.98 (CH), 114.94 (CH), 112.66 (CH), 106.64 (CH), 61.70 (CH_2), 55.78 (CH_3), 47.98 (2 x CH_3). **HRMS** (ES + ve), $C_{16}H_{19}N_8O_4$ (M + H)$^+$: Calculated 387.1529. Obtained 387.1491.

*6-{[1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-4-(2,2-dimethylhydrazinyl)-5-nitropyrimidine (**7c**).* The crude product was purified by flash chromatography on silica (25 → 75% EtOAc in hexane) to provide the tittle compound as a light brown oil (5.5 mg, 0.014 mmol, 7% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.41 (1H, s, CH), 8.27 (1H, s, CH), 7.82 – 7.75 (1H, m, CH), 7.47 – 7.38 (1H, m, CH), 7.15 – 7.05 (2H, m, 2 x CH), 5.77 (2H, s, OCH_2), 4.67 (1H, bs, NH), 3.90 (3H, s, CH_3), 2.69 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.57 (C), 159.47 (CH), 157.42 (C), 156.14 (C), 151.27 (C), 142.22 (C), 130.38 (CH), 126.31 (C), 126.09 (CH), 125.65 (CH), 121.39 (CH), 112.41 (CH), 61.89 (CH_2), 56.15 (CH_3), 48.03 (2 x CH_3). **HRMS** (ES + ve), $C_{16}H_{19}N_8O_4$ $(M + H)^+$: Calculated 387.1529. Obtained 387.1522.

*6-({1-[2-(methoxycarbonyl)phenyl]-1H-1,2,3-triazol-4-yl}methoxy)-4-(2,2-dimethylhydrazinyl)-5-nitropyrimidine (**7d**).* The crude product was purified by flash chromatography on silica (25 → 85% EtOAc in hexane) to provide the tittle compound as an orange oil (13.9 mg, 0.033 mmol, 15% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.40 (1H, s, CH), 8.02 (1H, dd, *J* = 7.7, 1.7 Hz, CH), 7.99 (1H, s, CH), 7.68 (1H, td, *J* = 7.7, 1.7 Hz, CH), 7.61 (1H, td, *J* = 7.6, 1.4 Hz, CH), 7.51 (1H, dd, *J* = 7.8, 1.4 Hz, CH), 5.76 (2H, s, OCH_2), 3.70 (3H, s, CH_3), 3.14 (1H, s, NH), 2.69 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.27 (C), 165.60 (C), 163.43 (C), 159.39 (CH), 156.09 (C), 142.64 (C), 136.17 (C), 132.91 (CH), 131.48 (CH), 130.20 (CH), 127.63 (C), 127.05 (CH), 125.76 (CH), 61.76 (CH_2), 52.77 (CH_3), 47.99 (2 x CH_3). **HRMS** (ES + ve), $C_{17}H_{19}N_8O_5$ $(M + H)^+$: Calculated 415.1478. Obtained 415.1463.

*6-({1-[2-(methoxycarbonyl)thiophen-3-yl]-1H-1,2,3-triazol-4-yl}methoxy)-4-(2,2-dimethylhydrazinyl)-5-nitropyrimidine (**7e**).* The crude product was purified by flash chromatography on silica (25 → 85% EtOAc in hexane) to provide the tittle compound as a light yellow solid (13.4 mg, 0.032 mmol, 15% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.53 (1H, s,

CH), 8.41 (1H, s, CH), 7.62 (1H, d, *J* = 5.4 Hz, CH), 7.51 (1H, d, *J* = 5.4 Hz, CH), 5.76 (2H, s, OCH_2), 5.29 (1H, s, NH), 3.85 (3H, s, CH_3), 2.69 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 163.30 (C), 160.73 (C), 159.40 (CH), 156.12 (C), 141.99 (C), 138.26 (C), 131.22 (CH), 126.94 (CH), 126.76 (CH), 122.43 (C), 110.12 (C), 61.57 (CH_2), 52.77 (CH_3), 48.00 (2 x CH_3). **HRMS** (ES + ve), $C_{15}H_{17}N_8O_5S$ $(M + H)^+$: Calculated 421.1043. Obtained 421.1025.

*4-(2,2-dimethylhydrazinyl)-5-nitro-6-{[1-(thiazol-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}pyrimidine (**7f**).* The crude product was purified by flash chromatography on silica (0 → 10% MeOH in EtOAc) to provide the tittle compound as a yellow oil (45.8 mg, 0.121 mmol, 48% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.80 (1H, d, *J* = 2.0 Hz, CH), 8.35 (1H, s, CH), 7.87 (1H, s, CH), 7.31 (1H, d, *J* = 1.9 Hz, CH), 5.70 (2H, d, *J* = 0.7 Hz, CH_2), 5.64 (2H, s, OCH_2), 2.67 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 163.30 (C), 159.31 (CH), 156.08 (C), 154.20 (CH), 150.44 (C), 143.10 (C), 134.03 (C), 124.20 (CH), 118.04 (CH), 61.66 (CH_2), 49.75 (CH_2), 47.94 (2 x CH_3). **HRMS** (ES + ve), $C_{13}H_{16}N_9O_3S$ $(M + H)^+$: Calculated 378.1097. Obtained 378.1075.

*4-(2,2-dimethylhydrazinyl)-5-nitro-6-{[1-(pyridin-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}pyrimidine (**7g**).* The crude product was purified by flash chromatography on silica (0 → 20% MeOH in EtOAc) to provide the tittle compound as a yellow oil (47 mg, 0.126 mmol, 50% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.59 (2H, d, *J* = 6.0 Hz, 2 x CH), 8.34 (1H, s, CH), 7.71 (1H, s, CH), 7.10 (2H, d, *J* = 6.0 Hz, 2 x CH), 5.65 (2H, s, OCH_2), 5.55 (2H, s, CH_2), 2.66 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 163.20 (C), 159.26 (CH), 155.99 (C), 150.59 (2 x CH), 149.45 (C), 143.76 (C), 143.53 (C), 123.92 (CH), 122.20 (2 x CH), 61.65 (CH_2), 52.85 (CH_2), 47.90 (2 x CH_3). **HRMS** (ES + ve), $C_{15}H_{18}N_9O_3$ $(M + H)^+$: Calculated 372.1533. Obtained 372.1513.

*5-amino-6-{[1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-4-(2,2-dimethylhydrazinyl)-pyrimidine (**8a**).* The crude product was purified by flash chromatography on silica (100% EtOAc) to provide the tittle compound as a yellow oil (17.5 mg, 0.049 mmol, 12% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.02 (1H, s, CH), 7.89 (1H, s, CH), 7.60 (2H, d, *J* = 8.5 Hz, 2 x CH), 7.00 (2H, d, *J* = 8.5 Hz, 2 x CH), 5.62 (2H, s, OCH_2), 4.31 (2H, bs, NH_2), 3.85 (3H, s, CH_3), 2.57 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.03 (C), 156.80 (C), 149.54 (C), 144.97 (CH), 144.32 (C), 130.54 (C), 122.44 (CH), 122.42 (2 x CH), 114.90 (2 x CH), 114.18 (C), 59.50 (CH_2), 55.76 (CH_3), 48.58 (2 x CH_3). **HRMS** (ES + ve), $C_{16}H_{21}N_8O_2$ $(M + H)^+$: Calculated 357.1787. Obtained 357.1753.

*5-amino-6-{[1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-4-(2,2-dimethylhydrazinyl)-pyrimidine (**8b**).* The crude product was purified by flash chromatography on silica (100% EtOAc) to provide the tittle compound as a yellow solid (71.9 mg, 0.201 mmol, 79% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.09 (1H, s, CH), 7.88 (1H, s, CH), 7.40 – 7.18 (3H, m, 3 x CH), 6.96 – 6.90 (1H, m, CH), 5.94 (1H, bs, NH), 5.61 (2H, s, OCH_2), 4.99 (2H, bs, NH_2), 3.84 (3H, s, CH_3), 2.56 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.62 (C), 156.43 (C), 149.24 (C), 144.35 (CH), 144.23 (C), 137.96 (C), 130.58 (CH), 122.33 (CH), 114.73 (CH), 113.88 (C), 112.53 (CH), 106.53 (CH), 59.45 (CH_2), 55.70 (CH_3), 48.39 (2 x CH_3). **HRMS** (ES + ve), $C_{16}H_{21}N_8O_2$ $(M + H)^+$: Calculated 357.1787. Obtained 357.1789.

*5-amino-4-(2,2-dimethylhydrazinyl)-6-{[1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}pyrimidine (**8c**).* The crude product was purified by flash chromatography on silica (0 → 2% MeOH in EtOAc) to provide the tittle compound as a yellow oil (12.44 mg, 0.038 mmol, 15% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.23 (1H, s, CH), 7.90 (1H, s, CH), 7.81 – 7.74 (1H, m, CH), 7.47 – 7.38 (1H, m, CH), 7.14 – 7.05 (2H, m, 2 x CH), 5.64 (2H, s, OCH_2),

3.88 (3H, s, CH_3), 2.59 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 155.90 (C), 155.01 (C), 151.22 (C), 146.97 (C), 142.60 (CH), 130.42 (CH), 126.46 (C), 126.37 (CH), 126.22 (C), 125.60 (CH), 121.38 (CH), 112.41 (CH), 60.17 (CH_2), 56.17 (CH_3), 48.35 (2 x CH_3). **HRMS** (ES + ve), $C_{16}H_{21}N_8O_2$ $(M + H)^+$: Calculated 357.1787. Obtained 357.1803.

*5-amino-6-({1-[2-(methoxycarbonyl)phenyl]-1H-1,2,3-triazol-4-yl}methoxy)-4-(2,2-dimethylhydrazinyl)-pyrimidine (**8d**).* The crude product was purified by flash chromatography on silica (100% EtOAc) to provide the tittle compound as a yellow oil (27.6 mg, 0.072 mmol, 24% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.99 (1H, dd, *J* = 7.8, 1.6 Hz, CH), 7.95 (1H, s, CH), 7.87 (1H, s, CH), 7.66 (1H, td, *J* = 7.7, 1.6 Hz, CH), 7.59 (1H, td, *J* = 7.6, 1.3 Hz, CH), 7.48 (1H, dd, *J* = 7.8, 1.3 Hz, CH), 5.65 (2H, s, OCH_2), 5.59 (1H, bs, NH), 4.19 (2H, bs, NH_2), 3.65 (3H, s, CH_3), 2.57 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.64 (C), 156.78 (C), 149.51 (C), 144.95 (CH), 143.63 (C), 136.19 (C), 132.86 (CH), 131.40 (CH), 130.08 (CH), 127.57 (C), 126.95 (CH), 125.99 (CH), 114.19 (C), 59.49 (CH_2), 52.64 (CH_3), 48.56 (2 x CH_3). **HRMS** (ES + ve), $C_{17}H_{21}N_8O_3$ $(M + H)^+$: Calculated 385.1737. Obtained 385.1703.

*5-amino-6-({1-[2-(methoxycarbonyl)thiophen-3-yl]-1H-1,2,3-triazol-4-yl}methoxy)-4-(2,2-dimethylhydrazinyl)-pyrimidine (**8e**).* The crude product was purified by flash chromatography on silica (100% EtOAc) to provide the tittle compound as a yellow oil (87.5 mg, 0.224 mmol, 59% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.48 (1H, s, CH), 7.90 (1H, s, CH), 7.60 (1H, d, *J* = 5.2 Hz, CH), 7.49 (1H, d, *J* = 5.2 Hz, CH), 6.02 (1H, bs, NH), 5.63 (2H, s, OCH_2), 4.59 (2H, bs, NH_2), 3.80 (3H, s, CH_3), 2.58 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.61 (C), 156.78 (C), 149.64 (C), 145.27 (CH), 142.95 (C), 138.26 (C), 131.13 (CH), 126.89 (CH), 126.63 (CH), 122.19 (C), 114.06 (C), 60.42 (CH_2), 52.63 (CH_3), 48.50 (2 x CH_3). **HRMS** (ES + ve), $C_{15}H_{19}N_8O_3S$ $(M + H)^+$: Calculated 391.1301. Obtained 391.1283.

*5-amino-4-(2,2-dimethylhydrazinyl)-6-{[1-(thiazol-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}pyrimidine (**8f**).* The crude product was purified by flash chromatography on silica (0 → 4% MeOH in EtOAc) to provide the tittle compound as a yellow oil (83.8 mg, 0.241 mmol, 62% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.78 (1H, d, *J* = 2.0 Hz, CH), 7.82 (1H, s, CH), 7.81 (1H, s, CH), 7.29 (1H, d, *J* = 2.0 Hz, CH), 5.67 (2H, s, OCH_2), 5.62 (1H, bs, NH), 5.50 (2H, s, CH_2), 4.76 (2H, bs, NH_2), 2.52 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.79 (C), 154.16 (CH), 150.47 (C), 149.69 (C), 145.17 (CH), 144.09 (C), 124.33 (CH), 117.99 (CH), 114.01 (C), 59.43 (CH_2), 49.62 (CH_2), 48.45 (2 x CH_3). **HRMS** (ES + ve), $C_{13}H_{18}N_9OS$ $(M + H)^+$: Calculated 348.1355. Obtained 348.1352.

*5-amino-4-(2,2-dimethylhydrazinyl)-6-{[1-(pyridin-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}pyrimidine (**8g**).* The crude product was purified by flash chromatography on silica (0 → 10% MeOH in EtOAc) to provide the tittle compound as a yellow solid (57.4 mg, 0.168 mmol, 57% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.57 (2H, d, *J* = 6.0 Hz, 2 x CH), 7.80 (1H, s, CH), 7.66 (1H, s, CH), 7.07 (2H, d, *J* = 6.0 Hz, 2 x CH), 5.53 (2H, s, OCH_2), 5.52 (2H, s, CH_2), 5.37 (1H, bs, NH), 4.36 (2H, bs, NH_2), 2.53 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.80 (C), 150.59 (2 x CH), 149.90 (C), 145.47 (CH), 144.77 (C), 143.56 (C), 124.28 (CH), 122.19 (2 x CH), 114.09 (C), 59.31 (CH_2), 52.77 (CH_2), 48.54 (2 x CH_3). **HRMS** (ES + ve), $C_{15}H_{20}N_9O$ $(M + H)^+$: Calculated 342.1791. Obtained 342.1787.

*6-{[1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-9-(dimethylamino)-9H-purine (**9a**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a white solid (20.5 mg, 0.056 mmol, 41% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.56 (1H, s, CH), 8.08 (1H, s, CH), 7.99 (1H, s, CH), 7.60 (2H, d, *J* = 8.9 Hz, 2 x CH), 7.00 (2H, d, *J* = 8.9 Hz, 2 x CH), 5.85 (2H, s, OCH_2), 3.85 (3H, s, CH_3), 3.15

(6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.39 (C), 160.02 (C), 151.52 (CH), 151.30 (C), 143.89 (C), 142.12 (CH), 130.58 (C), 122.47 (2 x CH), 122.31 (CH), 120.68 (C), 114.90 (2 x CH), 60.39 (CH_2), 55.75 (CH_3), 47.02 (2 x CH_3). **HRMS** (ES + ve), $C_{17}H_{19}N_8O_2$ $(M + H)^+$: Calculated 367.1631. Obtained 367.1605.

*6-{[1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-9-(dimethylamino)-9H-purine (**9b**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a white solid (29.9 mg, 0.081 mmol, 60% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.56 (1H, s, CH), 8.16 (1H, s, CH), 7.99 (1H, s, CH), 7.42 – 7.21 (3H, m, 3 x CH), 6.99 – 6.92 (1H, m, CH), 5.86 (2H, s, OCH_2), 3.86 (3H, s, CH_3), 3.15 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.71 (C), 160.34 (C), 151.50 (CH), 151.31 (C), 144.07 (C), 142.14 (CH), 138.12 (C), 130.62 (CH), 122.19 (CH), 120.66 (C), 114.90 (CH), 112.66 (CH), 106.55 (CH), 60.32 (CH_2), 55.76 (CH_3), 47.01 (2 x CH_3). **HRMS** (ES + ve), $C_{17}H_{19}N_8O_2$ $(M + H)^+$: Calculated 367.1631. Obtained 367.1620.

*6-{[1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-9-(dimethylamino)-9H-purine (**9c**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a yellow solid (35.7 mg, 0.097 mmol, 72% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.56 (1H, s, CH), 8.27 (1H, s, CH), 7.98 (1H, s, CH), 7.73 (1H, dd, J = 7.9, 1.7 Hz, CH), 7.43 – 7.36 (1H, m, CH), 7.12 – 7.03 (2H, m, 2 x CH), 5.86 (2H, s, OCH_2), 3.86 (3H, s, CH_3), 3.14 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.47 (C), 151.49 (CH), 151.32 (C), 151.23 (C), 142.58 (C), 141.98 (CH), 130.29 (CH), 126.34 (C), 126.27 (CH), 125.71 (CH), 121.29 (CH), 120.65 (C), 112.33 (CH), 60.33 (CH_2), 56.07 (CH_3), 47.00 (2 x CH_3). **HRMS** (ES + ve), $C_{17}H_{19}N_8O_2$ $(M + H)^+$: Calculated 367.1631. Obtained 367.1606.

*6-({1-[2-(methoxycarbonyl)phenyl]-1H-1,2,3-triazol-4-yl}methoxy)9-(dimethylamino)-9H-purine (**9d**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a yellow solid (22.6 mg, 0.057 mmol, 41% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.56 (1H, s, CH), 8.02 (1H, s, CH), 8.01 – 7.96 (2H, m, 2 x CH), 7.65 (1H, td, *J* = 7.7, 1.6 Hz, CH), 7.58 (1H, td, *J* = 7.6, 1.3 Hz, CH), 7.47 (1H, dd, *J* = 7.9, 1.3 Hz, CH), 5.88 (2H, s, OCH_2), 3.66 (3H, s, CH_3), 3.15 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.68 (C), 160.40 (C), 151.51 (CH), 151.29 (C), 143.20 (C), 142.09 (CH), 136.22 (C), 132.84 (CH), 131.39 (CH), 130.06 (CH), 127.66 (C), 126.90 (CH), 125.85 (CH), 120.66 (C), 60.30 (CH_2), 52.69 (CH_3), 47.01 (2 x CH_3). **HRMS** (ES + ve), $C_{18}H_{19}N_8O_3$ $(M + H)^+$: Calculated 395.1580. Obtained 395.1610.

*6-({1-[2-(methoxycarbonyl)thiophen-3-yl]-1H-1,2,3-triazol-4-yl}methoxy)-9-(dimethylamino)-9H-purine (**9e**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a light yellow solid (39.5 mg, 0.098 mmol, 71% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.55 (1H, s, CH), 8.54 (1H, s, CH), 7.97 (1H, s, CH), 7.59 (1H, d, *J* = 5.4 Hz, CH), 7.47 (1H, d, *J* = 5.4 Hz, CH), 5.85 (2H, s, OCH_2), 3.80 (3H, s, CH_3), 3.13 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.67 (C), 160.35 (C), 151.47 (CH), 151.23 (C), 142.46 (C), 141.99 (CH), 138.34 (C), 131.14 (CH), 127.02 (CH), 126.73 (CH), 122.30 (C), 120.62 (C), 60.04 (CH_2), 52.65 (CH_3), 46.98 (2 x CH_3). **HRMS** (ES + ve), $C_{16}H_{17}N_8O_3S$ $(M + H)^+$: Calculated 401.1144. Obtained 401.1111.

*9-(dimethylamino)-6-{[1-(thiazol-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine (**9f**).* The crude product was purified by flash chromatography on silica (0 → 20% MeOH in EtOAc) to provide the tittle compound as a white solid (14.9 mg, 0.042 mmol, 42% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.81 (1H, d, *J* = 2.0 Hz, CH), 8.54 (1H, s, CH), 7.97 (1H, s, CH), 7.91 (1H, s,

CH), 7.31 (1H, d, *J* = 2.0 Hz, CH), 5.77 (2H, s, OCH_2), 5.70 (2H, s, CH_2), 3.15 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.40 (C), 154.15 (CH), 151.52 (CH), 151.27 (C), 150.60 (C), 143.69 (C), 142.05 (CH), 124.32 (CH), 120.63 (C), 118.07 (CH), 60.35 (CH_2), 49.76 (CH_2), 47.03 (2 x CH_3). **HRMS** (ES + ve), $C_{14}H_{16}N_9OS$ $(M + H)^+$: Calculated 358.1199. Obtained 358.1174.

*9-(dimethylamino)-6-{[1-(pyridin-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine (**9g**).* The crude product was purified by flash chromatography on silica (0 → 20% MeOH in EtOAc) to provide the tittle compound as a white solid (26.1 mg, 0.074 mmol, 74% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.60 (2H, d, *J* = 6.0 Hz, 2 x CH), 8.53 (1H, s, CH), 7.98 (1H, s, CH), 7.74 (1H, s, CH), 7.11 (2H, d, *J* = 6.0 Hz, 2 x CH), 5.78 (2H, s, OCH_2), 5.54 (2H, s, CH_2), 3.14 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.29 (C), 151.48 (CH), 151.29 (C), 150.72 (2 x CH), 144.31 (C), 143.49 (C), 142.16 (CH), 124.08 (CH), 122.29 (2 x CH), 120.59 (C), 60.30 (CH_2), 52.89 (CH_2), 47.02 (2 x CH_3). **HRMS** (ES + ve), $C_{16}H_{18}N_9O$ $(M + H)^+$: Calculated 352.1634. Obtained 352.1623.

*6-{[1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-8-methyl-9-(dimethylamino)-9H-purine (**10a**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a white solid (11.2 mg, 0.029 mmol, 22% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.49 (1H, s, CH), 8.07 (1H, s, CH), 7.60 (2H, d, *J* = 8.8 Hz, 2 x CH), 7.00 (2H, d, *J* = 8.8 Hz, 2 x CH), 5.83 (2H, s, OCH_2), 3.85 (3H, s, CH_3), 3.14 (6H, s, 2 x CH_3), 2.55 (3H, s, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.00 (C), 159.22 (C), 152.68 (C), 152.45 (C), 150.29 (CH), 144.05 (C), 130.63 (C), 122.49 (2 x CH), 122.30 (CH), 119.23 (C), 114.90 (2 x CH), 60.18 (CH_2), 55.75 (CH_3), 45.78 (2 x CH_3), 13.60 (CH_3). **HRMS** (ES + ve), $C_{18}H_{21}N_8O_2$ $(M + H)^+$: Calculated 381.1787. Obtained 381.1763.

*6-{[1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-8-methyl-9-(dimethylamino)-9H-purine (**10b**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a yellow solid (34.5 mg, 0.09 mmol, 68% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.48 (1H, s, CH), 8.14 (1H, s, CH), 7.41 – 7.19 (3H, m, 3 x CH), 6.98 – 6.92 (1H, m, CH), 5.82 (2H, s, OCH_2), 3.86 (3H, s, CH_3), 3.13 (6H, s, 2 x CH_3), 2.55 (3H, s, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.70 (C), 159.15 (C), 152.69 (C), 152.44 (C), 150.26 (CH), 144.22 (C), 138.14 (C), 130.61 (CH), 122.15 (CH), 119.19 (C), 114.88 (CH), 112.66 (CH), 106.51 (CH), 60.10 (CH_2), 55.75 (CH_3), 45.76 (2 x CH_3), 13.58 (CH_3). **HRMS** (ES + ve), $C_{18}H_{21}N_8O_2$ $(M + H)^+$: Calculated 381.1787. Obtained 381.1769.

*6-{[1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-8-methyl-9-(dimethylamino)-9H-purine (**10c**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a yellow oil (31 mg, 0.081 mmol, 62% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.48 (1H, s, CH), 8.25 (1H, s, CH), 7.72 (1H, dd, J = 7.9, 1.7 Hz, CH), 7.43 – 7.36 (1H, m, CH), 7.10 – 7.02 (2H, m, 2 x CH), 5.83 (2H, s, OCH_2), 3.86 (3H, s, CH_3), 3.13 (6H, s, 2 x CH_3), 2.54 (3H, s, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.31 (C), 152.52 (C), 152.37 (C), 151.34 (C), 150.24 (CH), 142.73 (C), 130.25 (CH), 126.38 (C), 126.23 (CH), 125.73 (CH), 121.27 (CH), 119.20 (C), 112.31 (CH), 60.11 (CH_2), 56.04 (CH_3), 45.74 (2 x CH_3), 13.55 (CH_3). **HRMS** (ES + ve), $C_{18}H_{21}N_8O_2$ $(M + H)^+$: Calculated 381.1787. Obtained 381.1772.

*6-({1-[2-(methoxycarbonyl)phenyl]-1H-1,2,3-triazol-4-yl}methoxy)-8-methyl-9-(dimethylamino)-9H-purine (**10d**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as an off-white solid (11.3 mg, 0.027 mmol, 30% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.48 (1H, s, CH), 8.01 (1H, s, CH),

7.99 (1H, dd, *J* = 7.8, 1.6 Hz, CH), 7.66 (1H, td, *J* = 7.7, 1.6 Hz, CH), 7.58 (1H, td, *J* = 7.7, 1.3 Hz, CH), 7.47 (1H, dd, *J* = 7.9, 1.3 Hz, CH), 5.86 (2H, s, OCH_2), 3.66 (3H, s, CH_3), 3.14 (6H, s, 2 x CH_3), 2.55 (3H, s, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.74 (C), 159.25 (C), 152.65 (C), 152.46 (C), 150.29 (CH), 143.40 (C), 136.26 (C), 132.83 (CH), 131.39 (CH), 130.03 (CH), 127.70 (C), 126.89 (CH), 125.77 (CH), 119.23 (C), 60.11 (CH_2), 52.69 (CH_3), 45.78 (2 x CH_3), 13.60 (CH_3). **HRMS** (ES + ve), $C_{19}H_{21}N_8O_3$ $(M + H)^+$: Calculated 409.1737. Obtained 409.1714.

*6-({1-[2-(methoxycarbonyl)thiophen-3-yl]-1H-1,2,3-triazol-4-yl}methoxy)-8-methyl-9-(dimethylamino)-9H-purine (**10e**).* The crude product was purified by flash chromatography on silica (25 → 90% EtOAc in hexane) to provide the tittle compound as a light yellow solid (28.6 mg, 0.069 mmol, 73% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.52 (1H, s, CH), 8.48 (1H, s, CH), 7.60 (1H, d, *J* = 5.4 Hz, CH), 7.47 (1H, d, *J* = 5.4 Hz, CH), 5.83 (2H, s, OCH_2), 3.80 (3H, s, CH_3), 3.13 (6H, s, 2 x CH_3), 2.54 (3H, s, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.70 (C), 159.23 (C), 152.56 (C), 152.41 (C), 150.27 (CH), 142.66 (C), 138.40 (C), 131.11 (CH), 126.99 (CH), 126.79 (CH), 122.37 (C), 119.21 (C), 59.85 (CH_2), 52.66 (CH_3), 45.75 (2 x CH_3), 13.57 (CH_3). **HRMS** (ES + ve), $C_{17}H_{19}N_8O_3S$ $(M + H)^+$: Calculated 415.1301. Obtained 415.1299.

*8-methyl-9-(dimethylamino)-6-{[1-(thiazol-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine (**10f**).* The crude product was purified by flash chromatography on silica (0 → 10% MeOH in EtOAc) to provide the tittle compound as a yellow solid (27.5 mg, 0.074 mmol, 74% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.80 (1H, d, *J* = 2.0 Hz, CH), 8.44 (1H, s, CH), 7.90 (1H, s, CH), 7.30 (1H, d, *J* = 2.0 Hz, CH), 5.72 (2H, s, OCH_2), 5.69 (2H, s, CH_2), 3.12 (6H, s, 2 x CH_3), 2.53 (3H, s, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.13 (C), 154.23 (CH), 152.61 (C), 152.30 (C), 150.51 (C), 150.28 (CH), 143.72 (C), 124.34 (CH), 119.04 (C), 118.12 (CH), 60.07

(CH_2), 49.69 (CH_2), 45.74 (2 x CH_3), 13.57 (CH_3). **HRMS** (ES + ve), $C_{15}H_{18}N_9OS$ $(M + H)^+$: Calculated 372.1355. Obtained 372.1373.

*8-methyl-9-(dimethylamino)-6-{[1-(pyridin-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine (**10g**).* The crude product was purified by flash chromatography on silica (0 → 20% MeOH in EtOAc) to provide the tittle compound as a white solid (23.1 mg, 0.063 mmol, 63% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.59 (2H, d, *J* = 5.1 Hz, 2 x CH), 8.43 (1H, s, CH), 7.72 (1H, s, CH), 7.09 (2H, d, *J* = 5.1 Hz, 2 x CH), 5.74 (2H, s, OCH_2), 5.52 (2H, s, CH_2), 3.12 (6H, s, 2 x CH_3), 2.53 (3H, s, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.08 (C), 152.70 (C), 152.41 (C), 150.68 (2 x CH), 150.21 (CH), 144.41 (C), 143.49 (C), 124.07 (CH), 122.30 (2 x CH), 119.10 (C), 60.05 (CH_2), 52.83 (CH_2), 45.74 (2 x CH_3), 13.56 (CH_3). **HRMS** (ES + ve), $C_{17}H_{20}N_9O$ $(M + H)^+$: Calculated 366.1791. Obtained 366.1771.

*6-{[1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-9-(dimethylamino)-8-phenyl-9H-purine (**11a**).* The crude product was purified by flash chromatography on silica (50% EtOAc in hexane) to provide the tittle compound as a white solid (13.6 mg, 0.031 mmol, 43% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.55 (1H, s, 1H), 8.25 – 8.17 (2H, m, 2 x CH), 8.10 (1H, s, CH), 7.61 (2H, d, *J* = 8.8 Hz, 2 x CH), 7.52 – 7.42 (3H, m, 3 x CH), 7.00 (2H, d, *J* = 8.8 Hz, 2 x CH), 5.90 (2H, s, OCH_2), 3.85 (3H, s, CH_3), 3.23 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.02 (C), 159.96 (C), 153.40 (C), 151.28 (C), 150.70 (CH), 144.03 (C), 130.63 (C), 130.53 (CH), 129.54 (2 x CH), 129.07 (C), 128.38 (2 x CH), 122.49 (2 x CH), 122.44 (CH), 120.02 (C), 114.90 (2 x CH), 60.28 (CH_2), 55.76 (CH_3), 45.56 (2 x CH_3). **HRMS** (ES + ve), $C_{23}H_{23}N_8O_2$ $(M + H)^+$: Calculated 443.1944. Obtained 443.1907.

*6-{[1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-9-(dimethylamino)-8-phenyl-9H-purine (**11b**).* The crude product was purified by flash chromatography on silica (25 → 66%

EtOAc in hexane) to provide the tittle compound as a white solid (23.6 mg, 0.053 mmol, 63% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.56 (1H, s, CH), 8.25 – 8.19 (2H, m, 2 x CH), 8.18 (1H, s, CH), 7.51 – 7.43 (3H, m, 3 x CH), 7.43 – 7.22 (3H, m, 3 x CH), 7.00 – 6.93 (1H, m, CH), 5.90 (2H, s, OCH_2), 3.87 (3H, s, CH_3), 3.24 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.73 (C), 159.92 (C), 153.41 (C), 151.32 (C), 150.70 (CH), 144.23 (C), 138.17 (C), 130.64 (CH), 130.54 (CH), 129.54 (2 x CH), 129.05 (C), 128.39 (2 x CH), 122.32 (CH), 120.01 (C), 114.91 (CH), 112.70 (CH), 106.58 (CH), 60.23 (CH_2), 55.78 (CH_3), 45.56 (2 x CH_3). **HRMS** (ES + ve), $C_{23}H_{23}N_8O_2$ $(M + H)^+$: Calculated 443.1944. Obtained 443.1902.

*6-{[1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-9-(dimethylamino)-8-phenyl-9H-purine (**11c**).* The crude product was purified by flash chromatography on silica (25 → 66% EtOAc in hexane) to provide the tittle compound as a white solid (18.5 mg, 0.042 mmol, 48% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.55 (1H, s, CH), 8.29 (1H, s, CH), 8.25 – 8.17 (2H, m, 2 x CH), 7.75 (1H, dd, *J* = 7.9, 1.7 Hz, CH), 7.50 – 7.43 (3H, m, 3 x CH), 7.43 – 7.38 (1H, m, CH), 7.12 – 7.04 (2H, m, 2 x CH), 5.91 (2H, s, OCH_2), 3.87 (3H, s, CH_3), 3.23 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.10 (C), 153.36 (C), 151.36 (C), 151.16 (C), 150.69 (CH), 142.76 (C), 130.48 (CH), 130.27 (CH), 129.53 (2 x CH), 129.11 (C), 128.36 (2 x CH), 126.43 (C), 126.40 (CH), 125.76 (CH), 121.33 (CH), 120.04 (C), 112.35 (CH), 60.27 (CH_2), 56.08 (CH_3), 45.54 (2 x CH_3). **HRMS** (ES + ve), $C_{23}H_{23}N_8O_2$ $(M + H)^+$: Calculated 443.1944. Obtained 443.1907.

*6-({1-[2-(methoxycarbonyl)phenyl]-1H-1,2,3-triazol-4-yl}methoxy)-9-(dimethylamino)-8-phenyl-9H-purine (**11d**).* The crude product was purified by flash chromatography on silica (33 → 60% EtOAc in hexane) to provide the tittle compound as a white oil (17.7 mg, 0.037 mmol, 43% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.54 (1H, s, CH), 8.25 – 8.17 (2H, m, 2 x CH), 8.04

(1H, s, CH), 7.99 (1H, dd, *J* = 7.8, 1.6 Hz, CH), 7.65 (1H, td, *J* = 7.7, 1.6 Hz, CH), 7.58 (1H, td, *J* = 7.6, 1.3 Hz, CH), 7.52 – 7.43 (4H, m, 4 x CH), 5.92 (2H, s, OCH_2), 3.67 (3H, s, CH_3), 3.23 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.74 (C), 159.96 (C), 153.38 (C), 151.23 (C), 150.69 (CH), 143.35 (C), 136.23 (C), 132.83 (CH), 131.38 (CH), 130.52 (CH), 130.03 (CH), 129.50 (2 x CH), 129.05 (C), 128.38 (2 x CH), 127.68 (C), 126.90 (CH), 125.93 (CH), 120.00 (C), 60.21 (CH_2), 52.70 (CH_3), 45.54 (2 x CH_3). **HRMS** (ES + ve), $C_{24}H_{23}N_8O_3$ $(M + H)^+$: Calculated 471.1893. Obtained 471.1881.

*6-({1-[2-(methoxycarbonyl)thiophen-3-yl]-1H-1,2,3-triazol-4-yl}methoxy)-9-(dimethylamino)-8-phenyl-9H-purine (**11e**).* The crude product was purified by flash chromatography on silica (50% EtOAc in hexane) to provide the tittle compound as a white solid (16.9 mg, 0.035 mmol, 51% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.56 (1H, s, CH), 8.55 (1H, s, CH), 8.25 – 8.18 (2H, m, 2 x CH), 7.60 (1H, d, *J* = 5.4 Hz, CH), 7.49 (1H, d, *J* = 5.4 Hz, CH), 7.48 – 7.44 (3H, m, 3 x CH), 5.91 (2H, s, OCH_2), 3.82 (3H, s, CH_3), 3.23 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.74 (C), 159.99 (C), 153.37 (C), 151.16 (C), 150.70 (CH), 142.66 (C), 138.42 (C), 131.13 (CH), 130.48 (CH), 129.53 (2 x CH), 129.11 (C), 128.36 (2 x CH), 127.15 (CH), 126.82 (CH), 122.38 (C), 120.03 (C), 60.00 (CH_2), 52.69 (CH_3), 45.54 (2 x CH_3). **HRMS** (ES + ve), $C_{22}H_{21}N_8O_3S$ $(M + H)^+$: Calculated 477.1457. Obtained 477.1432.

*9-(dimethylamino)-8-phenyl-6-{[1-(thiazol-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine (**11f**).* The crude product was purified by flash chromatography on silica (0 → 2.5% MeOH in EtOAc) to provide the tittle compound as a light yellow solid (25.9 mg, 0.06 mmol, 68% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.79 (1H, d, *J* = 2.0 Hz, CH), 8.52 (1H, s, CH), 8.23 – 8.16 (2H, m, 2 x CH), 7.91 (1H, s, CH), 7.51 – 7.42 (3H, m, 3 x CH), 7.31 (1H, d, *J* = 2.0 Hz, CH), 5.80 (2H, s, OCH_2), 5.70 (2H, s, CH_2), 3.22 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz,

$CDCl_3$): δ 159.95 (C), 154.11 (CH), 153.33 (C), 151.17 (C), 150.67 (CH), 150.61 (C), 143.78 (C), 130.48 (CH), 129.50 (2 x CH), 129.06 (C), 128.35 (2 x CH), 124.42 (CH), 119.95 (C), 118.06 (CH), 60.22 (CH_2), 49.72 (CH_2), 45.53 (2 x CH_3). **HRMS** (ES + ve), $C_{20}H_{20}N_9OS$ $(M + H)^+$: Calculated 434.1512. Obtained 434.1515.

*9-(dimethylamino)-8-phenyl-6-{[1-(pyridin-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine (**11g**).* The crude product was purified by flash chromatography on silica (0 → 5% MeOH in EtOAc) to provide the tittle compound as a white solid (23.8 mg, 0.055 mmol, 65% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.59 (2H, d, *J* = 6.0 Hz, 2 x CH), 8.51 (1H, s, CH), 8.21 – 8.14 (2H, m, 2 x CH), 7.76 (1H, s, CH), 7.51 – 7.41 (3H, m, 3 x CH), 7.11 (2H, d, *J* = 6.0 Hz, 2 x CH), 5.82 (2H, s, CH_2), 5.54 (2H, s, CH_2), 3.22 (6H, s, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.85 (C), 153.38 (C), 151.32 (C), 150.66 (2 x CH), 150.64 (CH), 144.40 (C), 143.57 (C), 130.57 (CH), 129.49 (2 x CH), 128.99 (C), 128.40 (2 x CH), 124.25 (CH), 122.32 (2 x CH), 119.92 (C), 60.18 (CH_2), 52.86 (CH_2), 45.55 (2 x CH_3). **HRMS** (ES + ve), $C_{22}H_{22}N_9O$ $(M + H)^+$: Calculated 428.1947. Obtained 428.1951.

*6-{[1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-9-(piperidin-1-yl)-9H-purine (**15a**).* The crude product was purified by flash chromatography on silica (60% EtOAc in hexane) to provide the tittle compound as a white solid (82.6 mg, 0.203 mmol, 82% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.57 (1H, s, CH), 8.17 (1H, s, CH), 8.02 (1H, s, CH), 7.42 – 7.21 (3H, m, 3 x CH), 6.98 – 6.93 (1H, m, CH), 5.86 (2H, s, OCH_2), 3.86 (3H, s, CH_3), 3.46 (4H, t, *J* = 5.4 Hz, 2 x CH_2), 1.85 – 1.77 (4H, m, 2 x CH_2), 1.64 – 1.55 (2H, m, CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.74 (C), 160.33 (C), 151.46 (CH), 151.40 (C), 144.12 (C), 142.39 (CH), 138.15 (C), 130.63 (CH), 122.17 (CH), 120.58 (C), 114.94 (CH), 112.68 (CH), 106.54 (CH), 60.35 (CH_2), 56.07 (2

x CH_2), 55.77 (CH_3), 26.19 (2 x CH_2), 23.15 (CH_2). **HRMS** (ES + ve), $C_{20}H_{23}N_8O_2$ $(M + H)^+$: Calculated 407.1944. Obtained 407.1979.

*6-{[1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-9-(morpholin-4-yl)-9H-purine (**15b**).* The crude product was purified by flash chromatography on silica (100% EtOAc) to provide the tittle compound as a white solid (61.8 mg, 0.151 mmol, 53% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.58 (1H, s, CH), 8.16 (1H, s, CH), 8.03 (1H, s, CH), 7.43 – 7.19 (3H, m, 3 x CH), 6.96 (1H, m, CH), 5.87 (2H, s, OCH_2), 3.91 (4H, t, J = 4.7 Hz, 2 x CH_2), 3.87 (3H, s, CH_3), 3.57 (4H, t, 2 x CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.75 (C), 160.43 (C), 151.71 (CH), 151.35 (C), 144.01 (C), 142.08 (CH), 138.13 (C), 130.65 (CH), 122.23 (CH), 120.65 (C), 114.94 (CH), 112.68 (CH), 106.59 (CH), 67.00 (2 x CH_2), 60.38 (CH_2), 55.79 (CH_3), 55.03 (2 x CH_2). **HRMS** (ES + ve), $C_{19}H_{21}N_8O_3$ $(M + H)^+$: Calculated 409.1737. Obtained 409.1741.

*6-{[1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-9-(4-methylpiperazin-1-yl)-9H-purine (**15c**).* The crude product was purified by flash chromatography on silica (30% MeOH in EtOAc in hexane) to provide the tittle compound as a white solid (75 mg, 0.178 mmol, 68% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.56 (1H, s, CH), 8.16 (1H, s, CH), 8.04 (1H, s, CH), 7.42 – 7.19 (3H, m, 3 x CH), 6.98 – 6.93 (1H, m, CH), 5.86 (2H, s, OCH_2), 3.87 (3H, s, CH_3), 3.54 (4H, t, 2 x CH_2), 2.68 (4H, t, 2 x CH_2), 2.39 (3H, s, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.73 (C), 160.35 (C), 151.73 (CH), 151.40 (C), 144.08 (C), 141.80 (CH), 138.14 (C), 130.64 (CH), 122.21 (CH), 120.50 (C), 114.93 (CH), 112.68 (CH), 106.56 (CH), 60.34 (CH_2), 55.78 (CH_3), 54.93 (2 x CH_2), 54.47 (2 x CH_2), 45.80 (CH_3). **HRMS** (ES + ve), $C_{20}H_{24}N_9O_2$ $(M + H)^+$: Calculated 422.2053. Obtained 422.2047.

*9-isopropyl-6-{[1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine (**15d**).* The crude product was purified by flash chromatography on silica (100% EtOAc) to provide the tittle

compound as a yellow oil (91.6 mg, 0.25 mmol, 75% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.56 (1H, s, CH), 8.17 (1H, s, CH), 8.02 (1H, s, CH), 7.39 – 7.17 (3H, m, 3 x CH), 6.96 – 6.90 (1H, m, CH), 5.85 (2H, s, OCH_2), 4.93 – 4.83 (1H, m, CH), 3.84 (3H, s, CH_3), 1.60 (6H, d, *J* = 6.8 Hz, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.66 (C), 160.19 (C), 151.85 (C), 151.67 (CH), 144.15 (C), 140.18 (CH), 138.08 (C), 130.79 (C), 130.57 (CH), 122.14 (CH), 114.84 (CH), 112.61 (CH), 106.49 (CH), 60.26 (CH_2), 55.72 (CH_3), 47.70 (CH), 22.66 (2 x CH_3). **HRMS** (ES + ve), $C_{18}H_{20}N_7O_2$ $(M + H)^+$: Calculated 366.1678. Obtained 366.1669.

*9-(tert-butyl)-6-{[1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine (**15e**).* The crude product was purified by flash chromatography on silica (10% EtOAc in hexane) to provide the tittle compound as a yellow oil (77.2 mg, 0.203 mmol, 69% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.55 (1H, s, CH), 8.17 (1H, s, CH), 8.07 (1H, s, CH), 7.40 – 7.17 (3H, m, 3 x CH), 6.96 – 6.89 (1H, m, CH), 5.85 (2H, s, OCH_2), 3.84 (3H, s, CH_3), 1.78 (9H, s, 3 x CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.65 (C), 160.46 (C), 151.06 (C), 150.93 (CH), 144.22 (C), 140.18 (C), 138.09 (CH), 130.55 (CH), 130.52 (C), 122.12 (CH), 114.82 (CH), 112.62 (CH), 106.49 (CH), 60.16 (CH_2), 57.94 (C), 55.74 (CH_3), 29.08 (3 x CH_3). **HRMS** (ES + ve), $C_{19}H_{22}N_7O_2$ $(M + H)^+$: Calculated 380.1835. Obtained 380.1823.

*8-phenyl-9-(piperidin-1-yl)-6-{[1-(thiazol-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine (**17a**).* The crude product was purified by flash chromatography on silica (100% EtOAc) to provide the tittle compound as a light green solid (81.8 mg, 0.173 mmol, 82% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.80 (1H, bs, CH), 8.52 (1H, s, CH), 8.26 – 8.21 (2H, m, 2 x CH), 7.95 (1H, s, CH), 7.51 – 7.42 (3H, m, 3 x CH), 7.32 (1H, bs, CH), 5.81 (2H, s, OCH_2), 5.70 (2H, s, CH_2), 4.05 (2H, t, CH_2), 3.18 (2H, t, CH_2), 1.90 – 1.64 (6H, m, 3 x CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.90 (C), 154.13 (CH), 153.56 (C), 151.16 (C), 150.67 (CH), 150.63 (C), 143.84

(C), 130.53 (CH), 129.67 (2 x CH), 128.89 (C), 128.28 (2 x CH), 124.46 (CH), 119.62 (C), 118.08 (CH), 60.34 (CH_2), 54.28 (2 x CH_2), 49.75 (CH_2), 26.32 (2 x CH_2), 23.16 (CH_2). **HRMS** (ES + ve), $C_{23}H_{24}N_9OS$ $(M + H)^+$: Calculated 474.1825. Obtained 474.1845.

*9-(morpholin-4-yl)-8-phenyl-6-{[1-(thiazol-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine (**17b**).* The crude product was purified by flash chromatography on silica (25 → 100% EtOAc in hexane) to provide the tittle compound as a white solid (74.1 mg, 0.156 mmol, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.80 (1H, bs, CH), 8.52 (1H, s, CH), 8.23 – 8.16 (2H, m, 2 x CH), 7.94 (1H, s, CH), 7.54 – 7.42 (3H, m, 3 x CH), 7.33 (1H, bs, CH), 5.81 (2H, s, OCH_2), 5.70 (2H, s, CH_2), 4.37 (2H, t, CH_2), 3.88 (4H, t, 2 x CH_2), 3.08 (2H, t, CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.00 (C), 154.13 (CH), 153.34 (C), 151.06 (C), 150.95 (CH), 150.62 (C), 143.72 (C), 130.68 (CH), 129.59 (2 x CH), 128.73 (C), 128.41 (2 x CH), 124.47 (CH), 119.69 (C), 118.11 (CH), 67.15 (2 x CH_2), 60.34 (CH_2), 53.49 (2 x CH_2), 49.74 (CH_2). **HRMS** (ES + ve), $C_{22}H_{22}N_9O_2S$ $(M + H)^+$: Calculated 476.1617. Obtained 476.1608.

*9-(4-methylpiperazin-1-yl)-8-phenyl-6-{[1-(thiazol-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine (**17c**).* The crude product was purified by flash chromatography on silica (10% MeOH in EtOAc) to provide the tittle compound as a white solid (61.7 mg, 0.126 mmol, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.78 (1H, d, J = 2.0 Hz, CH), 8.46 (1H, s, CH), 8.24 – 8.14 (2H, m, 2 x CH), 7.90 (1H, s, CH), 7.50 – 7.39 (3H, m, 3 x CH), 7.29 (1H, d, J = 2.0 Hz, CH), 5.78 (2H, s, OCH_2), 5.68 (2H, s, CH_2), 4.36 (2H, t, CH_2), 3.09 (4H, t, 2 x CH_2), (2H, t, CH_2), 2.36 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.89 (C), 154.07 (CH), 153.52 (C), 150.95 (C), 150.72 (CH), 150.58 (C), 143.72 (C), 130.44 (CH), 129.51 (2 x CH), 128.92 (C), 128.27 (2 x CH), 124.44 (CH), 119.77 (C), 118.02 (CH), 60.16 (CH_2), 55.14 (2 x CH_2), 52.59 (2

x CH_2), 49.68 (CH_2), 45.88 (CH_3). **HRMS** (ES + ve), $C_{23}H_{25}N_{10}OS$ $(M + H)^+$: Calculated 489.1934. Obtained 489.1946.

*9-(isopropyl)-8-phenyl-6-{[1-(thiazol-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine **(17d)**.* The crude product was purified by flash chromatography on silica (100% EtOAc) to provide the tittle compound as a white solid (78 mg, 0.18 mmol, 82% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.79 (1H, d, *J* = 2.0 Hz, CH), 8.55 (1H, s, CH), 7.93 (1H, s, CH), 7.66 – 7.59 (2H, m, 2 x CH), 7.56 – 7.47 (3H, m, 3 x CH), 7.30 (1H, d, *J* = 2.0 Hz, CH), 5.79 (2H, s, OCH_2), 5.69 (2H, d, *J* = 0.7 Hz, CH_2), 4.76 (1H, m, CH), 1.72 (6H, d, *J* = 6.8 Hz, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.85 (C), 154.07 (CH), 153.66 (C), 153.08 (C), 150.90 (CH), 150.62 (C), 143.86 (C), 130.43 (CH), 129.84 (C), 129.65 (2 x CH), 128.86 (2 x CH), 124.34 (CH), 121.59 (C), 118.03 (CH), 60.28 (CH_2), 50.05 (CH), 49.73 (CH_2), 21.38 (2 x CH_3). **HRMS** (ES + ve), $C_{21}H_{21}N_8OS$ $(M + H)^+$: Calculated 433.1559. Obtained 433.1540.

*9-(tert-butyl)-8-phenyl-6-{[1-(thiazol-4-ylmethyl)-1H-1,2,3-triazol-4-yl]methoxy}-9H-purine **(17e)**.* The crude product was purified by flash chromatography on silica (90% EtOAc in hexane) to provide the tittle compound as a yellow oil (32.5 mg, 0.073 mmol, 86% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.78 (1H, bs, CH), 8.57 (1H, s, CH), 7.94 (1H, s, CH), 7.49 – 7.37 (5H, m, 5 x CH), 7.30 (1H, bs, CH), 5.75 (2H, s, OCH_2), 5.68 (2H, s, 2 x CH_2), 1.65 (9H, s, 3 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.87 (C), 154.27 (C), 154.08 (CH), 153.32 (C), 150.60 (C), 150.45 (CH), 143.79 (C), 129.92 (2 x CH), 129.81 (CH), 128.88 (C), 128.01 (2 x CH), 124.33 (CH), 120.99 (C), 118.07 (CH), 61.30 (C), 60.31 (CH_2), 49.71 (CH_2), 30.99 (3 x CH_3). **HRMS** (ES + ve), $C_{22}H_{23}N_8OS$ $(M + H)^+$: Calculated 447.1716. Obtained 447.1726.

General procedure for the synthesis of compounds 12d–e. To a 0.2 M solution of **3** (1 equiv.) in DCM was added triethylamine (1.5 equiv.). Then the corresponding amine (isopropylamine or *tert*-butylamine) (1.5 equiv.) was added dropwise and the mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue partitioned between DCM and H_2O. The layers were separated and the organic phase washed with saturated brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica.

*4-(isopropylamino)-5-nitro-6-(prop-2-yn-1-yloxy)pyrimidine (**12d**).* The crude product was purified by flash chromatography on silica (10% EtOAc in hexane) to provide the tittle compound as a yellow solid (1.04 g, 4.386 mmol, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (1H, s, CH), 8.21 (1H, bs, NH), 5.11 (2H, d, J = 2.4 Hz, OCH_2), 4.56 – 4.41 (1H, m, CH), 2.52 (1H, t, J = 2.5 Hz, CH), 1.29 (6H, d, J = 6.6 Hz, 2 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 163.28 (C), 158.68 (CH), 156.40 (C), 115.70 (C), 77.70 (C), 75.67 (CH), 55.30 (CH_2), 44.01 (CH), 22.74 (2 x CH_3). **HRMS** (ES + ve), $C_{10}H_{13}N_4O_3$ $(M + H)^+$: Calculated 237.0988. Obtained 237.0995.

*4-(tert-butylamino)-5-nitro-6-(prop-2-yn-1-yloxy)pyrimidine (**12e**).* The crude product was purified by flash chromatography on silica (6% EtOAc in hexane) to provide the tittle compound as a yellow oil (1.60 g, 6.372 mmol, 90% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.36 (1H, bs, NH), 8.24 (1H, s, CH), 5.09 (2H, d, J = 2.4 Hz, OCH_2), 2.51 (1H, t, J = 2.4 Hz, CH), 1.51 (9H, s, 3 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 163.06 (C), 157.64 (CH), 156.76 (C), 116.11 (C), 77.74 (C), 75.58 (CH), 55.10 (CH_2), 53.87 (C), 29.14 (3 x CH_3). **HRMS** (ES + ve), $C_{11}H_{15}N_4O_3$ $(M + H)^+$: Calculated 251.1144. Obtained 251.1156.

Determination of clogD. clogD were determined using Chemicalize by ChemAxon Ltd.[16] at the pH of 7.4 to represent the molecules in a physiological environment.

AUTHOR INFORMATION

Corresponding Authors

* M. J. Pineda de las Infantas y Villatoro. Email: mjpineda@ugr.es

* A. Unciti-Broceta. Email: Asier.Unciti-Broceta@igmm.ed.ac.uk

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ORCID

0000-0001-9510-714X (Álvaro Lorente-Macías)

0000-0002-3599-1954 (Juan J. Díaz-Mochón)

0000-0002-0617-6408 (María José Pineda de las Infantas y Villatoro)

0000-0003-1029-2855 (Asier Unciti-Broceta)

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

CuAAC, copper(I)-catalyzed alkyne-azide [3 + 2] cycloadditions; clogD, calculated distribution coefficient; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM, dichloromethane; DMSO,

dimethylsulphoxide; EtOAc, ethyl acetate; EtOH, ethanol; HRMS, high-resolution mass spectra; MeOH, methanol; NMR, nuclear magnetic resonance; S_NAr, nucleophilic aromatic substitution; TEA, triethylamine; THF, tetrahydrofuran.

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