Supporting Information

Identification of purine-scaffold small-molecule inhibitors of Stat3 activity by quantitative structure activity relationships

Vijay M. Shahani[a,b#], Peibin Yue[c#], Sina Haftchenary[a,b], Wei Zhao [c], Julie Lukkarila[a,b], Xiaolei Zhang[c], Steven Fletcher,[a,b] Daniel Ball[b], Christina Nona[b], Patrick T. Gunning[a,b*], and James Turkson[c,*]

Results and Discussion

Molecular Modeling, Quantitative Structure Activity Relationship, and Pharmacophore Modeling.

The crystal structure of the Stat3:Stat3-DNA ternary complex [1] revealed the structural composition and topology of the SH2 domain binding 'hotspot.' Analysis revealed three solvent-accessible sub-pockets on the SH2 domain protein surface, **A**, **B** and **C** (**Fig. 1A**). To interact with the key residues of sub-pocket **A**, the pharmacophore must incorporate an anionic functional group or a concentrated array of HBD and HBA groups to engage the cationic side chains or the numerous HBA and HBD residues present. This was achieved previously with the use of tetrazole, phosphate, phosphonate, salicylic acid or malonate functionality [2-5], [6]. In contrast to **A**, sub-pockets **B** and **C** are predominantly non-polar and hydrophobic. Sub-pocket **B** is derived from the tetramethylene portion of the side chains of Lys592, Arg595, Ile597 and Ile634. Sub-pocket **C** is composed of Trp623, Val637, Ile659, Phe716 and Lys626. Sub-pocket **B** has been generally accessed by lipophilic, hydrophobic moieties, such as tosylates, phenyl rings, alkyl groups and heterocycles [7]. Similarly, sub-pocket **C** is predominantly hydrophobic in nature (with the exception of a polar Lys626 residue) and has been previously engaged with isopropyl, hexyl, benzyl and cyclohexylbenzyl substituents [7]. We concluded that a predominantly

hydrophobic appendage would be best suited to this binding cleft, but that a terminally situated HBA group or carboxylate might be advantageously employed to interact with Lys626.

Stat3's SH2 domain phosphopeptide binding interface is relatively planar with the notable exception of pocket **A**, which is moderately more cavernous when compared to both **B** and **C**, presumably to accommodate the bulky pTyr moiety of the cognate phosphopeptide binding sequence. Given the planarity of the protein surface, we speculated that a central scaffold with limited flexibility would facilitate suitably situated binding groups to access all three sub-pockets. Thus, we proposed a Stat3 pharmacophore model for the rapid and facile identification of Stat3 SH2 domain inhibitors. Based upon our pharmacophore plot, new classes of Stat3 inhibitors can be designed to incorporate the key binding functionality at the desired coordinates.

To effectively target sub-pocket **A** and replicate the pTyr moiety, all purine scaffolds in this study were regioselectively furnished with a carboxylate appendage on N9 using previously reported facile Mitsunobu conditions [8, 9]. This synthetic study investigates the incorporation of binding groups at both the exogenous N2 amino group (position X, Table 1) and C6 carbon atom (position Y, Table 1.) of the purine core to afford optimal spatial access to sub-pockets B and C, respectively). In most cases, published small-molecule Stat3 inhibitors have been evaluated in dimerization assays, which assess the degree of disruption of Stat3 binding to a high-affinity pTyr peptide probe, or in a Stat3 DNA-binding assay. Herein, we report the use of Surface Plasmon Resonance (SPR) analysis, as we previously reported [6], to study the interactions of novel 2,6,9-trisubstituted purines (analyte) with Stat3 (target) in terms of the association and dissociation characteristics, and to evaluate agents.

We first installed a lipophilic pentyl chain at N2 to afford hydrophobic interactions with the alkyl side chains of Ile634 and Ile597, and the tetramethylene portion of the side-chain of Lys592. To the Y position, whilst keeping X = pentyl, we incorporated a focused set of aliphatic and aromatic amine substituents to probe sub-pocket C. Aromatic inhibitors S3I-V2-74 (Y = NHBn, X = pentyl), and S3I-V2-72 (Y = NHPh, X = pentyl) showed promising activity with K_D values of 2.2 and 2.5 μM, respectively. Initial incorporation of aliphatic primary and secondary amines at C6 also showed encouraging results (Table 1, SPR, entries 5–12: K_D 6-7 μM for select agents). Comparative GOLD docking studies revealed that the benzene moiety in the three aromatic inhibitors displayed an additional edge to face π-π stacking interaction with the side chain of Trp623, possibly accounting for the differences in observed affinity between aromatic and aliphatic substituents. In addition, we attached an amphiphilic morpholine group to C6 (Table 1, SPR, entry 13) in an effort to improve water solubility and make additional hydrogen bonds via the terminal HBA oxygen atom, which improved binding affinity (S3I-S3-32: K_D = 4.2 μM, Table 1, SPR). We speculated that the enhanced affinity might be due to an additional hydrogen bond between the ether group and an SH2 domain backbone NH or due to a different pharmacophore binding pattern.

More interesting is the general observation that Stat3 binding affinity improved with the incorporation a larger hydrophobic, cyclohexylbenzyl unit at position X (Table 1, SPR, entries 16-36) to access sub-pocket B [3, 10]. As before, we coupled a similar set of privileged binding groups to the Y position and evaluated the relative binding potencies of the inhibitors. Overall, when X = cyclohexybenzyl, we observed equipotent or moderate increases in affinity for the

different aromatic Y substituents (S3I-V3-27 (X = cyclohexylbenzyl, Y = $N(CH_3)Bn$): K_D = 4.0 μM *cf.* S3I-V2-73 (X = pentyl, Y = $N(CH_3)Bn$): K_D = 38.4 μM). As illustrated in Fig. 1E, the cyclohexylbenzyl group beneficially orientates the purine skeleton to optimally project both the Z functionality and the carboxylate group into sub-pockets C and A, respectively. Most significantly, of the twenty cyclohexylbenzyl analogs synthesized, over 75% showed promising affinity for the SH2 domain, as assessed by SPR. Moreover, computational docking showed that lead inhibitors, S3I-V3-32, S3I-S3-30, S3I-S2-36, S3I-S2-32, S3I-S2-30, S3I-S2-29, S3I-S2-38 and S3I-V3-31 elegantly projected the binding groups within the proposed pharmacophore plot. Introduction of an amide linkage to increase structural rigidity (X = cyclohexylbenzamide, Table 1, entries 36-38) conferred minimal benefits. Finally, to further probe sub-pocket B's apparent tolerance for bulky hydrophobic moieties, we replaced the cyclohexylbenzyl group with both a cyclohexylamide (S3I-V4-01, (17b)) and an N-(Boc)pentyl substituent (Table 1., SPR, entries 40-47). With the exception of S3I-V2-66 (7ac) (K_D = 0.9 μM) and S3I-S3-41 (7am) (K_D = 2.0 μM), which showed moderate increases in binding activity, similar or decreased affinities were reported. Overall, the nM to low micromolar affinities exhibited by the novel purine-scaffold small-molecules is encouraging.

Synthesis of compounds

Chemical Methods

Anhydrous solvents methanol, DMSO, CH_2Cl_2, THF and DMF were purchased from Sigma Aldrich and used directly from Sure-Seal bottles. Molecular sieves were activated by heating to 300 °C under vacuum overnight. All reactions were performed under an atmosphere of dry nitrogen in oven-dried glassware and were monitored for completeness by thin-layer

chromatography (TLC) using silica gel (visualized by UV light, or developed by treatment with $KMnO_4$ stain or phosphomolybdic acid stain). ^1H and ^{13}C NMR spectra were recorded on Bruker 400 MHz and a Varian 500 MHz spectrometers in either $CDCl_3$, CD_3OD or d_6-DMSO. Chemical shifts (δ) are reported in parts per million after calibration to residual isotopic solvent. Coupling constants (*J*) are reported in Hz. Before biological testing, inhibitor purity was evaluated by reversed-phase HPLC (rpHPLC). Analysis by rpHPLC was performed using a Microsorb-MV 300 A C18 250 mm x 4.6 mm column run at 1 mL/min, and using gradient mixtures of (A) water with 0.1M CH_3COONH_4 and (B) methanol. Ligand purity was confirmed using linear gradients from 75 % A and 25 % B to 100 % B after an initial 2 minute period of 100 % A. The linear gradient consisted of a changing solvent composition of either (I) 4.7 % per minute and UV detection at 254nm or (II) 1.4 % per minute and detection at 254nm, each ending with 5 minutes of 100% B. For reporting HPLC data, percentage purity is given in parentheses after the retention time for each condition. All biologically evaluated compounds are > 95 % chemical purity as measured by HPLC. The HPLC traces for all tested compounds are provided in supporting information.

Experimental Procedure

General Procedures

General Procedure A. Alkylation of N2 using Mitsunobu conditions: To a stirring solution of purine **4** (1.0 eq) in THF (0.1M) at room temperature the desired alcohol (1.2 eq) was added and triphenylphosphine (PPh_3, 1.3 eq). After ~2 min, di*iso*propylazodicarboxylate (DIAD, 1.3 eq) was added dropwise (over ~30 s – 1 min). Reaction mixture stirred for 0.5-2 hrs before THF was removed under reduced pressure. Resulting residue was columned on Biotage Isolera using a

gradient of EtOAc and hexanes.

General Procedure B. Nucleophilic aromatic substitution at C6 with amines: To a solution of the appropriate chloro-purine (1.0 eq) in DMSO (0.15M), the desired amine (2.0 eq) and DIPEA (3.0eq) were added. The resulting mixture was sealed in a tube vessel and irradiated in a Biotage Initiator microwave reactor (30 mins, 135 °C). After cooling, reaction was diluted with water and repeatedly extracted with EtOAc. The combined organics were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Resulting residue was adsorbed onto silica gel from CH_2Cl_2 and columned using a Biotage Isolera in a gradient of EtOAc and Hexanes.

General Procedure C. Nucleophilic aromatic substitution at C6 with anilines: To a solution of di-substituted chloro-purine (1.0 eq) in DMSO (0.2M), the appropriate aniline (3.0 eq) and DIPEA (3.0eq) were added. The resulting mixture was sealed in a tube vessel and irradiated in a Biotage Initiator microwave reactor (3 hrs, 135°C). After cooling, reaction was diluted with water and repeatedly extracted into EtOAc. The combined organics were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was dry-loaded onto silica gel from CH_2Cl_2 and columned using a Biotage Isolera in a gradient of EtOAc and Hexanes.

General Procedure D. Nucleophilic aromatic substitution at C6 with phenols: To a solution of the desired chloro-purine (1.0 eq) in DMSO (0.2M), DABCO (1.1 eq) and DIPEA (1.5eq) were added and stirred. The solution was allowed to stir for 1 hr at room temperature before it

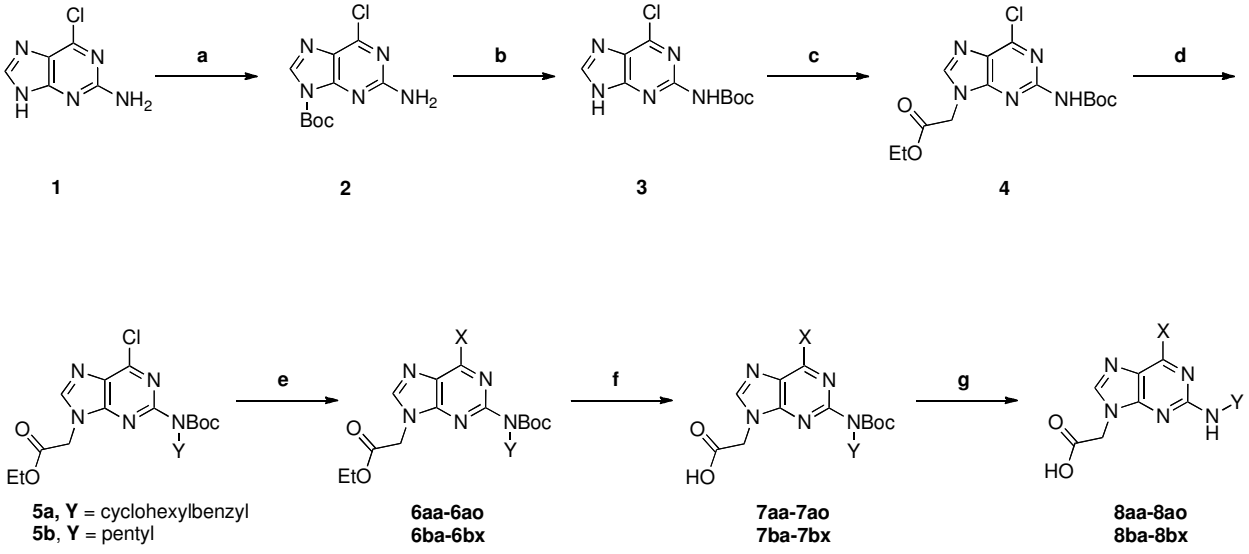
was deemed complete, at which point a pre-made solution of the appropriate phenol (2.0 eq) and DIPEA (1.5 eq) in DMSO was combined with the chloro-purine to make a 0.1M solution. Reaction was left at room temperature for 16 hours, then diluted with water and repeatedly extracted with EtOAc. The combined organics were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was columned using a Biotage Isolera in a gradient of EtOAc and Hexanes.

General Procedure E. Ester hydrolysis with LiOH: LiOH (1.1eq) was added at room temperature to a stirring solution (0.1M) of the appropriate purine (1.0 eq) in THF:H_2O (3:1). Reaction was deemed complete after 30 minutes, then diluted with water acidified (pH~5.5) by KH_2PO_4, and continuously extracted into EtOAc. Organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Reaction was purified by flash column chromatography using an isocratic solvent system (35:7:1 DCM:MeOH:H_2O) on the Biotage Isolera. Dried product was suspended in a mixture of millicule water:acetonitrile (6:1) and lyophilized.

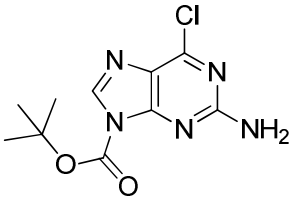
General Procedure F. Boc deprotection: The appropriate purine (1.0 eq) was dissolved in TFA:DCM (1:1) (0.1M solution). The reaction was stirred for one hour at room temperature, co-evaporated with MeOH to near dryness, and dry-loaded onto silica and purified using a Biotage Isolera flash chromatographer using an isocratic system (65:25:4 DCM:MeOH:H_2O). Pure product was suspended in a mixture of milicule water:acetonitrile (6:1) and lyophilized.

General Procedure G. Acylation of N6: To a stirring solution of the required purine (1.0 eq) in pyridine (0.1M) was the appropriate acid chloride added (1.1eq). Reaction complete within 15 minutes, diluted with water acidified by 1M HCl (pH ~ 2), and repeatedly extracted into EtOAc. Combined organics were washed with several times with acidified water (pH ~ 2) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was columned using the Biotage Isolera in a gradient of DCM and (92:7:1 DCM:MeOH:NH_4OH) and dried under reduced pressure.

SCHEME 1

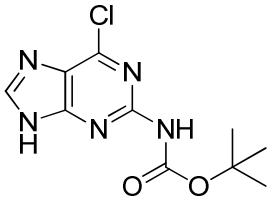


Scheme 1. a) boc anhydride, DMSO, DMAP(cat), 0 °C r.t., 30 mins, 75 %; b) NaH, THF, r.t., 30 mins, 95 %; c) (i) ethyl 2-hydroxyacetate, PPh_3, THF, r.t., 2 mins; (ii) DIAD, r.t., 15 mins, 83 %; d) (i) Y-OH, PPh_3, THF, r.t., 2 mins; (ii) DIAD, r.t., 15 mins, 82-74 %; e) X (HNR'R"), DIPEA, DMSO, 105 °C, 40 mins, microwave assisted, 65-97 %; f) LiOH, THF:H_2O(3:1), r.t., 15 mins, 75-97 %; g) TFA:CH_2Cl_2 (1:1), r.t., 1 hr, 63-95 %.



N^9-Boc-2-amino-6-chloropurine (2)

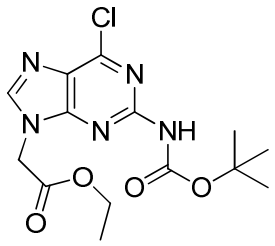
A rapidly stirred solution of 2-amino-6-chloropurine (1 eq) and di-*tert*-butyl dicarbonate (Boc_2O; 1 eq) in anhydrous DMSO (0.3M) was briefly cooled over ice under an N_2 atmosphere. After 5 min (or sooner if the DMSO begins to freeze), the reaction flask was removed from the ice bath and catalytic DMAP (0.05 eq) was added. The septum was then immediately equipped with a venting needle. After stirring for 30 min at room temperature, TLC indicated the reaction was complete. The reaction mixture was diluted with water and repetitively extracted into EtOAc. The EtOAc layers were combined and washed with water, dried on anhydrous Na_2SO_4, filtered and concentrated to afford N^9-Boc-2-amino-6-chloropurine (**2**) as a white solid (75 %): δ_H (400 MHz, d_6-DMSO) 1.60 (s, 9H, $(CH_3)_3$), 7.19 (br s, 2H, NH_2), 8.38 (s, 1H, H-8); δ_C (100 MHz, $CDCl_3$) 27.9, 87.1, 125.4, 140.1, 145.5, 152.3, 153.3, 160.4; LRMS (ES-MS) calcd for $C_{10}H_{12}ClN_5O_2Na$ [M + Na^+] *m/z* = 292.06, obsd 291.96.



***tert*-butyl (6-chloro-9H-purin-2-yl)carbamate (3)**

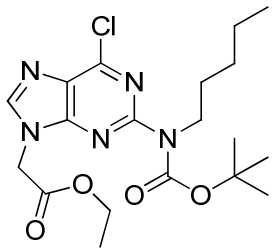
To a stirred solution of purine **2** (1.00 eq) in anhydrous THF (0.1M) at room temperature was carefully added NaH (60% dispersion in mineral oil; 2.25 eq) in one portion under an N_2 atmosphere. After 2 h, the Boc transfer reaction was complete. The reaction mixture was cooled to 0 °C then quenched with brine dropwise. The solvent was concentrated down and then poured

into a separatory funnel containing saturated aqueous $NaHCO_3$ solution. The organics were extracted into EtOAc, dried on anhydrous Na_2SO_4, filtered and concentrated. The residue was dry-loaded onto silica gel from CH_2Cl_2, then purified by flash column chromatography (92:7:1 CH_2Cl_2:MeOH:NH_4OH) to afford product as a white powder (95%): δ_H (400 MHz, d_6-DMSO) 1.47 (s, 9H, $(CH_3)_3$), 8.46 (s, 1H, H-8), 10.22 (s, 1H, NHBoc), 13.60 (br s, 1H, H-9); δ_C (100 MHz, $CDCl_3$) 28.0, 82.2, 127.8, 145.3, 150.8, 151.1, 151.5, 153.0; LRMS (ES-MS) calcd for $C_{10}H_{12}ClN_5O_2Na$ [M + Na^+] *m/z* = 292.06, obsd 291.90.



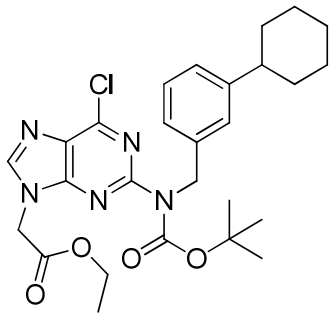
ethyl 2-(2-((*tert*-butoxycarbonyl)amino)-6-chloro-9H-purin-9-yl)acetate (4)

To a stirred solution of purine **3** (1 eq) in THF (0.1M) at room temperature was added ethyl glycolate (1.1 eq) followed by triphenylphosphine (PPh_3; 1.1 eq) under an N_2 atmosphere. To the homogenous solution, di*iso*propylazodicarboxylate (DIAD, 1 eq) was added dropwise (over 30 s). TLC indicated the reaction was complete after 15 min and the solvent was removed *in vacuo*, then the residue was dry-loaded onto silica gel from CH_2Cl_2, and purified by flash column chromatography (2:1 EtOAc:Hex) to furnish **4** as an off-white foam (83%); mp 129–136 °C; IR (KBr, cm^{-1}) 3462, 3249, 3166, 3106, 2988, 2948, 2362, 1751, 1693, 1612, 1572, 1523, 1499, 1447, 1421; δ_H (400 MHz, DMSO-d_6) 1.22 (t, *J* = 7.1 Hz, 3H, CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 4.18 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 5.11 (s, 2H, CH_2CO_2Et), 8.46 (s, 1H, H-8), 10.33 (s, 1H, NHBoc); δ_C (100 MHz, DMSO-d_6) 13.9, 27.8, 44.2, 61.6, 79.7, 126.3, 146.4, 149.0, 150.8, 152.6, 152.9, 167.3; HRMS (ESI^+) calcd for $C_{14}H_{18}ClN_5O_4Na$ [M+Na^+] *m/z* = 378.0939, obsd 378.0945.



ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-chloro-9H-purin-9-yl)acetate (5a)

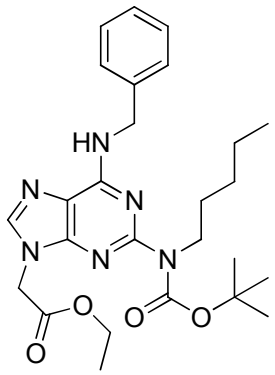
Purine **4** was treated according to general procedure **A**, where ROH was 1-pentanol, to yield final product **5a** as a white solid (82 %): IR (KBr, cm^{-1}) 3479, 3104, 2960, 2934, 2872, 1754, 1713, 1611, 1563, 1511, 1452, 1407, 1273, 1213, 1136, 1061, 1024; δ_H (400 MHz, $CDCl_3$) 0.88 (t, J = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.25-1.34 (m, 7H, $CO_2CH_2C\underline{H}_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.50 (s, 9H, $C(CH_3)_3$), 1.65 (p, J = 7.4 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.89-3.93 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.27 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.96 (s, 2H, $C\underline{H}_2CO_2Et$), 8.07 (s, 1H, CH (H-8)); LRMS (MS-ES) calcd for $C_{19}H_{29}ClN_5O_4$ [M+H] m/z = 426.18, fnd. 426.43.



ethyl 2-(2-((*tert*-butoxycarbonyl)(3-cyclohexylbenzyl)amino)-6-chloro-9H-purin-9-yl) acetate (5b)

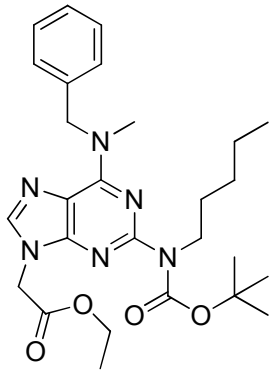
Purine **4** was treated according to general procedure **A**, where ROH was 4-cyclohexyl-benzyl alcohol, to yield final product **5a** as a white solid (74%): m.p. = 66 -71; IR (KBr, cm^{-1}) 2981, 2927, 2852, 1752, 1713, 1564, 1514, 1448, 1405, 1368, 1295, 1278, 1220, 1158, 1109; δ_H (400 MHz, $CDCl_3$) 1.20-1.38 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.46 (s, 9H, $C(CH_3)_3$),

1.70-1.83 (m, 5H (cyclohexyl)), 2.43-2.46 (m, 1H, CH), 4.25 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.93 (s, 2H, CH_2Ar), 5.15 (s, 2H, CH_2CO_2Et), 7.10 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.28 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 8.05 (s, 1H, CH (H-8)); LRMS (MS-ES) calcd for $C_{27}H_{35}ClN_5O_4$ [M+H] *m/z* = 528.23, fnd. 528.32.



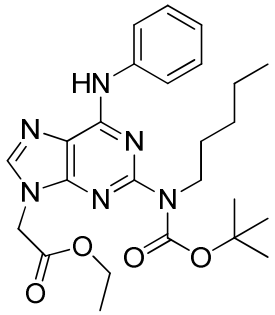
ethyl 2-(6-(benzylamino)-2-((tert-butoxycarbonyl)(pentyl)amino)-9H-purin-9-yl)acetate (6aa)

Purine **5a** was treated with benzylamine according to general procedure **B**, yielding the final product **6aa** as a white solid (52 %): m.p. = 106-112 °C; IR (KBr, cm^{-1}) 3425, 3275, 2980, 2940, 2868, 1761, 1705, 1625, 1495, 1390, 1270, 1208; δ_H (400 MHz, $CDCl_3$) 0.85 (t, *J* = 7.0 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.29-1.33 (m, 7H, $CO_2CH_2C\underline{H}_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.58-1.65 (m, 2H, $(CH_2)_3C\underline{H}_2CH_3$), 3.77-3.81 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.25 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.83 (bs, 2H, $C\underline{H}_2Ar$), 4.90 (s, 2H, $C\underline{H}_2CO_2Et$), 6.05 (bs, 1H, NH), 7.09 (t, *J* = 7.5 Hz, 1H, CH (Ar)), 7.27-7.38 (m, 4H, CH (Ar)), 7.75 (s, 1H, CH (H-8)); LRMS (MS- ES) calcd for $C_{26}H_{37}N_6O_4$ [M+H] *m/z* = 497.28, fnd. 497.27.



ethyl 2-(6-(benzyl(methyl)amino)-2-((*tert*-butoxycarbonyl)(pentyl)amino)-9H-purin-9-yl)acetate (6ab)

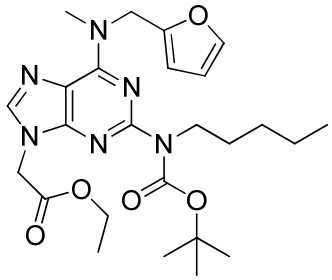
Purine **5a** was treated with *N*-methylbenzylamine according to general procedure **B**, yielding the final product **6ab** as a clear viscous oil (88 %): IR (KBr, cm^{-1}) 2958, 2931, 1755, 1701, 1488, 1453, 1385, 1276, 1212, 1145; δ_H (400 MHz, $CDCl_3$) 0.81-0.85 (t, J = 7.0 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.24-1.32 (m, 7H, $CO_2CH_2C\underline{H}_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.46 (s, 9H, $C(CH_3)_3$), 1.57-1.67 (m, 2H, $(CH_2)_3C\underline{H}_2CH_3$), 3.12-3.69 (bm, 3H, NCH_3), 3.76-3.80 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.25 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.91 (s, 2H, $C\underline{H}_2CO_2Et$), 4.99-5.63 (bm, 2H, $C\underline{H}_2Ar$), 7.23-7.33 (m, 5H, CH (Ar)), 7.75 (s, 1H, CH (H-8)); LRMS (MS-ES) calcd for $C_{27}H_{39}N_6O_4$ [M+H] *m/z* = 511.30, fnd. 511.39.



ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(phenylamino)-9H-purin-9-yl)acetate (6ac)

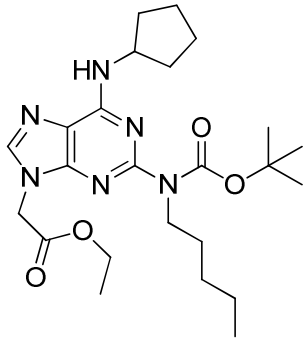
Purine **5a** was treated with aniline according to general procedure **C**, yielding the final product

6ac as a clear viscous oil (63 %): (KBr, cm^{-1}) 3234, 2932, 1753, 1584, 1499, 1459, 1385, 1274, 1213, 1136; δ_H (400 MHz, $CDCl_3$) 0.88 (t, J = 7.0 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.29-1.33 (m, 7H, $CO_2CH_2C\underline{H}_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.66-1.73 (m, 2H, $(CH_2)_3C\underline{H}_2CH_3$), 3.86-3.90 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.27 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.94 (s, 2H, $C\underline{H}_2CO_2Et$), 7.09 (t, J = 7.5 Hz, 1H, CH (Ar)), 7.35 (t, J = 8.0 Hz, 2H, 2 CH (Ar)), 7.66 (bs, 1H, NH), 7.83 (d, J = 7.7 Hz, 2H, 2 CH (Ar)), 7.85 (s, 1H, CH (H-8)); LRMS (MS-ES) calcd for $C_{25}H_{35}N_6O_4$ [M+H] *m/z* = 483.26, fnd. 483.31.



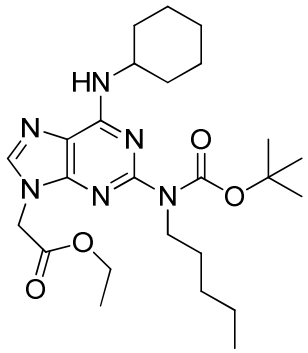
ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-((furan-2-ylmethyl)(methyl)amino)-9H-purin-9-yl)acetate (6ad)

Purine **5a** was treated with *N*-methylfurfurylamine according to general procedure **B**, yielding the final product **6ad** as a clear viscous oil (91 %): IR (KBr, cm^{-1}) 3538, 3475, 3400, 3225, 2925, 2860, 1750, 1700, 1600, 1435, 1380, 1210; δ_H (400 MHz, $CDCl_3$) 0.86 (t, J = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.25-1.34 (m, 7H, $CO_2CH_2C\underline{H}_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.65 (p, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.56(vbs, 3H, CH_3(furfuryl)), 3.81 (t, J = 7.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.25 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.93 (s, 2H, $C\underline{H}_2CO_2Et$), 5.35 (vbs, 2H, CH_2 (furfuryl)), 6.28-6.31 (m, 2H, CH (furfuryl)), 7.34-7.35 (m, 1H, (furfuryl)) 7.78 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{25}H_{37}N_6O_5$ [M+H] *m/z* = 501.27, fnd. 501.30.



ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(cyclopentylamino)-9H-purin-9-yl) acetate (6ae)

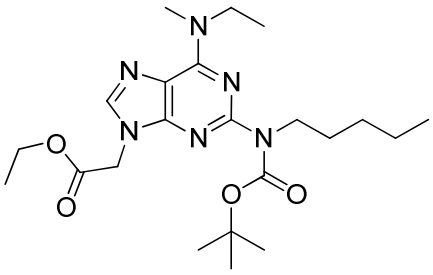
Purine **5a** was treated with cyclopentanamine according to general procedure **B**, yielding the final product **6ae** as a clear viscous oil (83 %): IR (KBr, cm^{-1}) 3546, 3475, 3410, 3230, 2950, 2865, 1760, 1710, 1625, 1480, 1400, 1270; δ_H (400 MHz, $CDCl_3$) 0.87 (t, J = 7.0 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.25-1.34 (m, 7H, $CO_2CH_2C\underline{H}_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.54-1.84 (m, 8H, $CH_2C\underline{H}_2(CH_2)_2CH_3$ and 3 CH_2 (cyclopentyl)), 2.11 (m, 2H, CH_2 (cyclopentyl)), 3.81 (t, J = 7.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.25 (q, J = 7.0 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.53 (bs, 1H, CH (cyclopentyl)), 4.89 (s, 2H, $C\underline{H}_2CO_2Et$), 5.68 (bs, 1H, NH), 7.76 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{24}H_{39}N_6O_4$ [M+H] m/z = 475.30, fnd. 475.37.



ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(cyclohexylamino)-9H-purin-9-yl)acetate (6af)

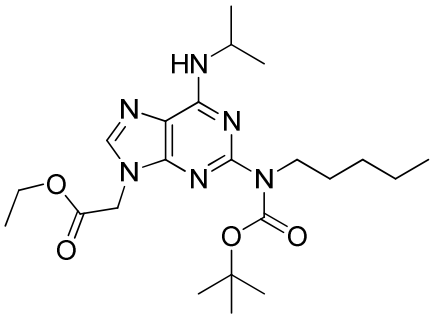
Purine **5a** was treated with cyclohexanamine according to general procedure **B**, yielding the final

product **6af** as a clear viscous oil (70 %): IR (KBr, cm^{-1}) 2940, 2586, 1760, 1390, 1150; δ_H (400 MHz, $CDCl_3$) 0.88 (t, *J* = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.25-1.44 (m, 13H, $CO_2CH_2C\underline{H}_3$, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$ and 3 CH_2 (cyclohexyl)), 1.49 (s, 9H, $C(CH_3)_3$), 1.62-1.71 (m, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 1.76-1.84 (m, 2H, CH_2 (cyclohexyl)), 2.06-2.13 (m, 2H, CH_2 (cyclohexyl)), 3.80 (t, *J* = 7.7 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.10 (bs, 1H, CH (cyclohexyl)), 4.25 (q, *J* = 7.1Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.88 (s, 2H, $C\underline{H}_2CO_2Et$), 5.62 (bs, 1H, NH), 7.76 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{25}H_{41}N_6O_4$ [M+H] *m/z* = 489.31, fnd. 489.34.



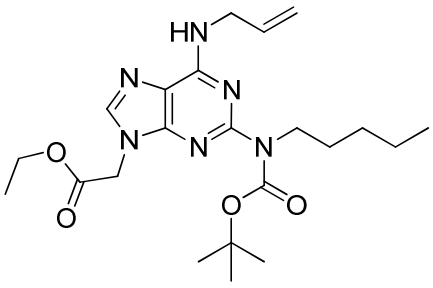
ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(ethyl(methyl)amino)-9H-purin-9-yl) acetate (6ag)

Purine **5a** was treated with *N*-methylethylamine according to general procedure **B**, yielding the final product **6ag** as a clear viscous oil (84 %): IR (KBr, cm^{-1}) 3530, 3475, 3413, 2970, 2950, 2880, 1760, 1700, 1600, 1475, 1440, 1390; δ_H (400 MHz, $CDCl_3$) 0.87 (t, *J* = 7.0 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.24-1.33 (m, 10H, $CO_2CH_2C\underline{H}_3$, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$ and $NCH_2C\underline{H}_3$), 1.47 (s, 9H, $C(CH_3)_3$), 1.67 (p, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.42 (bm, 3H, NCH_3), 3.79 (t, *J* = 7.7 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.04 (bm, 2H, $NC\underline{H}_2CH_3$), 4.24 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.89 (s, 2H, $C\underline{H}_2CO_2Et$), 7.74 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{22}H_{37}N_6O_4$ [M+H] *m/z* = 449.28, fnd. 449.44



ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(isopropylamino)-9H-purin-9-yl)acetate (6ah)

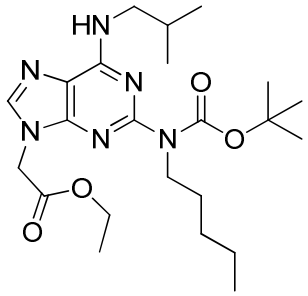
Purine **5a** was treated with isopropylamine according to general procedure **B**, yielding the final product **6ah** as a clear viscous oil (75 %): IR (KBr, cm^{-1}) 3546, 3475, 3410, 2975, 2925, 1775, 1700, 1615, 1475, 1380, 1370, 1225; δ_H (400 MHz, $CDCl_3$) 0.87 (t, *J* = 7.0 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.24-1.33 (m, 13H, $CO_2CH_2C\underline{H}_3$, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$ and $CH(C\underline{H}_3)_2$), 1.48 (s, 9H, $C(CH_3)_3$), 1.66 (p, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.80 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.25 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.45 (bs, 1H, $C\underline{H}(CH_3)_2$), 4.89 (s, 2H, $C\underline{H}_2CO_2Et$), 5.56(bs, 1H, NH), 7.76 (s, 1H, CH (H-8));LRMS (MS-ES), calcd for $C_{22}H_{37}N_6O_4$ [M+H] *m/z* = 449.28, fnd. 449.38.



ethyl 2-(6-(allylamino)-2-((*tert*-butoxycarbonyl)(pentyl)amino)-9H-purin-9-yl)acetate (6ai)

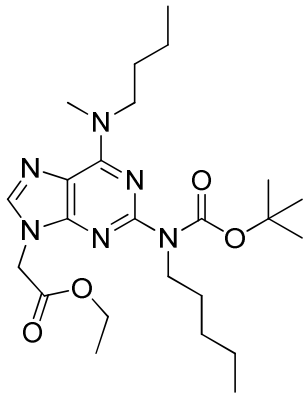
Purine **5a** was treated with allylamine according to general procedure **B**, yielding the final product **6ai** as a white solid (72 %): m.p. = 67-78 °C; IR (KBr, cm^{-1}) 3546, 3476, 3413, 3276, 2940, 1760, 1710, 1680, 1625, 1490, 1380, 1200; δ_H (400 MHz, $CDCl_3$) 0.87 (t, *J* = 6.8 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.25-1.33 (m, 7H, $CO_2CH_2C\underline{H}_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.49 (s, 9H, $C(CH_3)_3$),

1.65 (p, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.82 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.25 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.27 (vbs, 2H, $C\underline{H}_2CHCH_2$), 4.90 (s, 2H, $C\underline{H}_2CO_2Et$), 5.18 (d, *J* = 9.9Hz, 1H, $CH_2CHC\underline{H}_2$), 5.31 (d, *J* = 17.4 Hz, 1H, $CH_2CHC\underline{H}_2$), 5.85(bs, 1H, NH), 5.94-6.04 (m, 1H, $CH_2C\underline{H}CH_2$), 7.80 (s, 1H, CH (H-8));. LRMS (MS-ES), calcd for $C_{22}H_{35}N_6O_4$ [M+H] *m/z* = 447.26, fnd. 447.36.



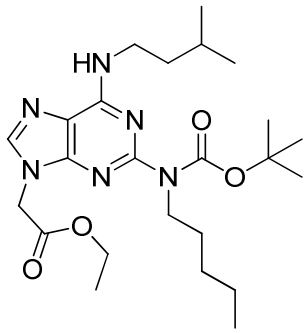
ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(isobutylamino)-9H-purin-9-yl)acetate (6aj)

Purine **5a** was treated with isobutylamine according to general procedure **B**, yielding the final product **6aj** as a a white solid (83 %): m.p. = 89-93 °C; IR (KBr, cm^{-1}) 3425, 3290, 2960, 2925, 2885, 1760, 1670, 1630, 1580, 1380, 1249, 1200; δ_H (400 MHz, $CDCl_3$) 0.87 (t, *J* = 6.8 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 0.99 (s, 3H, $CH(C\underline{H}_3)_2$), 1.00 (s, 3H, $CH(C\underline{H}_3)_2$), 1.25-1.34 (m, 7H, $CO_2CH_2C\underline{H}_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.66 (p, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 1.97 (septet, *J* = 6.6 Hz, 1H, $C\underline{H}(CH_3)_2$), 3.43 (bs, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.81 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.25 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.89 (s, 2H, $C\underline{H}_2CO_2Et$), 5.79 (bs, 1H, NH), 7.76 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{23}H_{39}N_6O_4$ [M+H] *m/z* = 463.30, fnd. 463.41.



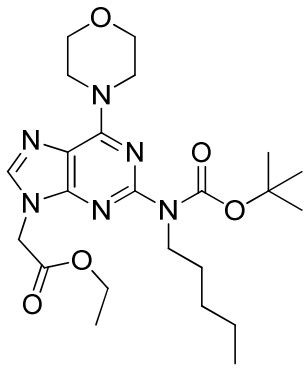
2ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(butyl(methyl)amino)-9H-purin-9-yl)acetate (6ak)

Purine **5a** was treated with *N*-butylmethylamine according to general procedure **B**, yielding the final product **6ak** as a clear viscous oil (63 %): IR (KBr, cm^{-1}) 3550, 3460, 3410, 2950, 2925, 2860, 1760, 1700, 1600, 1440, 1400, 1200; δ_H (400 MHz, $CDCl_3$) 0.88 (t, J = 7.0 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 0.96 (t, J = 7.3 Hz, 3H, $(CH_2)_3C\underline{H}_3$), 1.26-1.45 (m, 9H, $CO_2CH_2C\underline{H}_3$, $CH_2CH_2C\underline{H}_2CH_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.49 (s, 9H, $C(CH_3)_3$), 1.62-1.73 (4H, $CH_2C\underline{H}_2CH_2CH_3$ and $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.20-4.24 (m, 5H, $C\underline{H}_2(CH_2)_2CH_3$ and $C\underline{H}_2(CH_2)_3CH_3$), 3.79 (t, J = 7.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.25 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.91 (s, 2H, $C\underline{H}_2CO_2Et$), 7.74 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{24}H_{41}N_6O_4$ [M+H] m/z = 477.31, fnd. 477.38.



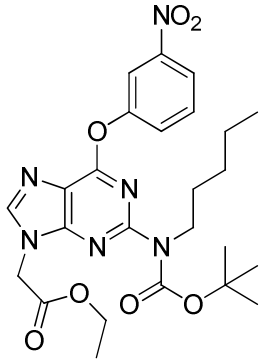
ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(isopentylamino)-9H-purin-9-yl)acetate (6al)

Purine **5a** was treated with isoamylamine according to general procedure **B**, yielding the final product **6al** as a white solid (70 %): m.p. = 70-91 °C; IR (KBr, cm^{-1}) 3546, 3475, 3410, 2960, 2925, 2860, 1760, 1700, 1608, 1380, 1250, 1213; δ_H (400 MHz, $CDCl_3$) 0.87 (t, *J* = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 0.95 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 0.96 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 1.25-1.34 (m, 7H, $CO_2CH_2C\underline{H}_3$, and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.49(s, 9H, $C(CH_3)_3$), 1.53-1.78 (m, 5H, $CH_2C\underline{H}_2(CH_2)_2CH_3$ and $CH_2C\underline{H}_2C\underline{H}(CH_3)_2$), 3.62 (bs, 2H, $C\underline{H}_2(CH_2)_2(CH_3)_2$), 3.81 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.25 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.89 (s, 2H, $C\underline{H}_2CO_2Et$) 5.76 (bs, 1H, NH), 7.77(s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{24}H_{41}N_6O_4$ [M+H] *m/z* = 477.3, fnd 477.32.



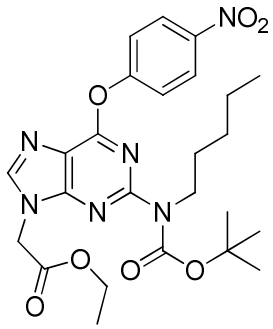
ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-morpholino-9H-purin-9-yl)acetate (6am)

Purine **5a** was treated with morpholine according to general procedure **B**, yielding the final product **6am** as a clear viscous oil (83 %): IR (KBr, cm^{-1}) 2960, 2931, 2858, 1755, 1712, 1589, 1478, 1444, 1386, 1365, 1220, 1146, 1117; δ_H (400 MHz, $CDCl_3$) 0.87 (t, *J* = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.25-1.31 (m, 7H, $CO_2CH_2C\underline{H}_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 1.65 (p, *J* = 7.4 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.78-3.84 (m, 6H, $C\underline{H}_2(CH_2)_3CH_3$ and 2 CH_2 (morpholine)), 4.25 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.26 (bs, 4H, 2 CH_2 (morpholine)), 4.89 (s, 2H, $C\underline{H}_2CO_2Et$), 7.75 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{23}H_{36}N_6O_4Na$ [M+Na] *m/z* = 499.27, fnd 499.43.



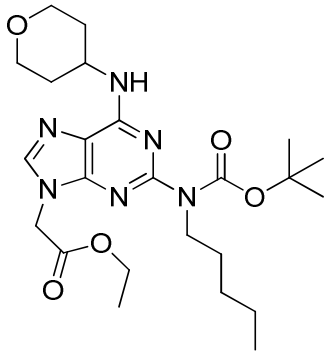
ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(3-nitrophenoxy)-9H-purin-9-yl)acetate (6an)

Purine **5a** was treated with 3-nitrophenol according to general procedure **D**, yielding the final product **6an** as a clear viscous oil (73 %): IR (KBr, cm^{-1}) 2959, 2931, 1752, 1713, 1578, 1533, 1448, 1407, 1354, 1276, 1222, 1149; δ_H (400 MHz, $CDCl_3$) 0.82 (t, *J* = 7.3 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.04-1.21 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.32 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.40 (s, 9H, $C(CH_3)_3$), 1.44-1.52 (m, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.65-3.69 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.28 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.98 (s, 2H, $C\underline{H}_2CO_2Et$), 7.60 (t, *J* = 8.2 Hz, 1H, CH (Ar)), 7.68 (d, *J* = 8.2 Hz, 1H, CH (Ar)), 8.02 (s, 1H, CH (H-8)), 8.14 (d, *J* = 8.2 Hz, 1H, 1 CH (Ar)), 8.23(d, *J* = 2.2 Hz, 1H, 1 CH (Ar)); LRMS (MS- ES), calcd for $C_{24}H_{33}N_6O_7$ [M+H] *m/z* = 529.23, fnd 529.45.



ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(4-nitrophenoxy)-9H-purin-9-yl)acetate (6ao)

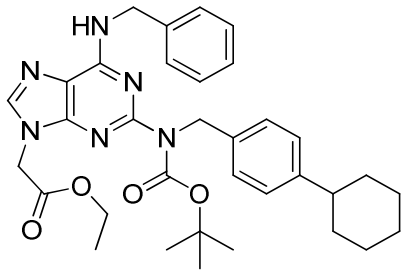
Purine **5a** was treated with 4-nitrophenol according to general procedure **D**, yielding the final product **6ao** as a white solid (68 %): m.p. > 99-110 °C; IR (KBr, cm^{-1}) 3100, 3080, 2940, 2870, 1760, 1725, 1608, 1570, 1530, 1345, 1250, 1230; δ_H (400 MHz, $CDCl_3$) 0.82 (t, *J* = 7.1 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.01-1.26 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.32 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.43 (s, 9H, $C(CH_3)_3$), 1.51 (p, *J* = 7.6 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.68-3.72 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.28 (q, *J* = 7.6 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.98 (s, 2H, $C\underline{H}_2CO_2Et$), 7.54 (d, *J* = 9.1 Hz, 2H, 2 CH (Ar)), 8.02 (s, 1H, CH (H-8)), 8.31 (d, *J* = 9.1 Hz, 2H, 2 CH (Ar)); LRMS (MS- ES), calcd for $C_{25}H_{32}N_6O_7Na$ [M+Na] *m/z* = 528.23, fnd. 551.27.



ethyl 2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-((tetrahydro-2H-pyran-4-yl)amino)-9H-purin-9-yl)acetate (6ay).

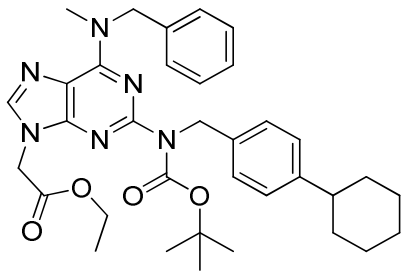
Purine **5a** was treated with tetrahydro-2*H*-pyran-4-amine according to general procedure **B**, yielding the final product **6ay** as a white solid (86 %): m.p. > 183 °C (dec); IR (KBr, cm^{-1}) 2953, 2850, 1760, 1683, 1472, 1441, 1400, 1383, 1366, 1298, 1277, 1208, 1140; δ_H (400 MHz, $CDCl_3$) 0.87 (t, *J* = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.25-1.34 (m, 7H, $CO_2CH_2C\underline{H}_3$, and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.58-1.73 (m, 4H, 2H, $C\underline{H}_2$, (tetrahydropyran) and $CH_2C\underline{H}_2(CH_2)_2CH_3$)), 2.04-2.08 (m, 2H, $C\underline{H}_2$, (tetrahydropyran)), 3.48-3.60 (m, 2H, $C\underline{H}_2$, (tetrahydropyran)), 3.79 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 3.95-4.07 (m, 2H, $C\underline{H}_2$, (tetrahydropyran)), 4.25 (q, *J* = 7.1 Hz,

2H, $CO_2C\underline{H}_2CH_3$), 4.33 (bs, 1H, CH), 4.89 (s, 2H, $C\underline{H}_2CO_2Et$) 6.01 (bs, 1H, NH), 7.77 (s, 1H, CH (H-8)); LRMS (MS- ES), calcd for $C_{24}H_{38}N_6O_5Na$ [M+Na] *m/z* = 513.29, fnd. 513.44.



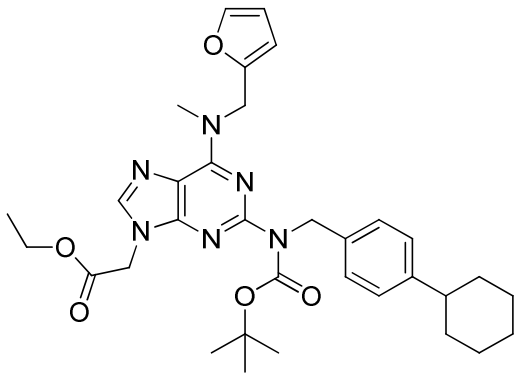
ethyl 2-(6-(benzylamino)-2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-9H-purin-9-yl)acetate (6ba)

Purine **5b** was treated with benzylamine according to general procedure **B**, yielding the final product **6ba** as a white solid (85 %): m.p. > 116 °C (dec); IR (KBr, cm^{-1}) 3325, 3140, 2990, 2925, 2850, 1750, 1697, 1625, 1600, 1390, 1370, 1225; δ_H (400 MHz, $CDCl_3$) 1.21-1.40 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.46 (s, 9H, $C(CH_3)_3$), 1.71-1.85 (m, 5H (cyclohexyl)), 2.41-2.46 (m, 1H, CH), 4.25 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.75 (bs, 2H, $HNC\underline{H}_2$), 4.90 (bs, 2H, CH_2Ar), 5.06 (s, 2H, CH_2CO_2Et), 7.08 (m, 2H, 2 CH (Ar)), 7.21-7.32 (m, 7H, 7 CH (Ar)), 7.43 (bs, 1H, NH), 7.87 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{34}H_{43}N_6O_4$ [M+H] *m/z* = 599.33, fnd. 599.49.



ethyl 2-(6-(benzyl(methyl)amino)-2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-9H-purin-9-yl)acetate (6bb)

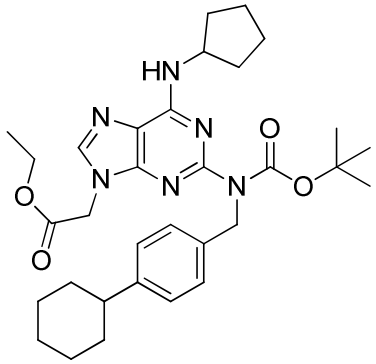
Purine **5b** was treated with *N*-methylbenzylamine according to general procedure **B**, yielding the final product **6bb** as a white solid (72 %): m.p. = 115-121 °C; IR (KBr, cm^{-1}) 3419, 2979, 2925, 2851, 1755, 1698, 1594, 1558, 1488, 1454, 1418, 1377, 1204, 1152, 1107; δ_H (400 MHz, $CDCl_3$) 1.29 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.33 - 1.41 (m, 5H, (cyclohexyl)), 1.41 (s, 9H, $C(CH_3)_3$), 1.71-1.82 (m, 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 3.06-3.71 (bm, 3H, $NC\underline{H}_3$), 4.24 (q, *J* = 7.2Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.89 (s, 2H, CH_2Ar), 5.03 (bs, 2H, CH_2CO_2Et), 5.17-5.61 (bm, 2H, $CH_3NC\underline{H}_2$), 7.03-7.05 (m, 2H, CH (Ar)), 7.23 -7.31 (m, H, 7 CH (Ar)), 7.73 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{35}H_{45}N_6O_4$ [M+H] *m/z* = 613.34, fnd. 613.50.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-((furan-2-ylmethyl)(methyl) amino)-9H-purin-9-yl)acetate (6bd)

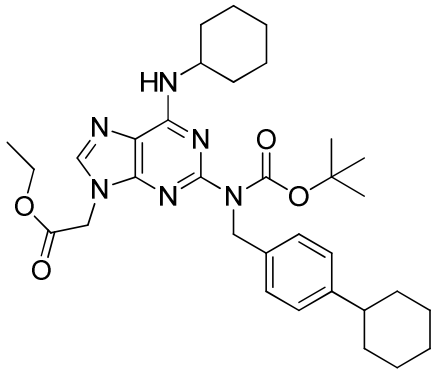
Purine **5b** was treated with *N*-methylfurfurylamine according to general procedure **B**, yielding the final product **6bd** as a white solid (67 %): m.p. > 120 °C (dec); IR (KBr, cm^{-1}) 1158, 1213, 1377, 1447, 1591, 1699, 1755, 2850, 2900, 2945; δ_H (400 MHz, $CDCl_3$) 1.26-1.39 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.41 (s, 9H, $C(CH_3)_3$), 1.71-1.83 (m, 5H (cyclohexyl)), 2.40-2.46 (m, 1H, CH), 3.14-3.75 (vbs, 3H, NCH_3), 4.23 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.88 (s, 2H, CH_2Ar), 5.05 (s, 2H, CH_2CO_2Et), 5.17 (vbs, 2H, CH_2 (furfuryl)), 6.17-6.23 (m, 1H, CH (furfuryl)), 6.28-6.29 (m, 1H, CH (furfuryl)), 7.07 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.27 (d, *J* =

8.2 Hz, 2H, 2 CH (Ar)), 7.32-7.33 (m, 1H, CH (furfuryl)), 7.75 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{33}H_{42}N_6O_5Na$ [M+Na] *m/z* = 625.32, fnd. 625.49.



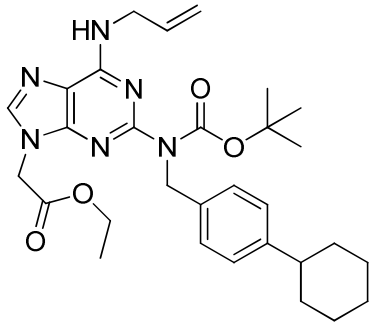
ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(cyclopentylamino)-9H-purin-9-yl)acetate (6be)

Purine **5b** was treated with cyclopentanamine according to general procedure **B**, yielding the final product **6be** as a white solid (81 %): m.p. > 133 °C (dec); IR (KBr, cm^{-1}) 3549, 2978, 2926, 2851, 1752, 1702, 1541, 1515, 1481, 1438, 1391, 1238, 1212, 1158, 1110, 1022; δ_H (400 MHz, $CDCl_3$) 1.18-1.46 (m, 14H, 5H (cyclohexyl) and $C(CH_3)_3$), 1.28 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.46-1.54 (m, 4H (cyclopentyl)), 1.71-1.82 (m, 7H, 5H (cyclohexyl) and 2H (cyclopentyl)), 2.03 (bs, 2H (cyclopentyl)), 2.41-2.47 (m, 1H, CH), 4.23 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.44 (bs, 1H, NC<u>H</u>), 4.87 (s, 2H, CH_2Ar), 5.05 (s, 2H, CH_2CO_2Et), 5.76 (bs, 1 H, NH), 7.09 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.30 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.74 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{32}H_{45}N_6O_4$ [M+H] *m/z* = 577.34, fnd. 577.46.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(cyclohexylamino)-9H-purin-9-yl)acetate (6bf)

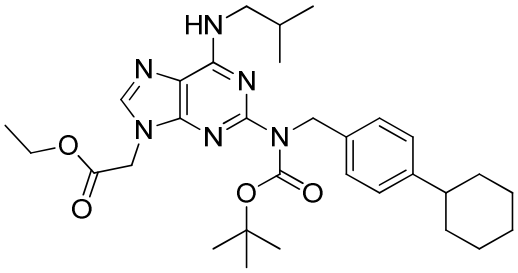
Purine **5b** was treated with cyclohexanamine according to general procedure **B**, yielding the final product **6bf** as a white solid (88 %): m.p. = 75–84 °C; IR (KBr, cm^{-1}) 3413, 2913, 2850, 1712, 1475, 1357, 1237, 1213, 1150; δ_H (400 MHz, $CDCl_3$) 1.15-1.40 (m, 13H, 5H, (cyclohexyl)), 5H, (NH-cyclohexyl) and $CO_2CH_2C\underline{H}_3$)), 1.42 (s, 9H, $C(CH_3)_3$), 1.57-1.86 (m, 10H, 5H, (cyclohexyl) and 5H, (NH-cyclohexyl)), 2.38-2.48 (m, 1H, CH), 4.02 (bs, 1H, HNC<u>H</u>), 4.24 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.87 (s, 2H, CH_2Ar), 5.03 (s, 2H, CH_2CO_2Et), 5.58 (bs, 1H, NH), 7.09 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.30 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.73 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{33}H_{47}N_6O_4$ [M+H] *m/z* = 591.36, fnd. 591.54.



ethyl 2-(6-(allylamino)-2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-9H-purin-9-

yl)acetate (6bi).

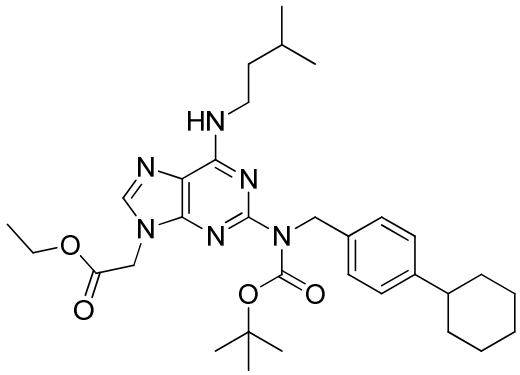
Purine **5b** was treated with allylamine according to general procedure **B**, yielding the final product **6bi** as a white solid (82 %): m.p. = 125–134 °C; IR (KBr, cm^{-1}) 3559, 3475, 3410, 3245, 2930, 2858, 1755, 1700, 1630, 1615, 1480, 1408; δ_H (400 MHz, $CDCl_3$) 1.25-1.40 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.41 (s, 9H, $C(CH_3)_3$), 1.70-1.86 (m, 5H (cyclohexyl)), 2.40-2.48 (m, 1H, CH), 4.25 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.26 (bs, 2 H, $C\underline{H}_2CHCH_2$), 4.88 (s, 2H, CH_2Ar), 5.05 (s, 2H, CH_2CO_2Et), 5.15 (dd, *J* = 10.3 and 1.5 Hz, 1H, $CH_2CHC\underline{H}_2$), 5.25 (dd, *J* = 17.1 and 1.5 Hz, 1H, $CH_2CHC\underline{H}_2$), 5.70 (bs, 1H, NH), 5.89-5.99 (m, 1H, $CH_2C\underline{H}CH_2$), 7.09 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.29 (d, *J* = 8.3 Hz, 2H, 2 CH (Ar)), 7.75 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{30}H_{41}N_6O_4$ [M+H] *m/z* = 549.31, fnd. 549.45.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(isobutylamino)-9H-purin-9-yl)acetate (6bj).

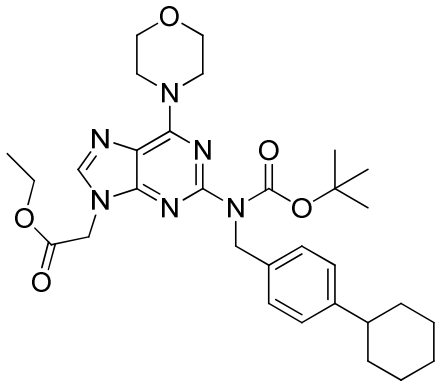
Purine **5b** was treated with isobutylamine according to general procedure **B**, yielding the final product **6bj** as a white solid (77 %): m.p. = 70 - 85 °C; IR (KBr, cm^{-1}) 2926, 1755, 1532, 1479, 1448, 1385, 1352, 1240, 1210, 1152; δ_H (400 MHz, $CDCl_3$) 0.93 (s, 3H, $CH_2CH(C\underline{H}_3)_2$), 0.95 (s, 3H, $CH_2CH(C\underline{H}_3)_2$), 1.21-1.40 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.42 (s, 9H, $C(CH_3)_3$), 1.67-1.84 (m, 5H (cyclohexyl)), 1.86-1.96 (m, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.40-2.47 (m, 1H, $CH(CH_3)_2$), 3.37 (bs, 2H, $C\underline{H}_2CH(CH_3)_2$), 4.24 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.88 (s, 2H, CH_2Ar), 5.04 (s, 2H, CH_2CO_2Et), 5.75 (bs, 1H, NH), 7.08 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.30

(d, J = 8.1 Hz, 2H, 2 CH (Ar)), 7.74 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{31}H_{44}N_6O_4Na$ [M+Na] *m/z* = 587.34, fnd. 587.51.



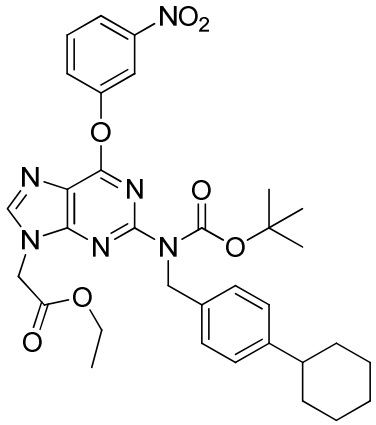
ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(isopentylamino)-9H-purin-9-yl)acetate (6bl).

Purine **5b** was treated with isoamylamine according to general procedure **B**, yielding the final product **6bl** as a clear viscous oil (88 %): IR (KBr, cm^{-1}) 2924, 2851, 1755, 1704, 1514, 1434, 1385, 1244, 1160, 1023; δ_H (400 MHz, $CDCl_3$) 0.91 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 0.93 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 1.25-1.39 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.41 (s, 9H, $C(CH_3)_3$), 1.49-1.55 (m, 1H, $(CH_2)_2C\underline{H}(CH_3)_2$), 1.65-1.83 (m, 7H, $CH_2C\underline{H}_2CH(CH_3)_2$ and 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 3.58 (bs, 2H, $C\underline{H}_2CH_2CH(CH_3)_2$), 4.24 (q, J = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.87 (s, 2H, CH_2Ar), 5.06 (s, 2H, CH_2CO_2Et), 5.58 (bs, 1H, NH), 7.08 (d, J = 8.1 Hz, 2H, 2 CH (Ar)), 7.30 (d, J = 8.1 Hz, 2H, 2 CH (Ar)), 7.73 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{32}H_{47}N_6O_4$ [M+H] *m/z* = 579.36, fnd. 579.48.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-morpholino-9H-purin-9-yl)acetate (6bm).

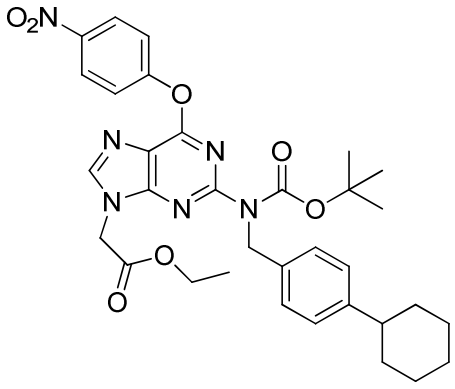
Purine **5b** was treated with morpholine according to general procedure **B**, yielding the final product **6bm** as a white solid (81 %): m.p. = 166-167 °C; IR (KBr, cm^{-1}) 2925, 2852, 1755, 1698, 1590, 1479, 1440, 1384, 1305, 1240, 1209, 1154, 1116; δ_H (400 MHz, $CDCl_3$) 1.21-1.40 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.41 (s, 9H, $C(CH_3)_3$), 1.75-1.84 (m, 5H (cyclohexyl)), 2.40-2.45 (m, 1H, CH), 3.77 (t, *J* = 4.7 Hz, 4H, 2 $C\underline{H}_2$, (morpholine)), 4.19 (bs, 4H, 2 $C\underline{H}_2$, (morpholine)), 4.24 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.88 (s, 2H, CH_2Ar), 5.03 (s, 2H, $C\underline{H}_2CO_2Et$), 7.08 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.27 (d, *J* = 7.5 Hz, 2H, 2 CH (Ar)), 7.73 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{31}H_{42}N_6O_5Na$ [M+Na] *m/z* = 601.32, fnd. 601.49.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(3-nitrophenoxy)-9H-purin-

9-yl)acetate (6bn).

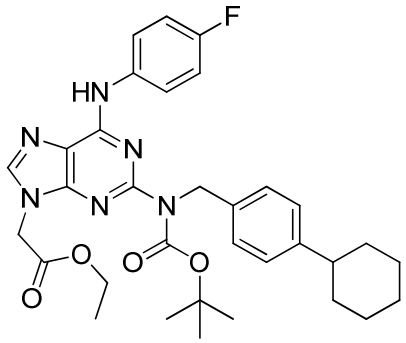
Purine **5b** was treated with 3-nitrophenol according to general procedure **D**, yielding the final product **6bn** as a white solid (82 %): m.p. = 57.8-79.3 °C; IR (KBr, cm^{-1}) 3546, 3480, 3425, 2930, 2846, 1750, 1708, 1625, 1580, 1545, 1455, 1360; δ_H (400 MHz, $CDCl_3$) 1.19-1.41 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.33 (s, 9H, $C(CH_3)_3$), 1.7-1.84 (m, 5H (cyclohexyl)), 2.40-2.45 (m, 1H, CH), 4.27 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.92 (s, 2H, CH_2Ar), 4.97 (s, 2H, $C\underline{H}_2CO_2Et$), 6.98-7.09 (m, 4H, 4 CH (Ar)), 7.52 (t, *J* = 8.2 Hz, 1H, CH (Ar)), 7.61 (d, *J* = 8.1 Hz, 1H, CH (Ar)), 8.01 (s, 1H, CH, (H-8)), 8.09 (d, *J* = 8.1 Hz, 1H, CH (Ar)), 8.2 (t, *J* = 2.2 Hz, 1H, CH (Ar)); LRMS (MS-ES), calcd for $C_{33}H_{38}N_6O_7Na$ [M+Na] *m/z* = 653.28, fnd. 653.39.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(4-nitrophenoxy)-9H-purin-9-yl)acetate (6bo).

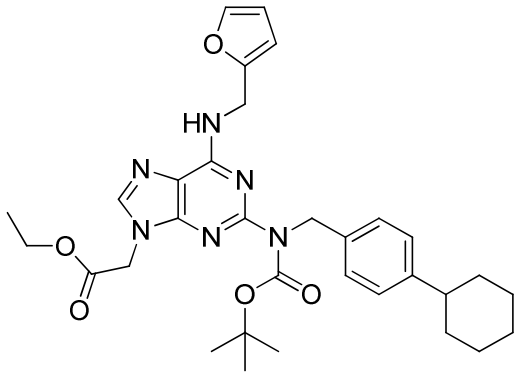
Purine **5b** was treated with 4-nitrophenol according to general procedure **B**, yielding the final product **6bo** as a clear viscous oil (79 %): IR (KBr, cm^{-1}) 3530, 3480, 3425, 2925, 2850, 1770, 1725, 1640, 1625, 1575, 1540, 1350; δ_H (400 MHz, $CDCl_3$) 1.20-1.33 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.36 (s, 9H, $C(CH_3)_3$), 1.7-1.83 (m, 5H (cyclohexyl)), 2.43-2.46 (m, 1H, CH), 4.25 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.94 (s, 2H, CH_2Ar), 4.99 (s, 2H, $C\underline{H}_2CO_2Et$), 7.06 (s, 4H, 4 CH (Ar)), 7.45 (d, *J* = 9.0 Hz, 2H, 2 CH (Ar)), 8.13 (s, 1H, CH (H-8)), 8.22 (d, *J* = 9.2 Hz,

2H, 2 CH (Ar)); LRMS (MS-ES), calcd for $C_{33}H_{38}N_6O_7Na$ [M+Na] *m/z* = 653.28, fnd. 653.30.



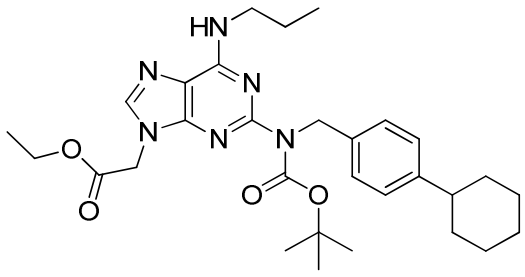
ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-((4-fluorophenyl)amino)-9H-purin-9-yl)acetate (6bp)

Purine **5b** was treated with 4-fluoroaniline according to general procedure **C**, yielding the final product **6bp** as a white solid (56 %): m.p. > 125 °C (dec); IR (KBr, cm^{-1}) 2926, 2852, 1707, 1593, 1389, 1229, 1157; δ_H (400 MHz, $CDCl_3$) 1.20-1.38 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.41 (s, 9H, $C(CH_3)_3$), 1.70-1.85 (m, 5H (cyclohexyl)), 2.43-2.48 (m, 1H, CH), 4.25 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.91 (s, 2H, CH_2Ar), 5.10 (s, 2H, CH_2CO_2Et), 6.91-6.96 (m, 2H, 2 CH (Ar)), 7.11 (d, *J* = 8.0 Hz, 2H, 2 CH (Ar)), 7.27 (d, *J* = 8.0 Hz, 2H, 2 CH (Ar)), 7.57 (bs, 1H, CH (Ar)), 7.67-7.72 (m, 2H, 2 CH (Ar)), 7.83 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{33}H_{39}FN_6O_4Na$ [M+Na] *m/z* = 625.30, fnd. 625.43.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-((furan-2-ylmethyl)amino)-9H-purin-9-yl)acetate (6bq)

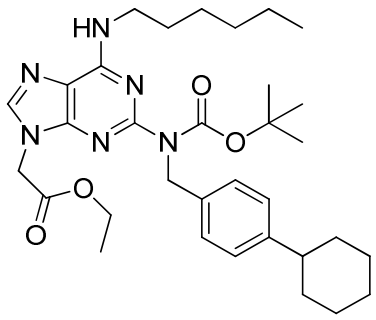
Purine **5b** was treated with furfurylamine according to general procedure **B**, yielding the final product **6bq** as a white solid (87 %): m.p. > 120 (dec) °C; IR (KBr, cm^{-1}) 2925, 2851, 1755, 1703, 1481, 1438, 1390, 1237, 1156, 1109; δ_H (400 MHz, $CDCl_3$) 1.25-1.40 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.41 (s, 9H, $C(CH_3)_3$), 1.71-1.82 (m, 5H (cyclohexyl)), 2.41-2.47 (m, 1H, CH), 4.23 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.76 (bs, 2H, CH_2 (furfuryl)), 4.88 (s, 2H, CH_2Ar), 5.07 (s, 2H, CH_2CO_2Et), 6.01 (bs, 1H, NH (furfuryl)), 6.19-6.20 (m, 1H, CH (furfuryl)), 6.29-6.30 (m, 1H, CH (furfuryl)), 7.09 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.29 (d, *J* = 8.0 Hz, 2H, 2 CH (Ar)), 7.34-7.35 (m, 1H, CH (furfuryl)), 7.75 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{32}H_{41}N_6O_5$ [M+H] *m/z* = 589.31, fnd. 589.43.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(propylamino)-9H-purin-9-

yl)acetate (6bs).

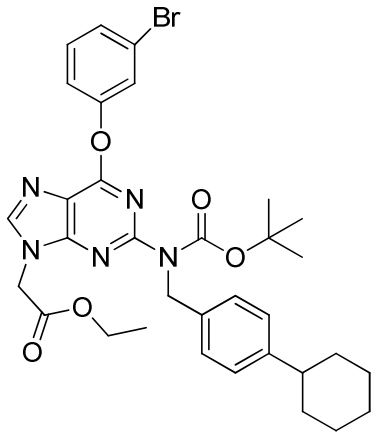
Purine **5b** was treated with n-propylamine according to general procedure **B**, yielding the final product **6bs** as a clear viscous oil (77 %): IR (KBr, cm^{-1}) 2926, 1703, 1384, 1213, 1156; δ_H (400 MHz, $CDCl_3$) 0.95 (t, *J* = 7.4 Hz, 3H, $NHCH_2CH_2C\underline{H}_3$), 1.20-1.33 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.42 (s, 9H, $C(CH_3)_3$), 1.64 (m, 2H, $NHCH_2C\underline{H}_2CH_3$) 1.7-1.83 (m, 5H (cyclohexyl)), 2.40-2.46 (m, 1H, CH), 3.52 (bs, 2H, $NHC\underline{H}_2CH_2CH_3$), 4.24 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.87 (s, 2H, CH_2Ar), 5.05 (s, 2H, $C\underline{H}_2CO_2Et$), 5.70 (bs, 1H, NH), 7.08 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.30 (d, *J* = 8.0Hz, 2H, 2 CH (Ar)), 7.73 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{30}H_{43}N_6O_4$ [M+H] *m/z* = 551.33, fnd. 551.54.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(hexylamino)-9H-purin-9-yl)acetate (6bt).

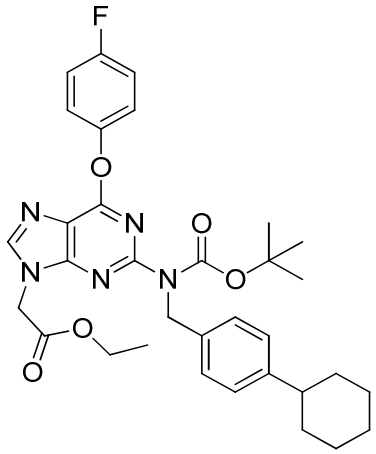
Purine **5b** was treated with n-hexylamine according to general procedure **B**, yielding the final product **6bt** as a white solid (81 %): m.p. = 115–121 °C; IR (KBr, cm^{-1}) 3546, 3490, 3425, 2925, 2860, 1770, 1700, 1625, 1530, 1440, 1360, 1246; δ_H (400 MHz, $CDCl_3$) 0.88 (t, *J* = 7.2 Hz, 3H, $NH(CH_2)_4C\underline{H}_3$), 1.16-1.34 (m, 14H, 5H (cyclohexyl) and 6H $NH(CH_2)_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$ and $CO_2CH_2C\underline{H}_3$), 1.42 (s, 9H, $C(CH_3)_3$), 1.51-1.76 (m, 7H, 5H (cyclohexyl) and $NHCH_2C\underline{H}_2(CH_2)_3CH_3$)), 2.40-2.46 (m, 1H, CH), 3.54 (bs, 2H, $NHC\underline{H}_2(CH_2)_4CH_3$), 4.24 (q, *J* =

7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.87 (s, 2H, CH_2Ar), 5.05 (s, 2H, CH_2CO_2Et), 5.93 (bs, 1H, NH), 7.08 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.30 (d, *J* = 8.0Hz, 2H, 2 CH (Ar)), 7.74 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{33}H_{49}N_6O_4$ [M+H] *m/z* = 593.37, fnd. 593.51.



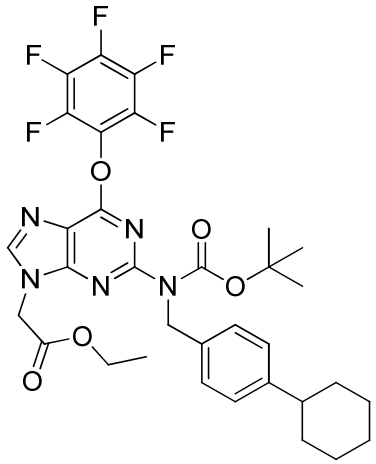
ethyl 2-(6-(3-bromophenoxy)-2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-9H-purin-9-yl)acetate (6bu).

Purine **5b** was treated with 3-bromophenol according to general procedure **D**, yielding the final product **6bu** as a clear viscous oil (76 %): IR (KBr, cm^{-1}) 3546, 3480, 3425, 3230, 2930, 2840, 1750, 1710, 1625, 1580, 1470, 1400; δ_H (400 MHz, $CDCl_3$) 1.14-1.34 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.35 (s, 9H, $C(CH_3)_3$), 1.67-1.86 (m, 5H, (cyclohexyl)), 2.38-2.49 (m, 1H, CH), 4.26 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.93 (s, 2H, CH_2Ar), 4.95 (s, 2H, CH_2CO_2Et), 7.12-7.07 (m, 4H, 4 CH (Ar)), 7.17-7.21 (m, 1H, CH (Ar)), 7.23-7.28 (m, 1H, CH (Ar)), 7.35-7.41 (m, 1H, CH (Ar)), 7.49 (t, *J* = 2.0 Hz, CH, (Ar)), 7.98 (s, 1H, CH, (H-8)); LRMS (MS-ES), calcd for $C_{33}H_{39}BrN_5O_5$ [M+H] *m/z* = 664.21, fnd. 664.28.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(4-fluorophenoxy)-9H-purin-9-yl)acetate (6bv).

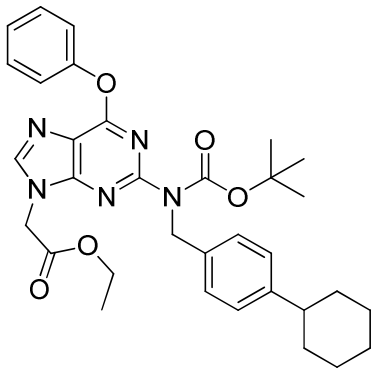
Purine **5b** was treated with 4-fluorophenol according to general procedure **D**, yielding the final product **6bv** as a white solid (67 %): m.p. = 93–97 °C; IR (KBr, cm^{-1}) 3546, 3470, 3408, 3230, 2925, 2846, 1760, 1700, 1625, 1500, 1440, 1400; δ_H (400 MHz, $CDCl_3$) 1.14-1.32 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.35 (s, 9H, $C(CH_3)_3$), 1.70-1.84 (m, 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 4.26 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.90 (s, 2H, CH_2Ar), 4.95 (s, 2H, $C\underline{H}_2CO_2Et$), 7.02-7.07 (m, 6H, 6 CH (Ar)), 7.18-7.21 (m, 2H, 2 CH (Ar)), 7.98 (s, 1H, CH, (H-8)); LRMS (MS-ES), calcd for $C_{33}H_{39}FN_5O_5$ [M+H] m/z = 604.29, fnd. 604.37.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(perfluorophenoxy)-9H-

purin-9-yl)acetate (6bw).

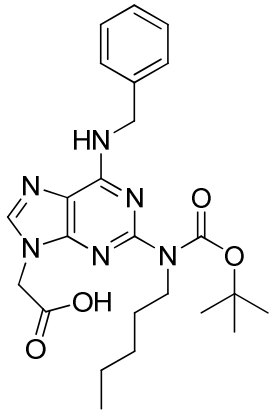
Purine **5b** was treated with pentafluorophenol according to general procedure **D**, yielding the final product **6bw** as a white solid (75 %): m.p. = 91–110 °C; IR (KBr, cm^{-1}) 3546, 3475, 3425, 2905, 2860, 1760, 1730, 1630, 1560, 1400, 1370, 1230; δ_H (400 MHz, $CDCl_3$) 1.21-1.34 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.37 (s, 9H, $C(CH_3)_3$), 1.71-1.84 (m, 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 4.28 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.88 (s, 2H, CH_2Ar), 4.98 (s, 2H, $C\underline{H}_2CO_2Et$), 6.98 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.04 (d, *J* = 8.2Hz, 2H, 2 CH (Ar)), 8.04 (s, 1H, CH, (H-8)); LRMS (MS-ES), calcd for $C_{33}H_{34}F_5N_5O_5Na$ [M+Na] *m/z* = 698.25, fnd. 698.34.



ethyl 2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-phenoxy-9H-purin-9-yl)acetate (6bx).

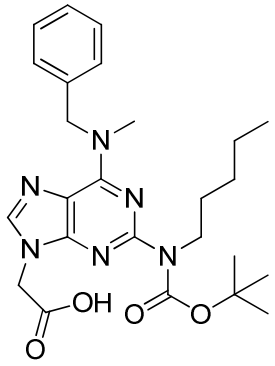
Purine **5b** was treated with phenol according to general procedure **D**, yielding the final product **6bx** as a white solid (79 %): m.p. = 104–110 °C; IR (KBr, cm^{-1}) 3546, 3470, 3425, 2940, 2850, 1750, 1700, 1630, 1570, 1490, 1395, 1230; δ_H (400 MHz, $CDCl_3$) 1.11-1.40 (m, 8H, 5H (cyclohexyl) and $CO_2CH_2C\underline{H}_3$), 1.34 (s, 9H, $C(CH_3)_3$), 1.70-1.83 (m, 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 4.26 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.91 (s, 2H, CH_2Ar), 4.95 (s, 2H, $C\underline{H}_2CO_2Et$), 7.01-7.07 (m, 4H, 4 CH (Ar)), 7.22-7.26 (m, 3H, 3 CH (Ar)), 7.37-7.42 (m, 2H, 2 CH (Ar)), 7.97 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{33}H_{40}N_5O_5$ [M+H] *m/z* = 586.30,

fnd. 586.43.



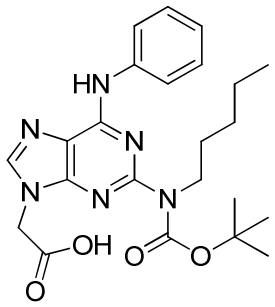
2-(6-(benzylamino)-2-((*tert*-butoxycarbonyl)(pentyl)amino)-9H-purin-9-yl)acetic acid (7aa)

Purine **6aa** was treated according to general procedure **E**, to yield lyophilized product **7aa** as a white solid (72 %): m.p. > 198 (dec) °C; IR (KBr, cm^{-1}) 3549, 3476, 3414, 2959, 1707, 1624, 1390, 1367, 1355, 1300, 1271, 1217; δ_H (400 MHz, DMSO-d_6) 0.77 (t, J = 7.0 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.09-1.23 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.35 (s, 9H, $C(CH_3)_3$), 1.52-1.59 (m, 2H, $CH_2C\underline{H}_2(CH_2)_2H_3$), 3.59 (t, J = 6.9 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.65 (bs, 2H, $C\underline{H}_2Ar$), 4.89 (s, 2H, $C\underline{H}_2CO_2H$), 7.20 (t, J = 7.2 Hz, 1H, CH (Ar)), 7.28 (t, J = 7.5 Hz, 2H, 2 CH (Ar)), 7.30-7.35 (m, 2H, 2 CH (Ar)), 8.07 (s, 1H, CH (H-8)), 8.43 (m, 1H, NH) 13.26 (vbs, 1H, $CH_2CO_2\underline{H}$); δ_C (100 MHz, DMSO-d_6) 13.8, 21.7, 27.8, 27.9, 28.3, 43.0, 43.7, 47.3, 79.3, 115.7, 126.5, 127.0, 127.1, 128.0, 140.0, 141.3, 149.8, 153.9, 155.2, 169.2; HRMS (MS- ES), calcd for $C_{24}H_{33}N_6O_4$ [M+H] m/z = 469.2562, fnd. 469.2557; *rp*HPLC t_R: condition (I) 14.246 (II) 39.742 minutes, purity 91.2 %and 93.4%.



2-(6-(benzyl(methyl)amino)-2-((*tert*-butoxycarbonyl)(pentyl)amino)-9H-purin-9-yl)acetic acid (7ab)

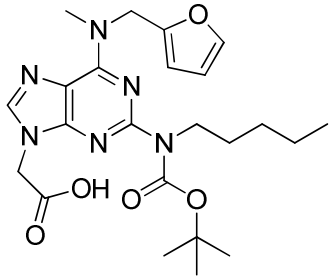
Purine **6ab** was treated according to general procedure **E**, to yield lyophilized product **7ab** as a white solid (87 %): m.p. = 116-127 °C; IR (KBr, cm^{-1}) 3294, 2924, 2444, 2356, 1399, 1198; δ_H (400 MHz, DMSO-d_6) 0.82 (m, 3H, $(CH_2)_4C\underline{H}_3$), 1.21-1.29 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.38 (s, 9H, $C(CH_3)_3$), 1.43-1.58 (m, 2H, $(CH_2)_3C\underline{H}_2CH_3$), 3.15-3.60 (bm, 3H, NCH_3), 3.60-3.70 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.78 (s, 2H, $C\underline{H}_2CO_2H$) , 4.86-5.55 (bm, 2H, CH_2Ar), 7.24-7.31 (m, 5H, 2 CH (Ar)), 7.71 (s, 1H, CH (H-8)), 13.23 (vbs, 1H, $CH_2CO_2\underline{H}$); HRMS (MS- ES), calcd for $C_{25}H_{35}N_6O_4$ [M+H] *m/z* = 483.2701, fnd. 483.2714; *rp*HPLC t_R: condition (I) 15.031 (II) 38.982 minutes, purity 90.0 %and 90.4%.



2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(phenylamino)-9H-purin-9-yl)acetic acid (7ac)

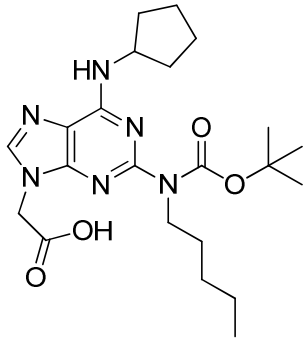
Purine **6ac** was treated according to general procedure **E**, to yield lyophilized product **7ac** as an off-white solid (75 %): m.p. > 139 °C (dec); IR (KBr, cm^{-1}) 3424, 2958, 1704, 1442, 1364, 1164;

δ_H (400 MHz, DMSO-d_6) 0.81 (t, J = 7.0 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.23-1.27 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.39 (s, 9H, $C(CH_3)_3$), 1.52-1.59 (m, 2H, $(CH_2)_3C\underline{H}_2CH_3$), 3.72 (t, J = 7.4 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.90 (s, 2H, $C\underline{H}_2CO_2H$), 7.03 (t, J = 7.3 Hz, 1H, CH (Ar)), 7.29 (t, J = 7.9 Hz, 2H, 2 CH (Ar)), 7.96 (d, J = 7.5Hz, 2H, 2 CH (Ar)), 8.21 (s, 1H, CH (H-8)), 9.93 (s, 1H, NH); δ_C (100 MHz, DMSO-d_6) 13.8, 21.7, 27.7, 27.9, 28.3, 44.2, 47.5, 79.6, 116.6, 120.4, 122.4, 128.1, 139.5, 142.3, 150.6, 151.5, 153.7, 154.7, 169.1;. HRMS (MS- ES), calcd for $C_{23}H_{31}N_6O_4$ [M+H] m/z = 455.2387, fnd. 455.2401; rpHPLC t_R: condition (I) 14.988 (II) 38.416 minutes, purity 93.1 %and 98.2%.



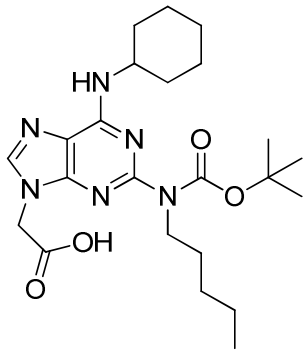
2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-((furan-2-ylmethyl)(methyl)amino)-9H-purin-9-yl)acetic acid (7ad)

Purine **6ad** was treated according to general procedure **E**, to yield product **7ad** as a clear viscous oil (92%): IR (KBr, cm^{-1}) 3549, 3471, 3415, 3120, 2958, 2925, 2855, 1703, 1637, 1618, 1591, 1460; δ_H (400 MHz, $CDCl_3$) 0.83-0.88 (m, 3H, $(CH_2)_4C\underline{H}_3$), 1.25-1.34 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.56-1.69 (m, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.50 (vbs, 3H, CH_3(furfuryl)), 3.80 (t, J = 7.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.86 (s, 2H, $C\underline{H}_2CO_2H$), 5.22 (vbs, 2H, CH_3(furfuryl)), 6.29-6.33 (m, 2H, CH (furfuryl)), 7.35-7.36 (m, 1H, CH (furfuryl)), 7.81 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{23}H_{31}N_6O_5$ [M-H] m/z = 471.24, fnd. 471.25.



2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(cyclopentylamino)-9H-purin-9-yl)acetic acid (7ae)

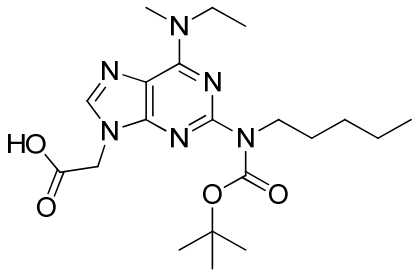
Purine **6ae** was treated according to general procedure **E**, to yield product **7ae** as a white solid (95 %): m.p. > 140-146 °C; IR (KBr, cm^{-1}) 3551, 3474, 3413, 2959, 2929, 2871, 1713, 1619, 1475, 1387, 1365, 1273; δ_H (400 MHz, $CDCl_3$) 0.82-0.90 (m, 3H, $(CH_2)_4C\underline{H}_3$), 1.23-1.32 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.49 (s, 9H, $C(CH_3)_3$), 1.56-1.80 (m, 8H, $CH_2C\underline{H}_2(CH_2)_2CH_3$ and 3 CH_2 (cyclopentyl)), 2.00-2.11 (m, 2H, CH_2 (cyclopentyl)), 3.80-3.86 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.45 (bs, 1H, CH (cyclopentyl)), 4.89 (s, 2H, $C\underline{H}_2CO_2H$), 7.10 (s, 1H, NH), 7.90 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{22}H_{33}N_6O_4$ [M-H] *m/z* = 445.26, fnd. 445.27.



2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(cyclohexylamino)-9H-purin-9-yl)acetic acid (7af)

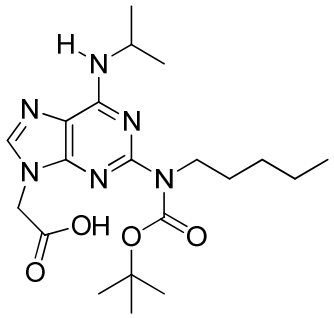
Purine **6af** was treated according to general procedure **E**, to yield product **7af** as a white solid (70

%): m.p. = 140-158 °C; IR (KBr, cm^{-1}) 3550, 3413, 2930, 2855, 1741, 1707, 1618, 1450, 1382, 1366, 1257, 1242; δ_H (400 MHz, $CDCl_3$) 0.82-0.90 (m, 3H, $(CH_2)_4C\underline{H}_3$), 1.17-1.42 (m, 10H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$ and 3 CH_2(cyclohexyl)), 1.49 (s, 9H, $C(CH_3)_3$), 1.60-1.72(m, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 1.75-1.83 (m, 2H, CH_2 (cyclohexyl)), 2.00-2.07 (m, 2H, CH_2 (cyclohexyl)), 3.78-3.85 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.03 (bs, 1H, CH (cyclohexyl)), 4.89 (s, 2H, $C\underline{H}_2CO_2H$), 6.90 (bs, 1H, NH), 7.89 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{23}H_{35}N_6O_4$ [M-H] *m/z* = 459.28, fnd. 459.35.



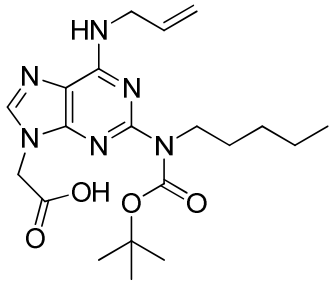
2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(ethyl(methyl)amino)-9H-purin-9-yl)acetic acid (7ag)

Purine **6ag** was treated according to general procedure **E**, to yield product **7ag** as a clear oil (94 %): IR (KBr, cm^{-1}) 3414, 2961, 2931, 2859, 1723, 1596, 1492, 1456, 1433, 1418, 1380, 1296; δ_H (400 MHz, $CDCl_3$) 0.89 (t, *J* = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.25-1.36 (m, 7H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$ and $NCH_2C\underline{H}_3$), 1.52 (s, 9H, $C(CH_3)_3$), 1.68 (p, 7.4 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.21-3.76 (bm, 3H, NCH_3), 3.85-3.91 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.28 (bs, 2H, $NC\underline{H}_2CH_3$), 5.00 (s, 2H, $C\underline{H}_2CO_2H$), 7.74 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{20}H_{31}N_6O_4$ [M-H] *m/z* = 419.25, fnd. 419.36.



2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(isopropylamino)-9H-purin-9-yl)acetic acid (7ah)

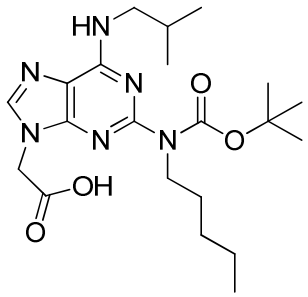
Purine **6ah** was treated according to general procedure **E**, to yield product **7ah** as a white solid (98 %): m.p. > 146 °C (dec); IR (KBr, cm^{-1}) 3413, 3314, 2976, 2929, 1714, 1613, 1468, 1403, 1384, 1367, 1325, 1275; δ_H (400 MHz, $CDCl_3$) 0.82-0.91 (m, 3H, $(CH_2)_4C\underline{H}_3$), 1.20-1.41 (m, 10H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$ and $CH(C\underline{H}_3)_2$), 1.52 (s, 9H, $C(CH_3)_3$), 1.58-1.72 (m, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.80-3.90 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.33 (bs, 1H, $C\underline{H}(CH_3)_2$), 4.92 (s, 2H, $C\underline{H}_2CO_2H$), 7.26 (bs, 1H, NH), 7.96 (bs, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{20}H_{31}N_6O_4$ [M-H] *m/z* = 419.25, fnd. 419.36.



2-(6-(allylamino)-2-((*tert*-butoxycarbonyl)(pentyl)amino)-9H-purin-9-yl)acetic acid (7ai)

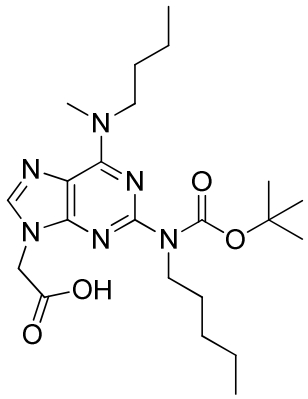
Purine **6ai** was treated according to general procedure **E**, to yield product **7ai** as a white solid (96%): m.p. = 174-176 °C; IR (KBr, cm^{-1}) 3550, 3475, 3414, 2931, 1711, 1619, 1477, 1445, 1403, 1386, 1365, 1349; δ_H (400 MHz, $CDCl_3$) 0.86 (t, *J* = 6.8 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.26-1.34 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.49 (s, 9H, $C(CH_3)_3$), 1.64 (p, *J* = 7.3 Hz, 2H,

$CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.82 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.24 (bs, 2H, $C\underline{H}_2CHCH_2$), 4.89 (s, 2H, $C\underline{H}_2CO_2H$), 5.16 (d, *J* = 10.1 Hz, 1H, $CH_2CHC\underline{H}_2$), 5.30 (d, *J* = 17.4 Hz, 1H, $CH_2CHC\underline{H}_2$), 5.91-6.03 (m, 1H, $CH_2C\underline{H}CH_2$), 7.86 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{20}H_{29}N_6O_4$ [M-H] *m/z* = 417.23, fnd. 417.37.



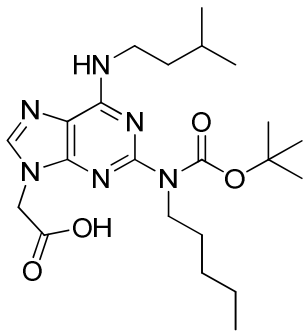
2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(isobutylamino)-9H-purin-9-yl)acetic acid (7aj)

Purine **6aj** was treated according to general procedure **E**, to yield product **7aj** as a white solid (96 %): m.p. = 160-162 °C; IR (KBr, cm^{-1}) 3413, 3315, 2958, 2928, 2872, 1704, 1621, 1597, 1478, 1430, 1404, 1383; δ_H (400 MHz, $CDCl_3$) 0.82-0.91 (m, 3H, $(CH_2)_4C\underline{H}_3$), 0.96-1.02 (m, 6H, $CH(C\underline{H}_3)_2$), 1.20-1.35 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.51 (s, 9H, $C(CH_3)_3$), 1.61-1.73 (m, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 1.94-2.08 (m, 1H, $C\underline{H}(CH_3)_2$), 3.36-3.44 (m, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.78-3.92 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.92 (s, 2H, $C\underline{H}_2CO_2H$), 7.94 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{21}H_{33}N_6O_4$ [M-H] *m/z* = 433.26, fnd. 433.37.



2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(butyl(methyl)amino)-9H-purin-9-yl)acetic acid (7ak)

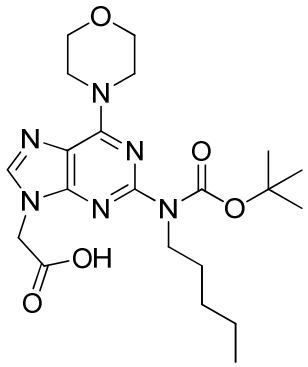
Purine **6ak** was treated according to general procedure **E**, to yield product **7ak** as a clear viscous oil (89 %): IR (KBr, cm^{-1}) 3549, 3476, 3414, 2958, 2926, 1702, 1637, 1618, 1384; δ_H (400 MHz, $CDCl_3$) 0.84-0.89 (m, 3H, $(CH_2)_4C\underline{H}_3$), 0.94 (t, *J* = 7.3 Hz, 3H, $(CH_2)_3C\underline{H}_3$), 1.25-1.43 (m, 6H, $CH_2CH_2C\underline{H}_2CH_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 1.59-1.70 (m, 4H, $CH_2C\underline{H}_2CH_2CH_3$ and $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.14-3.86 (bm, 4H, $C\underline{H}_2(CH_2)_2CH_3$ and $C\underline{H}_2(CH_2)_3CH_3$), 3.79 (t, *J* = 7.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.84 (s, 2H, $C\underline{H}_2CO_2H$), 7.78 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{22}H_{35}N_6O_4$ [M-H] *m/z* = 447.28, fnd. 447.38.



2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(isopentylamino)-9H-purin-9-yl)acetic acid (7al)

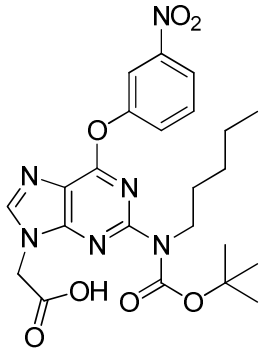
Purine **6al** was treated according to general procedure **E**, to yield product **7al** as a white solid (67

%): m.p. = 169-173 °C; IR (KBr, cm^{-1}) 3550, 3414, 3322, 2957, 2930, 2871, 1741, 1708, 1621, 1468, 1383, 1365; δ_H (400 MHz, $CDCl_3$) 0.82-0.90 (m, 3H, $(CH_2)_4C\underline{H}_3$), 0.92 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 0.94 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 1.19-1.35 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.50 (s, 9H, $C(CH_3)_3$), 1.54-1.76 (m, 5H, $CH_2C\underline{H}_2(CH_2)_2CH_3$ and $CH_2C\underline{H}_2C\underline{H}(CH_3)_2$), 3.57 (bs, 2H, $C\underline{H}_2(CH_2)_2(CH_3)_2$), 3.80-3.89 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.05 (bs, 1H, NH), 4.91 (s, 2H, $C\underline{H}_2CO_2H$), 7.92 (bs, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{22}H_{35}N_6O_4$ [M-H] *m/z* = 447.28, fnd. 447.38.



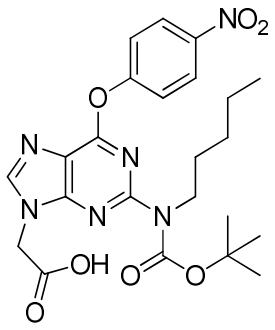
2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-morpholino-9H-purin-9-yl)acetic acid (7am)

Purine **6am** was treated according to general procedure **E**, to yield product **7am** as a lyophilized white powder (94 %): m.p. > 143 (dec); IR (KBr, cm^{-1}) 2959, 2929, 2857, 1588, 1478, 1446, 1388, 1304, 1266, 1241, 1137; δ_H (400 MHz, DMSO-d_6) 0.87 (t, *J* = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.17-1.26 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.38 (s, 9H, $C(CH_3)_3$), 1.52 (p, *J* = 7.3 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.64-3.75 (m, 6H, $C\underline{H}_2(CH_2)_3CH_3$ and 2 CH_2 (morpholine)), 4.17 (bs, 4H, 2 CH_2 (morpholine)), 4.76 (s, 2H, $C\underline{H}_2CO_2H$), 8.07 (s, 1H, CH (H-8)); δ_C (100 MHz, DMSO-d_6) 13.8, 21.6, 27.8, 27.9, 28.3, 44.6, 45.0, 47.3, 66.1, 79.3, 115.9, 141.0, 151.8, 152.9, 153.8, 154.5, 169.2; HRMS (MS-ES), calcd for $C_{21}H_{33}N_6O_5$ [M+H] *m/z* = 449.2506, fnd. 449.2497; *rp*HPLC t_R: condition (I) 13.883 (II) 32.404 minutes, purity 90.8 %and 90.9%.



2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(3-nitrophenoxy)-9H-purin-9-yl)acetic acid (7an)

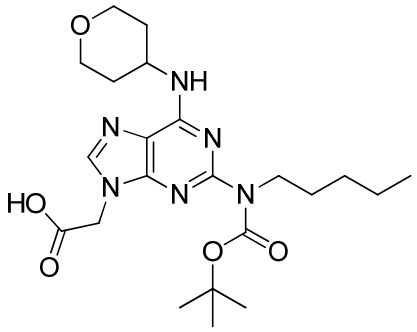
Purine **6an** was treated according to general procedure **E**, to yield product **7an** as a lyophilized white solid (62 %): m.p. > 85 °C (dec); IR (KBr, cm^{-1}) 3595, 3385, 3115, 2945, 1533, 1246; δ_H (400 MHz, DMSO-d_6) 0.75 (t, *J* = 7.2 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 0.97-1.13 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.29 (s, 9H, $C(CH_3)_3$), 1.31-1.38 (m, 2H, $(CH_2)_3C\underline{H}_2CH_3$), 3.52 (t, J = 7.4 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 5.03 (s, 2H, $C\underline{H}_2CO_2H$), 7.78 (t, *J* = 8.1 Hz, 1H, CH (Ar)), 7.85-7.88 (m, 1H, CH (Ar)), 8.18-8.21 (m, 1H, CH (Ar)), 8.28 (t, *J* = 2.2 Hz, 1H, CH (Ar), 8.43 (s, 1H, CH (H-8)), 13.44 (vbs, 1H, $CH_2CO_2\underline{H}$); δ_C (100 MHz, DMSO-d_6) 13.7, 21.6, 27.7, 28.2, 28.5, 44.3, 47.7, 80.2, 116.8, 117.6, 120.5, 129.1, 130.8, 145.4 148.3, 152.3, 153.2, 154.0, 154.2, 158.2, 168.9; HRMS (MS- ES), calcd for $C_{23}H_{29}N_6O_7$ [M+H] *m/z* = 501.2095, fnd. 501.2092; *rp*HPLC t_R: condition (I) 14.230 (II) 36.038 minutes, purity 98.3% and 97.16%.



2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-(4-nitrophenoxy)-9H-purin-9-yl)acetic acid

(7ao)

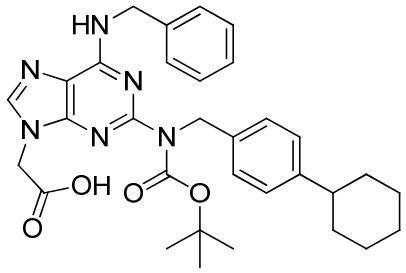
Purine **6ao** was treated according to general procedure **E**, to yield product **7ao** as a lyophilized white solid (70 %): m.p. > 194 °C (dec); IR (KBr, cm^{-1})3119, 2959, 2931, 2861, 1723, 1579, 1525, 1489, 1407, 1347, 1252, 1209, 1137, 1045; δ_H (400 MHz, DMSO-d_6) 0.74 (t, J = 7.2 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 0.99-1.17 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.31 (s, 9H, $C(CH_3)_3$), 1.34-1.39 (m, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 2.81-3.03 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 5.04 (s, 2H, $C\underline{H}_2CO_2H$), 7.66 (d, J = 9.0 Hz, 2H, 2 CH (Ar)), 8.43 (s, 1H, CH (H-8)), 8.35 (d, J = 9.1 Hz, 2H, 2 CH (Ar)); δ_C (100 MHz, DMSO-d_6) 13.7, 21.7, 27.6, 27.8, 28.3, 41.0, 44.3, 47.8, 112.9, 116.8, 123.2, 125.2, 144.7, 145.6, 153.1, 154.3, 157.2, 158.4, 168.8; HRMS (MS- ES), calcd for $C_{23}H_{29}N_6O_7$ [M+H] *m/z* = 501.2110, fnd. 501.2092; *rp*HPLC t_R: condition (I) 14.647 (II) 36.729 minutes, purity 98.2 %and 98.3%. (Decomposed- remaking)



2-(2-((*tert*-butoxycarbonyl)(pentyl)amino)-6-((tetrahydro-2H-pyran-4-yl)amino)-9H-purin-9-yl)acetic acid (7ay).

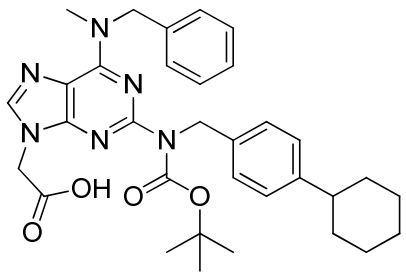
Purine **6ay** was treated according to general procedure **E**, to yield product **7ay** as a lyophilized a white powder (88 %): m.p. > 112 °C (dec); IR (KBr, cm^{-1}) 3666, 2958, 2927, 2856, 1707, 1475, 1384, 1367, 1275, 1241, 1151; δ_H (400 MHz, DMSO-d_6) 0.83 (t, J = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.08-1.26 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.38 (s, 9H, $C(CH_3)_3$), 1.47-1.88 (m, 6H, 2 $C\underline{H}_2$ (tetrahydropyran) and $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.34-3.51 (m, 2H, $C\underline{H}_2$ (tetrahyropyran)), 3.64 (t, J =

7.1 Hz, 2H, C<u>H</u>$_2$(CH$_2$)$_3$CH$_3$), 3.85-3.96 (m, 2H, C<u>H</u>$_2$ (tetrahydropyran)), 4.22 (bs, 1H, CH), 4.77 (s, 2H, C<u>H</u>$_2$CO$_2$Et) 7.74 (bs, 1H, NH), 8.02 (s, 1H, CH (H-8)); δ_C (100 MHz, DMSO-d_6); 13.9, 21.7, 27.9, 28.0, 28.4, 32.3, 44.3, 46.2, 47.5, 66.3, 79.2, 115.8, 141.3, 150.0, 153.5, 153.9, 155.2, 169.2 HRMS (MS- ES), calcd for $C_{22}H_{35}N_6O_5$ [M+H] *m/z* = 463.2666, fnd. 463.2663; *rp*HPLC t_R: condition (I) 13.944 (II) 32.497 minutes, purity 90.8 %and 91.6%.



2-(6-(benzylamino)-2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-9H-purin-9-yl)acetic acid (7ba)

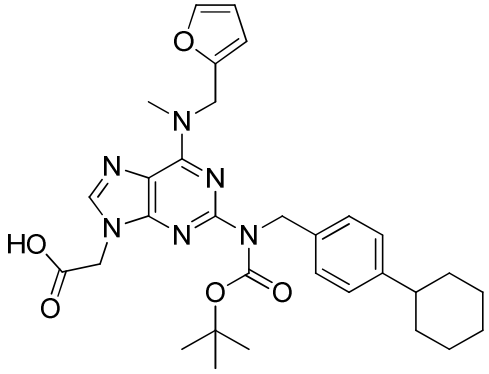
Purine **6ba** was treated according to general procedure **E**, to yield product **7ba** as a white solid (63 %): m.p. > 147 °C (dec); IR (KBr, cm^{-1}) 3552, 3476, 3414, 3261, 2919, 2849, 1741, 1631, 1478, 1446, 1421, 1398; δ_H (400 MHz, $CDCl_3$) 1.20-1.42 (m, 14H, 5H (cyclohexyl) and C(CH$_3$)$_3$), 1.69-1.81 (m, 5H (cyclohexyl)), 2.39-2.45 (m, 1H, CH), 4.72 (bs, 2H, HNC<u>H</u>$_2$), 4.87 (bs, 2H, CH$_2$Ar), 5.04 (s, 2H, C<u>H</u>$_2$CO$_2$H), 6.94-7.27 (m, 10H, NH and 9 CH (Ar)), 7.88 (bs, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{32}H_{37}N_6O_4$ [M-H] *m/z* = 569.30, fnd. 569.40.



2-(6-(benzyl(methyl)amino)-2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-9H-purin-

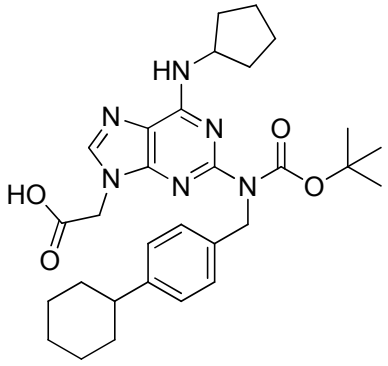
9-yl)acetic acid (7bb)

Purine **6bb** was treated according to general procedure **E**, to yield product **7bb** as a white solid (90 %): m.p. > 126-131 °C; IR (KBr, cm^{-1}) 3414, 2922, 2850, 1743, 1702, 1655, 1596, 1480, 1445, 1398, 1367, 1282; δ_H (400 MHz, $CDCl_3$) 1.28-1.43 (m, 14H, 5H (cyclohexyl) and $C(CH_3)_3$), 1.71-1.81 (m, 5H (cyclohexyl)), 2.38-2.42 (m, 1H, CH), 2.97-3.77 (bm, 3H, $NC\underline{H}_3$), 4.94 (s, 2H, CH_2Ar), 5.03 (bs, 2H, $C\underline{H}_2CO_2H$), 5.39-5.62 (bm, 2H, $CH_3NC\underline{H}_2$), 6.98-7.29 (m, 9H, 9 CH (Ar)), 7.73 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{33}H_{39}N_6O_4$ [M-H] *m/z* = 583.31, fnd. 583.38.



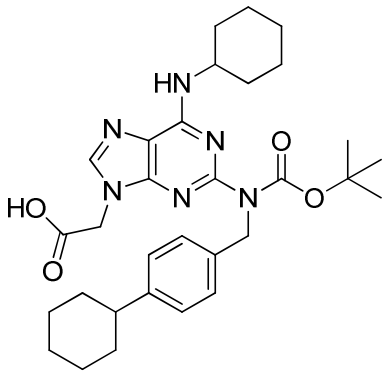
2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-((furan-2-ylmethyl) (methyl)amino)-9H-purin-9-yl)acetic acid (7bd)

Purine **6bd** was treated according to general procedure **E**, to yield product **7bd** as a white solid (72 %): m.p. > 130 °C (dec); IR (KBr, cm^{-1}) 2919, 2849, 1741, 1648, 1601, 1445, 1406, 1392, 1367, 1290, 1274, 1245; δ_H (400 MHz, $CDCl_3$) 1.20-1.40 (m, 5H, 5H (cyclohexyl)), 1.43 (s, 9H, $C(CH_3)_3$), 1.71-1.82 (m, 5H (cyclohexyl)), 2.42-2.47 (m, 1H, CH), 3.05-3.81(m, 5H, CH_2 and CH_3 (furfuryl)), 5.01 (bs, 2H, CH_2Ar), 5.12 (s, 2H, $C\underline{H}_2CO_2H$), 6.26-6.38 (m, 2H, 2 CH (furfuryl)), 7.10 (d, *J* = 7.7 Hz, 2H, 2 CH (Ar)), 7.24 (d, *J* = 8.3 Hz, 2H, 2 CH (Ar)), 7.34 (s, 1H, CH (furfuryl)), 7.77 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{31}H_{37}N_6O_5$ [M-H] *m/z* = 573.29, fnd. 573.37.



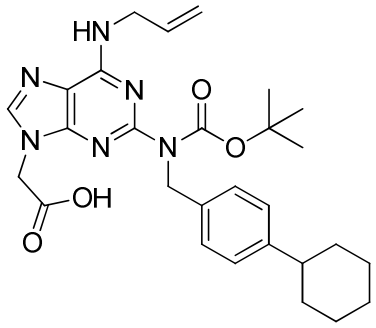
2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(cyclopentylamino)-9H-purin-9-yl)acetic acid (7be)

Purine **6be** was treated according to general procedure **E**, to yield product **7be** as a white solid (68 %): m.p. > 144 °C; IR (KBr, cm^{-1}) 3550, 3475, 3414, 2925, 2851, 1706, 1618, 1448, 1366, 1241; δ_H (400 MHz, $CDCl_3$) 1.18-1.46 (m, 14H, 5H (cyclohexyl) and $C(CH_3)_3$), 1.46-1.54 (m, 4H (cyclopentyl)), 1.71-1.82 (m, 7H, 5H (cyclohexyl) and 2H (cyclopentyl)), 1.91-1.99 (bs, 2H (cyclopentyl), 2.42-2.47 (m, 1H, CH), 4.40 (bs, 1H, NCH), 4.86 (s, 2H, CH_2Ar), 5.05(s, 2H, $C\underline{H}_2CO_2H$), 7.00 (bs, 1 H, NH), 7.07 (d, *J* = 7.7 Hz, 2H, 2 CH (Ar)), 7.28 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.79 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{30}H_{39}N_6O_4$ [M-H] *m/z* = 547.31, fnd. 547.44.



2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(cyclohexylamino)-9H-purin-9-yl)acetic acid (7bf)

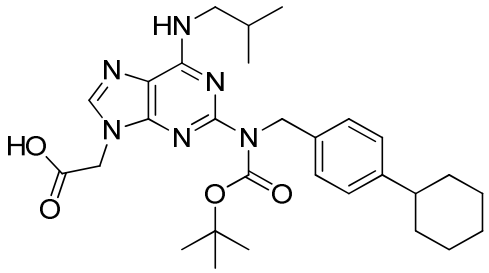
Purine **6bf** was treated according to general procedure **E**, to yield product **7bf** as a white solid (89 %): m.p. = 118-123 °C; IR (KBr, cm^{-1}) 2926, 2852, 1617, 1477, 1449, 1389, 1367, 1245, 1158, 1108; δ_H (400 MHz, $CDCl_3$) 1.16-1.38 (m, 10H, 5H (cyclohexyl) and 5H (NH-cyclohexyl)), 1.35 (s, 9H, $C(CH_3)_3$), 1.59-1.94 (m, 10H, 5H (cyclohexyl) and 5H (NH-cyclohexyl)), 2.38-2.48 (m, 1H, CH), 3.90 (bs, 1H, HNC<u>H</u>), 4.79 (s, 2H, CH_2Ar), 5.00 (s, 2H, C<u>H</u>$_2CO_2H$), 6.29 (bs, 1H, NH), 7.08 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.24 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.71 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{31}H_{41}N_6O_4$ [M-H] *m/z* = 561.33, fnd. 561.44.



2-(6-(allylamino)-2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-9H-purin-9-yl)acetic acid (7bi).

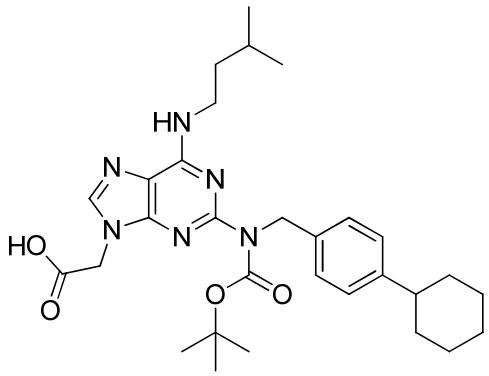
Purine **6bi** was treated according to general procedure **E**, to yield product **7bai** as a white solid (88 %): m.p. > 123 °C (dec); IR (KBr, cm^{-1}) 3549, 3476, 3414, 3275, 2920, 2849, 1745, 1618, 1449, 1404, 1366, 1249; δ_H (400 MHz, $CDCl_3$) 1.17-1.30 (m, 5H, (cyclohexyl)), 1.36 (s, 9H, $C(CH_3)_3$), 1.68-1.87 (m, 5H (cyclohexyl)), 2.36-2.49 (m, 1H, CH), 4.15 (bs, 2 H, C<u>H</u>$_2CHCH_2$), 4.88 (s, 2H, CH_2Ar), 5.06 (s, 2H, C<u>H</u>$_2CO_2H$), 5.12 (dd, *J* = 10.6 and 1.5 Hz, 1H, CH_2CHC<u>H</u>$_2$), 5.21 (dd, *J* = 17.2 and 1.5 Hz, 1H, CH_2CHC<u>H</u>$_2$), 5.79-5.97 (m, 1H, CH_2C<u>H</u>CH_2), 6.39 (bs, 1H, NH), 7.09 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.25 (d, *J* = 7.2 Hz, 2H, 2 CH (Ar)), 7.74 (s, 1H, CH

(H-8)); LRMS (MS-ES), calcd for $C_{28}H_{35}N_6O_4$ [M-H] *m/z* = 519.28, fnd. 519.30.



2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(isobutylamino)-9H-purin-9-yl)acetic acid (7bj).

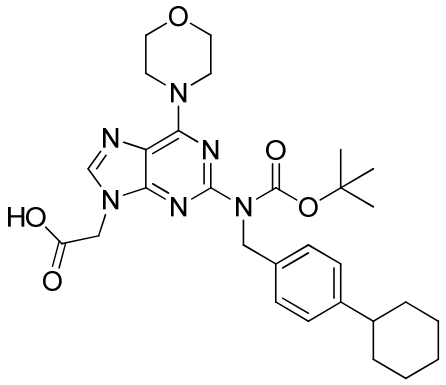
Purine **6bj** was treated according to general procedure **E**, to yield product **7bj** as a white solid (86 %): m.p. > 124-126 °C; IR (KBr, cm^{-1}) 3549, 3476, 3414, 3335, 2929, 1759, 1683, 1619, 1591, 1434, 1388, 1343; δ_H (400 MHz, $CDCl_3$) 0.93 (s, 3H, $CH_2CH(C\underline{H}_3)_2$), 0.95 (s, 3H, $CH_2CH(C\underline{H}_3)_2$), 1.19-1.38 (m, 5H (cyclohexyl), 1.39 (s, 9H, $C(CH_3)_3$), 1.67-1.79 (m, 5H, (cyclohexyl)), 1.84-1.93 (m, 1H, $CH_2C\underline{H}(CH_3)_2$) 2.40-2.47 (m, 1H, CH), 3.37 (bs, 2H, $C\underline{H}_2CH(CH_3)_2$), 4.88 (s, 2H, CH_2Ar), 5.04 (s, 2H, $C\underline{H}_2CO_2H$), 6.03 (bs, 1H, NH), 7.1 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.23 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.74 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{29}H_{39}N_6O_4$ [M-H] *m/z* = 535.31, fnd. 535.35.



2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(isopentylamino)-9H-purin-9-yl)acetic acid (7bl).

Purine **6bl** was treated according to general procedure **E**, to yield product **7bl** as a white solid (93

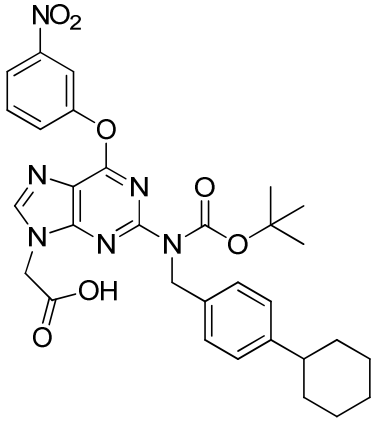
%): m.p. > 128 °C (dec); IR (KBr, cm^{-1}) 2925, 2852, 1707, 1485, 1440, 1400, 1379, 1246; δ_H (400 MHz, $CDCl_3$) 0.87 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 0.88 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 1.25-1.39 (m, 5H, (cyclohexyl)), 1.39 (s, 9H, $C(CH_3)_3$), 1.46-1.66 (m, 3H, $CH_2C\underline{H}_2C\underline{H}(CH_3)_2$), 1.67-1.84 (m, 5H, (cyclohexyl)), 2.39-2.47 (m, 1H, CH), 3.50 (bs, 2H, $C\underline{H}_2CH_2CH(CH_3)_2$), 4.88 (s, 2H, CH_2Ar), 5.08 (s, 2H, $C\underline{H}_2CO_2H$), 6.76 (bs, 1H, NH), 7.07 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.27 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.76 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{30}H_{41}N_6O_4$ [M-H] *m/z* = 549.33, fnd. 549.39.



2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-morpholino-9H-purin-9-yl)acetic acid (7bm)

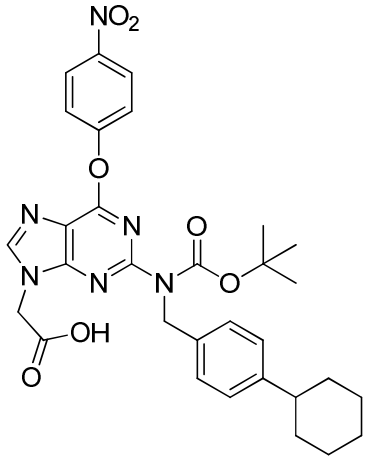
Purine **6bm** was treated according to general procedure **E**, to yield product **7bm** as a lyophilized white powder (83 %): m.p. = 166-167 °C; IR (KBr, cm^{-1}) 3666,2958, 2927, 2856, 1707, 1475, 1385, 1367, 1275, 1242, 1151, 1011; δ_H (400 MHz, DMSO-*d*$_6$) 1.17-1.36 (m, 5H, (cyclohexyl)), 1.37 (s, 9H, $C(CH_3)_3$), 1.66-1.77 (m, 5H, (cyclohexyl)), 2.38-2.44 (m, 1H, CH), 3.68 (t, *J* = 4.5 Hz, 4H, 2 CH_2, (morpholine)), 4.12 (bs, 4H, 2 CH_2, (morpholine)), 4.85 (s, 2H, CH_2Ar), 4.91 (s, 2H, $C\underline{H}_2CO_2H$), 7.1 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.21 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 8.07 (s, 1H, CH (H-8)); δ_C (100 MHz, DMSO-*d*$_6$) 25.5, 26.3, 27.8, 33.9, 43.4, 44.2, 50.3, 66.1, 79.9, 115.8, 126.3, 127.3, 136.5, 140.8, 145.9, 151.8, 152.7, 154.1, 154.5, 169.2; HRMS (MS-ES), calcd for $C_{29}H_{39}N_6O_5$ [M+H] *m/z* = 551.2962, fnd. 551.2976; *rp*HPLC t_R: condition (I) 15.722

(II) 41.975 minutes, purity 91.8% and 90.7%.



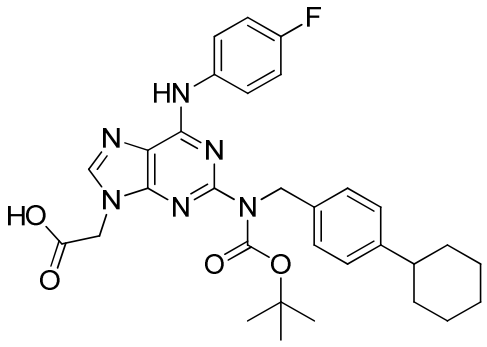
2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(3-nitrophenoxy)-9H-purin-9-yl)acetic acid (7bn).

Purine **6bn** was treated according to general procedure **E**, to yield product **7bn** as a white solid (90 %): m.p. = 103–107 °C; IR (KBr, cm^{-1}) 2925, 2852, 1578, 1532, 1448, 1402, 1368, 1351, 1275, 1236, 1154; δ_H (400 MHz, $CDCl_3$) 1.19 (s, 9H, $C(CH_3)_3$), 1.31-1.42 (m, 5H, (cyclohexyl)), 1.72-1.84 (m, 5H, (cyclohexyl)), 2.37-2.44 (m, 1H, CH), 4.79 (s, 2H, CH_2Ar), 4.88 (s, 2H, $C\underline{H}_2CO_2H$), 6.92 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 6.97 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.45-7.51 (m, 2H, 2 CH (Ar)), 7.99-8.08 (m, 2H, 2 CH (Ar)), 8.10 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{31}H_{33}N_6O_7$ [M-H] *m/z* = 601.25, fnd. 601.42.



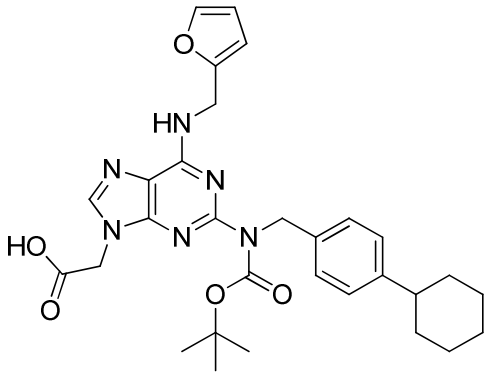
2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(4-nitrophenoxy)-9H-purin-9-yl)acetic acid (7bo).

Purine **6bo** was treated according to general procedure **E**, to yield product **7bo** as a white solid (83 %): m.p. > 126 °C (dec); IR (KBr, cm^{-1}) 3550, 3474, 3415, 2924, 2853, 1747, 1638, 1617, 1576, 1524, 1486, 1457; δ_H (400 MHz, $CDCl_3$) 1.19-1.28 (m, 5H, (cyclohexyl)), 1.35 (s, 9H, $C(CH_3)_3$), 1.7-1.83 (m, 5H, (cyclohexyl)), 2.40-2.49 (m, 1H, CH), 4.91 (s, 2H, CH_2Ar), 5.02 (s, 2H, $C\underline{H}_2CO_2H$), 6.95-7.12 (m, 4H, 4 CH (Ar)), 7.34-7.41 (m, 2H, 2 CH (Ar)), 8.02 (s, 1H, CH (H-8)), 8.17-8.22 (m, 2H, 2 CH (Ar)); LRMS (MS-ES), calcd for $C_{31}H_{33}N_6O_7$ [M-H] *m/z* = 601.25, fnd. 601.31.



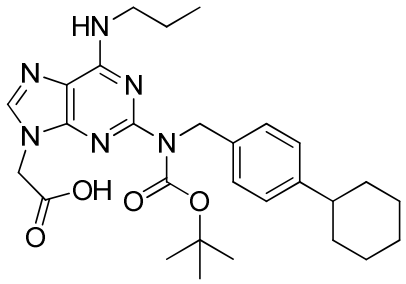
2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-((4-fluorophenyl)amino)-9H-purin-9-yl)acetic acid (7bp).

Purine **6bp** was treated according to general procedure **E**, to yield product **7bp** as a white solid (92 %): m.p. > 124 °C (dec); IR (KBr, cm^{-1}) 3549, 3475, 3415, 3238, 2925, 1710, 1638, 1617, 1509, 1474, 1449, 1408; δ_H (400 MHz, $CDCl_3$) 1.22-1.42 (m, 14H, 5H (cyclohexyl) and $C(CH_3)_3$), 1.67-1.85 (m, 5H (cyclohexyl)), 2.40-2.45 (m, 1H, CH), 4.99 (s, 2H, CH_2Ar), 5.10 (s, 2H, $C\underline{H}_2CO_2H$), 6.88-6.92 (m, 2H, 2 CH (Ar)), 7.10 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.25 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.68-7.72 (m, 2H, 2 CH (Ar)), 7.95 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{31}H_{34}FN_6O_4$ [M-H] *m/z* = 573.27, fnd. 573.37.



2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-((furan-2-ylmethyl)amino)-9H-purin-9-yl)acetic acid (7bq)

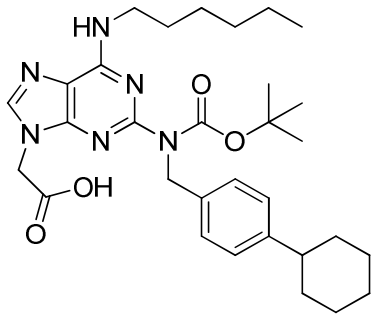
Purine **6bq** was treated according to general procedure **E**, to yield product **7bq** as a white solid (91 %): m.p. > 132 (dec) °C; IR (KBr, cm^{-1}) 2920, 2850, 1744, 1701, 1478, 1445, 1391, 1366, 1301, 1241, 1209, 1161, 1109; δ_H (400 MHz, $CDCl_3$) 1.19-1.38 (m, 5H, 5H (cyclohexyl)), 1.40 (s, 9H, $C(CH_3)_3$), 1.79-1.81 (m, 5H (cyclohexyl)), 2.39-2.45 (m, 1H, CH), 4.73 (bs, 2H, CH_2 (furfuryl)), 4.85 (s, 2H, CH_2Ar), 5.06 (s, 2H, $C\underline{H}_2CO_2H$), 6.16-6.17 (m, 1H, CH (furfuryl)), 6.26 (bs, 1H, NH), 6.26-6.27 (m, 1H, CH (furfuryl)), 7.07 (d, *J* = 7.5 Hz, 2H, 2 CH (Ar)), 7.29 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.30-7.31 (m, 1H, CH (furfuryl)), 7.76 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{30}H_{35}FN_6O_5$ [M-H] *m/z* = 559.27, fnd. 559.36.



2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(propylamino)-9H-purin-9-yl)acetic (7bs).

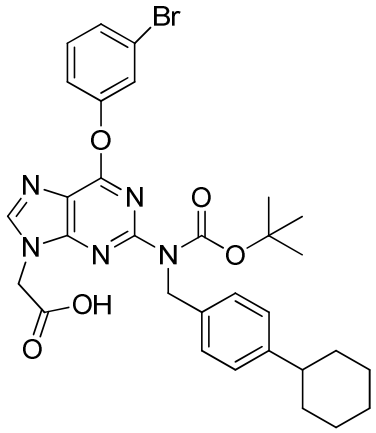
Purine **6bs** was treated according to general procedure **E**, to yield product **7bs** as a white solid (89 %): m.p. > 68°C (dec); IR (KBr, cm^{-1}) 3412, 2926, 2852, 1515, 1482, 1448, 1381, 1244,

1156; δ_H (400 MHz, $CDCl_3$) 0.91 (t, *J* = 7.3 Hz, 3H, $NHCH_2CH_2C\underline{H}_3$), 1.21 (s, 9H, $C(CH_3)_3$), 1.28-1.43 (m, 5H (cyclohexyl)), 1.59 (m, 2H, $NHCH_2C\underline{H}_2CH_3$), 1.7-1.83 (m, 5H (cyclohexyl)), 2.40-2.46 (m, 1H, CH), 3.42 (bs, 2H, $NHC\underline{H}_2CH_2CH_3$), 4.81 (s, 2H, CH_2Ar), 5.00 (s, 2H, $C\underline{H}_2CO_2H$), 6.12 (bs, 1H, NH), 7.08 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.23 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.67 (s, 1H, CH, (H-8)); LRMS (MS-ES), calcd for $C_{28}H_{37}N_6O_4$ [M-H] *m/z* = 521.30, fnd. 521.42.



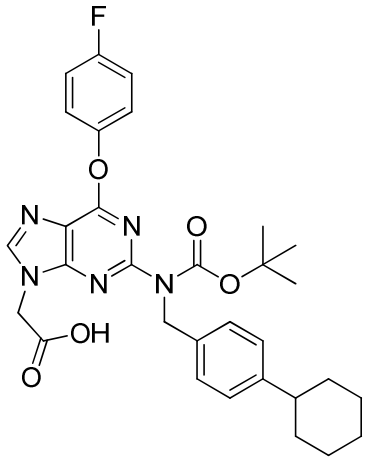
2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(hexylamino)-9H-purin-9-yl)acetic acid (7bt).

Purine **6bt** was treated according to general procedure **E**, to yield product **7bt** as a white solid (85 %): m.p. > 122 °C (dec); IR (KBr, cm^{-1}) 3414, 2956, 2926, 2853, 1707, 1619, 1514, 1449, 1389, 1242; δ_H (400 MHz, $CDCl_3$) 0.88 (t, *J* = 7.2 Hz, 3H, $NH(CH_2)_5C\underline{H}_3$), 1.11-1.23 (m, 11H, 5H (cyclohexyl), 6H, $NH(CH_2)_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.25 (s, 9H, $C(CH_3)_3$), 1.53-1.76 (m, 7H, 5H, (cyclohexyl) and $NH(CH_2)_4C\underline{H}_2CH_3$)), 2.36-2.47 (m, 1H, CH), 3.40 (bs, 2H, $NHC\underline{H}_2(CH_2)_4CH_3$), 4.53-4.75 (m, 2H, CH_2Ar), 4.95 (s, 2H, $C\underline{H}_2CO_2H$), 7.03-7.23 (m, 4H, 4 CH (Ar)), 7.58 (bs, 1H, NH),7.73 (s, 1H, CH, (H-8)); LRMS (MS-ES), calcd for $C_{31}H_{43}N_6O_4$ [M-H] *m/z* = 563.34, fnd. 563.43.



2-(6-(3-bromophenoxy)-2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-9H-purin-9-yl)acetic acid (7bu).

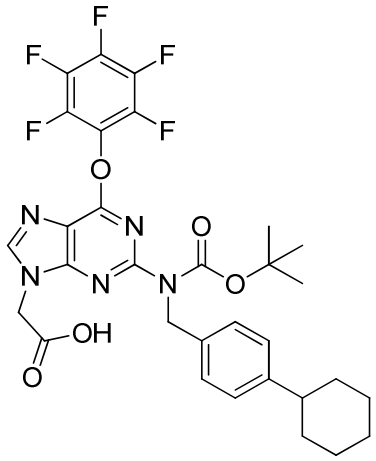
Purine **6bu** was treated according to general procedure **E**, to yield product **7bu** as a white solid (84 %): m.p. > 127 °C (dec); IR (KBr, cm^{-1}) 3550, 3478, 3415, 2924, 2851, 1721, 1709, 1626, 1602, 1577, 1515, 1473; δ_H (400 MHz, $CDCl_3$) 1.10-1.33 (m, 5H, (cyclohexyl)), 1.37 (s, 9H, $C(CH_3)_3$), 1.67-1.85 (m, 5H, (cyclohexyl)), 2.37-2.47 (m, 1H, CH), 4.90 (s, 2H, CH_2, (Ar)), 4.99 (s, 2H, $C\underline{H}_2CO_2H$), 6.98-7.07 (m, 4H, 4 CH (Ar)), 7.12-7.17 (m, 1H, CH (Ar)), 7.23 (t, *J* = 8.1 Hz, 1H, CH (Ar)), 7.36-7.40 (m, 1H, CH (Ar)), 7.45 (t, *J* = 2.0 Hz, 1H, CH (Ar)), 8.13 (s, 1H, CH, (H-8)); LRMS (MS-ES), calcd for $C_{31}H_{33}BrN_5O_5$ [M-H] *m/z* = 634.17, fnd. 634.33.



2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(4-fluorophenoxy)-9H-purin-9-

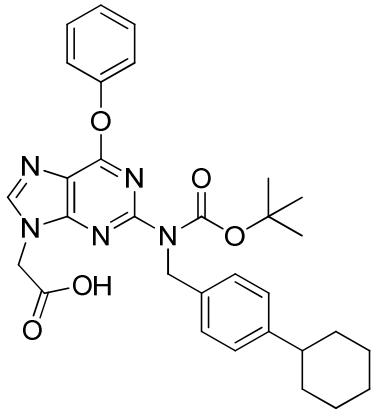
yl)acetic acid (7bv).

Purine **6bv** was treated according to general procedure **E**, to yield product **7bv** as a white solid (86 %): m.p. = 119-133 °C; IR (KBr, cm^{-1}) 3550, 3475, 3415, 3236, 2924, 2852, 1707, 1619, 1587, 1503, 1449, 1393; δ_H (400 MHz, $CDCl_3$) 1.11-1.34 (m, 5H, (cyclohexyl)), 1.36 (s, 9H, $C(CH_3)_3$), 1.70-1.84 (m, 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 4.87 (s, 2H, CH_2Ar), 4.99 (s, 2H, $C\underline{H}_2CO_2H$), 6.97-7.04 (m, 6H, 6 CH (Ar)), 7.12-7.15 (m, 2H, 2 CH (Ar)), 8.11 (s, 1H, CH, (H-8)); LRMS (MS-ES), calcd for $C_{31}H_{33}FN_5O_5$ [M-H] *m/z* = 574.25, fnd. 574.36.



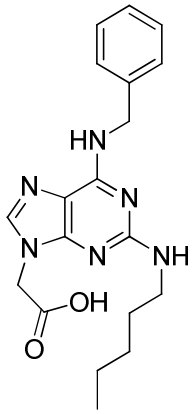
2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(perfluorophenoxy)-9H-purin-9-yl)acetic acid (7bw).

Purine **6bw** was treated according to general procedure **E**, to yield product **7bw** as a white solid (79 %): m.p. > 94.1–104 °C; IR (KBr, cm^{-1}) 3414, 2927, 2852, 1743, 1669, 1637, 1618, 1581, 1522, 1452, 1409, 1380; δ_H (400 MHz, $CDCl_3$) 1.18-1.28 (m, 5H (cyclohexyl)), 1.36 (s, 9H, $C(CH_3)_3$), 1.71-1.85 (m, 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 4.85 (s, 2H, CH_2Ar), 5.06 (s, 2H, $C\underline{H}_2CO_2H$) 6.93 (d, *J* = 8.2 Hz, 2H, 2 CH (Ar)), 7.03 (d, *J* = 8.1Hz, 2H, 2 CH (Ar)), 8.16 (s, 1H, CH, (H-8)); LRMS (MS-ES), calcd for $C_{31}H_{29}F_5N_5O_5$ [M-H] *m/z* = 646.22, fnd.646.35.



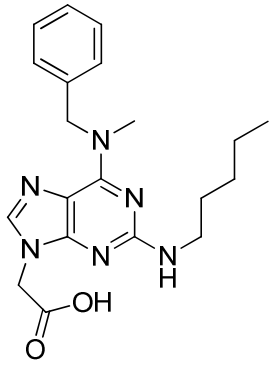
2-(2-((*tert*-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-phenoxy-9H-purin-9-yl)acetic acid (7bx).

Purine **6bx** was treated according to general procedure **E**, to yield product **7bx** as a white solid (83 %): m.p. > 129 °C (dec); IR (KBr, cm^{-1}) 3549, 3477, 3414, 2923, 2851, 1741, 1618, 1578, 1491, 1446, 1391, 1367; δ_H (400 MHz, $CDCl_3$) 1.11-1.34 (m, 5H, (cyclohexyl)), 1.36 (s, 9H, $C(CH_3)_3$), 1.70-1.84 (m, 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 4.87 (s, 2H, CH_2Ar), 4.99 (s, 2H, $C\underline{H}_2CO_2H$), 6.96-7.02 (m, 4H, 4 CH (Ar)), 7.16-7.26 (m, 3H, 3 CH (Ar)), 7.35-7.40 (m, 2H, 2 CH (Ar)), 8.04 (s, 1H, CH, (H-8)); LRMS (MS-ES), calcd for $C_{31}H_{34}N_5O_5$ [M-H] *m/z* = 556.26, fnd. 556.34.



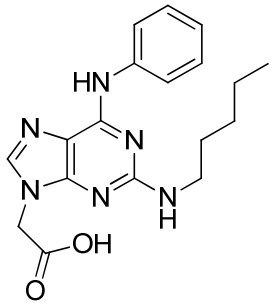
2-(6-(benzylamino)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8aa)

Purine **7aa** was treated according to general procedure **F**, to yield final product **8aa** as an off-white lyophilized powder (85 %): m.p. > 81 °C (dec); IR (KBr, cm^{-1}) 3504, 3281, 2934, 2485, 1351, 1184; δ_H (400 MHz, DMSO-d_6) 0.84 (m, 3H, $(CH_2)_4C\underline{H}_3$), 1.19-1.34 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.42-1.54 (m, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.26 (t, J = 6.9 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.67 (bs, 2H, $C\underline{H}_2Ar$), 4.89 (s, 2H, $C\underline{H}_2CO_2H$), 7.22-7.37 (m, 5H, CH (Ar)), 7.31 (bs, 1H, NH), 7.93 (s, 1H, , CH (H-8)), 8.89 (bs, 1H, NH); HRMS (MS- ES), calcd for $C_{19}H_{25}N_6O_2$ [M+H] *m/z* = 369.2035, fnd. 369.2033; *rp*HPLC t_R: condition (I) 13.814 (II) 33.928 minutes, purity 97.58 %and 96.7%.



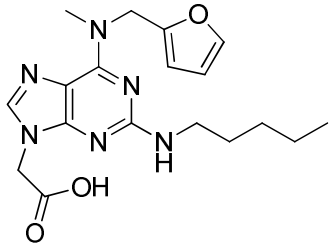
2-(6-(benzyl(methyl)amino)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8ab)

Purine **7ab** was treated according to general procedure **F**, to yield final product **8ab** as a white lyophilized powder (83 %): m.p. = 134-142 °C; IR (KBr, cm^{-1}) 3466, 3080, 1937, 1419, 1246, 1203, 1140; δ_H (400 MHz, DMSO-d_6) 0.82-0.87 (m, 3H, $(CH_2)_4C\underline{H}_3$), 1.12-1.30 (m, 4H, $CH_2CH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.49-1.53 (m, 2H, $CH_2C\underline{H}_2CH_2CH_2CH_3$), 3.04-3.67 (m, 3H, NCH_3), 3.23-3.31 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.67-5.59 (bm, 2H, CH_2Ar), 4.87 (s, 2H, $C\underline{H}_2CO_2H$), 7.22(bs, 1H, NH), 7.24-7.35 (m, 5H, CH (Ar)), 7.83 (s, 1H, CH (H-8)); δ_C (100 MHz, DMSO-d_6) 13.8, 21.8, 27.8, 28.6, 40.3, 41.0, 44.3, 47.4, 112.5, 126.8, 127.1, 127.2, 128.3, 137.0, 138.5, 154.1, 158.5, 169.1; HRMS (MS- ES), calcd for $C_{20}H_{27}N_6O_2$ [M+H] *m/z* = 383.2177, fnd. 383.2190; *rp*HPLC t_R: condition (I) 14.619 (II) 36.342 minutes, purity 97.6 %and 94.9%.



2-(2-(pentylamino)-6-(phenylamino)-9H-purin-9-yl)acetic acid (8ac)

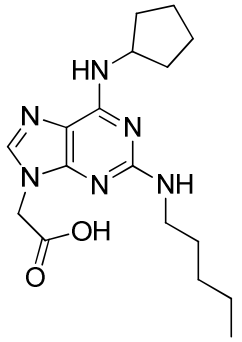
Purine **7aa** was treated according to general procedure **F**, to yield final product **8aa** as a white lyophilized powder (86 %): m.p. > 145 °C (dec); IR (KBr, cm^{-1}) 3071, 2962, 2934, 1736, 1554, 1439, 1359, 1245, 1186, 1142; δ_H (400 MHz, DMSO-d_6) 0.87 (t, J = 7.0 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.22-1.32 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.52-1.59 (m, 2H, $(CH_2)_3C\underline{H}_2CH_3$), 3.27 (t, J = 7.2 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.85 (s, 2H, $C\underline{H}_2CO_2H$), 6.95 (bs, 1H, $N\underline{H}CH_2$), 7.01 (t, J = 7.3 Hz, 1H, CH (Ar)), 7.29 (t, J = 7.9 Hz, 2H, 2 CH (Ar)), 7.93 (s, 1H, CH (H-8)), 7.97(d, J = 7.7Hz, 2H, 2 CH (Ar)), 9.64 (bs, 1H, ArNH); δ_C (100 MHz, DMSO-d_6) 13.9, 21.8, 28.7, 28.3, 41.7, 43.8, 116.6, 120.4, 122.4, 128.1, 139.5, 142.3, 150.6, 151.5, 153.7, 154.7, 169.1; HRMS (MS- ES), calcd for $C_{18}H_{23}N_6O_2$ [M+H] m/z = 355.1870, fnd. 355.1877; *rp*HPLC t_R: condition (I) 13.985 (II) 33.862 minutes, purity 99.09 %and 98.4%.



2-(6-((furan-2-ylmethyl)(methyl)amino)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8ad)

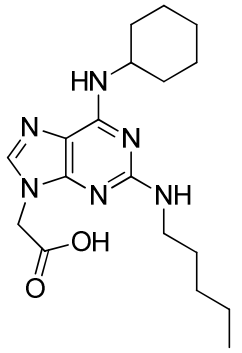
Purine **7ad** was treated according to general procedure **F**, to yield final product **8ad** as a white lyophilized powder (78 %): m.p. > 164 °C (dec); IR (KBr, cm^{-1}) 3631, 2925, 1561, 1456, 1384, 1313, 1147; δ_H (400 MHz, DMSO-d_6) (0.85, t, J = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.22-1.30 (m, 4H,

$(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.50 (p, *J* = 7.1 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.21 (q, *J* = 6.7 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 3.32 (vbs, 3H, NCH_3), 4.55 (s, 2H, $C\underline{H}_2CO_2H$), 5.26 (vbs, 2H, CH_2(furfuryl)), 6.27-6.29 (m, 1H, CH (furfuryl)), 6.33 (bs, 1H, NH), 6.37-6.39 (m, 1H, CH (furfuryl)), 7.55-7.57 (m, 1H, CH (furfuryl)), 7.66 (s, 1H, CH (H-8)); δ_C (100 MHz, DMSO-d_6) 13.9, 21.9, 22.5, 25.3, 28.8, 29.1, 37.7, 38.4, 41.0, 43.6, 112.5, 137.4, 151.0, 154.6, 159.4, 169.7; HRMS (MS-ES), calcd for $C_{18}H_{25}N_6O_3$ [M+H] *m/z* = 373.1994, fnd. 373.1982; *rp*HPLC t_R: condition (I) 14.074 (II) 33.425 minutes, purity 99.3 %and 94.0%.



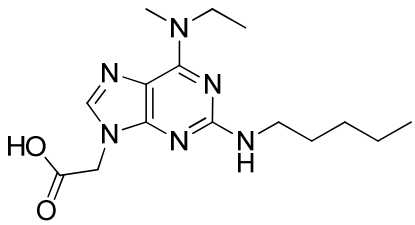
2-(6-(cyclopentylamino)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8ae)

Purine **7ae** was treated according to general procedure **F**, to yield final product **8ae** as a white lyophilized powder (92 %): m.p. > 139 °C (dec); IR (KBr, cm^{-1}) 3233, 3071, 2962, 2934, 1736, 1648, 1554, 1439, 1359, 1245, 1186, 1142; δ_H (400 MHz, DMSO-d_6) 0.87 (t, *J* = 6.8 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.21−1.35 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.50-1.77 (m, 8H, $CH_2C\underline{H}_2(CH_2)_2CH_3$ and 3 CH_2 (cyclopentyl)), 1.92-2.04 (m, 2H, CH_2 (cyclopentyl)), 3.27-3.33 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.35 (vbs, 1H, CH (cyclopentyl)), 4.88 (s, 2H, $C\underline{H}_2CO_2H$), 7.30 (vbs, 1H, NH), 7.96 (bs, 1H, NH), 8.32 (s, 1H, CH (H-8)), 13.34 (br s, 1H, $CH_2CO_2\underline{H}$); HRMS (MS-ES), calcd for $C_{17}H_{27}N_6O_2$ [M+H] *m/z* = 347.2192, fnd. 347.2190; *rp*HPLC t_R: condition (I) 14.582 (II) 34.685 minutes, purity 90.1 %and 97.6%.



2-(6-(cyclohexylamino)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8af)

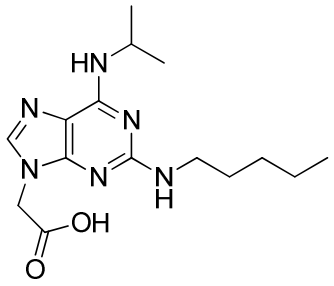
Purine **7af** was treated according to general procedure **F**, to yield final product **8af** as a white lyophilized powder (97 %): m.p. > 188 °C (dec); IR (KBr, cm^{-1}) 2929, 2857, 1736, 1439, 1391, 1246, 1194, 1185, 1141; δ_H (400 MHz, DMSO-d_6) 0.87 (t, J = 6.8 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.10-1.45 (m, 10H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$ and 3 CH_2(cyclohexyl)), 1.53 (p, J = 6.8 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 1.71-1.79 (m, 2H, CH_2 (cyclohexyl)), 1.84-1.99 (m, 2H, CH_2 (cyclohexyl)), 3.26 (t, J = 6.6, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 3.95 (bs, 1H, CH (cyclohexyl)), 4.84 (s, 2H, $C\underline{H}_2CO_2H$), 7.07 (vbs, 1H, NH), 7.86 (bs, 1H, NH), 8.32 (1H, s, CH (H-8)); HRMS (MS-ES), calcd for $C_{18}H_{29}N_6O_2$ [M+H] m/z = 361.2356, fnd. 361.2346; *rp*HPLC t_R: condition (I) 14.966 (II) 37.235 minutes, purity 94.7% and 91.5%.



2-(6-(ethyl(methyl)amino)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8ag)

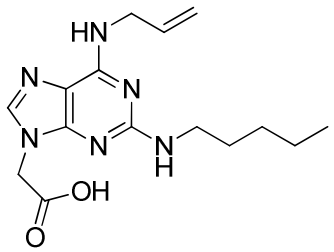
Purine **7ag** was treated according to general procedure **F**, to yield final product **8ag** as a white lyophilized powder (65 %): m.p. > 168 °C (dec); IR (KBr, cm^{-1})3626, 2958, 2931, 1385, 1326, 1183, 1057; δ_H (400 MHz, DMSO-d_6) 0.85 (t, J = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.13 (t, 7.0 Hz, 3H,

$NCH_2C\underline{H}_3$), 1.22-1.33 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.49 (p, *J* = 7.0 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.20 (q, *J* = 6.7 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 3.30 (vbs, 3H, NCH_3), 3.97 (vbs, 2H, $NC\underline{H}_2CH_3$), 4.59 (s, 2H, $C\underline{H}_2CO_2H$), 6.26 (bs, 1H, NH), 7.63 (s, 1H, CH (H-8)); HRMS (MS-ES), calcd for $C_{15}H_{25}N_6O_2$ [M+H] *m/z* = 321.2034, fnd. 321.2033; *rp*HPLC t_R: condition (I) 13.789 (II) 30.775 minutes, purity 99.7 %and 99.5%.



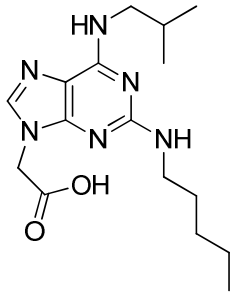
2-(6-(isopropylamino)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8ah)

Purine **7ah** was treated according to general procedure **F**, to yield final product **8ah** as a white lyophilized powder (73 %): m.p. = 173–176 °C; (KBr, cm^{-1})3685, 3653, 2926, 2857, 1581, 1420, 1383, 1304, 1202; δ_H (400 MHz, DMSO-*d*$_6$) 0.86 (t, *J* = 6.7 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.20 (s, 3H, $CH(C\underline{H}_3)_2$), 1.22 (s, 3H, $CH(C\underline{H}_3)_2$), 1.25-1.34 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.51 (p, *J* = 6.8 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.22-3.28 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.35 (bs, 1H, $C\underline{H}(CH_3)_2$), 4.79 (s, 2H, $C\underline{H}_2CO_2H$), 6.65 (bs, 1H, NH), 7.40 (bs, 1H, NH), 7.75 (s, 1H, CH (H-8)) 13.15 (vbs, 1H $CH_2CO_2\underline{H}$); HRMS (MS-ES), calcd for $C_{15}H_{25}N_6O_2$ [M+H] *m/z* = 321.2039, fnd. 321.2033; *rp*HPLC t_R: condition (I) 13.698 (II) 30.922 minutes, purity 94.6 %and 91.0%.



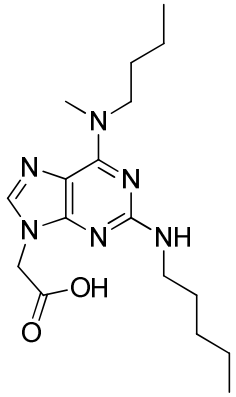
2-(6-(allylamino)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8ai)

Purine **7ai** was treated according to general procedure **F**, to yield final product **8ai** as a white lyophilized powder (76 %): m.p. > 153 °C (dec); IR (KBr, cm^{-1})3855, 3630, 1523, 1384, 1142; δ_H (400 MHz, DMSO-d_6) 0.85 (t, J = 6.9, 3H, $(CH_2)_4C\underline{H}_3$), 1.22-1.33 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.49 (p, J = 7.0 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.20 (q, J = 6.6 Hz, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.07 (bs, 2H, $C\underline{H}_2CHCH_2$), 4.47 (s, 2H, $C\underline{H}_2CO_2H$), 5.02 (dd, 1H, J = 10.3 Hz and 1.7 Hz, $CH_2CHC\underline{H}_2$), 5.14 (dd, 1H, J = 17.2 Hz and 1.8 Hz, $CH_2CHC\underline{H}_2$), 5.88-5.99 (m, 1H, $CH_2CHC\underline{H}_2$), 6.20 (bs, 1H, NH), 7.24 (bs, 1H, NH), 7.59 (s, 1H, CH (H-8)); δ_C (100 MHz, DMSO-d_6) 14.0, 21.9, 28.8, 29.0, 41.0, 45.0, 45.1, 112.5, 114.6, 136.4, 138.1, 144.5, 154.3, 159.2, 170.6; HRMS (MS-ES), calcd for $C_{15}H_{23}N_6O_2$ [M+H] m/z = 319.1869, fnd. 319.1877; *rp*HPLC t_R: condition (I) 13.326 (II) 28.780 minutes, purity 95.07 %and 90.4%.



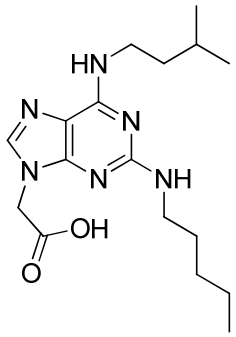
2-(6-(isobutylamino)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8aj)

Purine **7aj** was treated according to general procedure **F**, to yield final product **8aj** as a white lyophilized powder (75 %): m.p. = 139.1-147.8 °C; IR (KBr, cm^{-1}) 2956, 2926, 2854, 1467, 1385, 1246, 1186, 1142; δ_H (400 MHz, DMSO-d_6) 0.81-0.86 (m, 3H, $(CH_2)_4C\underline{H}_3$), 0.87-0.92 (m, 6H, $CH(C\underline{H}_3)_2$), 1.13-1.31 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.52 (p, J = 7.1 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 1.89-1.98 (m, 1H, $C\underline{H}(CH_3)_2$), 3.23-3.31 (m, 4H, $C\underline{H}_2(CH_2)_3CH_3$ and $C\underline{H}_2CH(CH_3)_2$), 4.76 (s, 2H, $C\underline{H}_2CO_2H$), 7.63 (bs, 1H, NH), 7.90 (s, 2H, CH (H-8) and NH); HRMS (MS-ES), calcd for $C_{16}H_{27}N_6O_2$ [M+H] m/z = 335.2201, fnd. 335.2190; *rp*HPLC t_R: condition (I) 14.357 (II) 22.765 minutes, purity 93.9 %and 93.5%.



2-(6-(butyl(methyl)amino)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8ak)

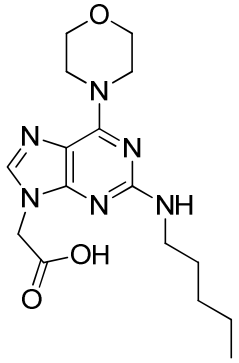
Purine **7ak** was treated according to general procedure **F**, to yield final product **8ak** as a white lyophilized powder (97 %): m.p. > 74 °C (dec); IR (KBr, cm^{-1}) 2959, 2931, 2859, 1561, 1459, 1396, 1324, 1203, 1137; δ_H (400 MHz, DMSO-d_6) 0.87 (t, J = 6.7 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 0.91 (t, 3H, J = 7.3 Hz, $(CH_2)_3C\underline{H}_3$), 1.22-1.36 (m, 6H, $CH_2CH_2C\underline{H}_2CH_3$ and $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.53 (p, J = 6.9 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 1.61 (p, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 3.23-4.17 (bm, 5H, $C\underline{H}_2(CH_2)_2CH_3$ and NCH_3), 3.27 (t, J =7.3 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 4.84 (s, 2H, $C\underline{H}_2CO_2H$), 6.90 (vbs, 1H, NH), 7.80 (s, 1H, CH (H-8)); HRMS (MS-ES), calcd for $C_{17}H_{29}N_6O_2$ [M+H] m/z = 349.2342, fnd. 349.2346; *rp*HPLC t_R: condition (I) 14.902 (II) 36.830 minutes, purity 97.8 %and 95.8%.



2-(6-(isopentylamino)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8al)

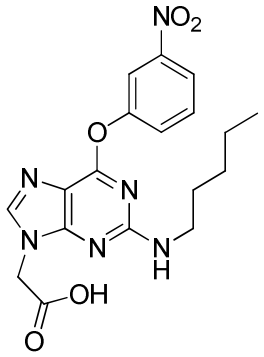
Purine **7al** was treated according to general procedure **F**, to yield final product **8al** as a white lyophilized powder (91 %): m.p. > 196 °C (dec); IR (KBr, cm^{-1}) 2956, 2928, 2858, 1578, 1470,

1431, 1409, 1367, 1306, 1224; δ_H (400 MHz, DMSO-*d*$_6$) 0.79-0.86 (m, 3H, $(CH_2)_4C\underline{H}_3$), 0.87 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 0.89 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 1.10-1.30 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.45-1.55 (m, 4H, $CH_2C\underline{H}_2(CH_2)_2CH_3$ and $CH_2C\underline{H}_2CH(CH_3)_2$), 1.59-1.67 (m, 1H, $CH_2CH_2C\underline{H}(CH_3)_2$), 3.25-3.33 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 3.41-3.53 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.77 (s, 2H, $C\underline{H}_2CO_2H$), 7.63 (bs, 1H, NH), 7.86 (s, 1H, CH (H-8)), 7.87 (bs, 1H, NH); δ_C (100 MHz, DMSO-*d*$_6$) 13.9, 21.9, 22.5, 25.3, 28.8, 29.1, 41.0, 43.6, 112.5, 131.0, 137.4, 154.6, 159.4, 169.7; HRMS (MS-ES), calcd for $C_{17}H_{29}N_6O_2$ [M+H] *m/z* = 349.2339, fnd. 349.2346; *rp*HPLC t_R: condition (I) 14.864 (II) 36.430 minutes, purity 90.3% and 96.1%.



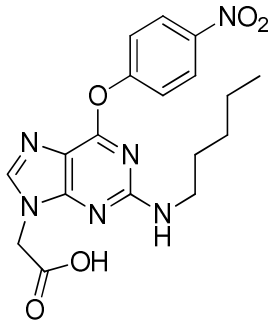
2-(6-morpholino-2-(pentylamino)-9H-purin-9-yl)acetic acid (8am)

Purine **7am** was treated according to general procedure **F**, to yield final product **8am** as a white lyophilized powder (86 %): m.p. > 162 °C (dec); IR (KBr, cm^{-1}) 2956, 2926, 2855, 1444, 1384, 1120; δ_H (400 MHz, DMSO-*d*$_6$) 0.85 (t, *J* = 6.9 Hz, 3H, $(CH_2)_4C\underline{H}_3$), 1.22-1.31 (m, 4H, $(CH_2)_2C\underline{H}_2C\underline{H}_2CH_3$), 1.49 (p, *J* = 6.9 Hz, 2H, $CH_2C\underline{H}_2(CH_2)_2CH_3$), 3.2 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 3.63-3.76 (m, 4H, 2 CH_2 (morpholine)), 4.11 (bs, 4H, 2 CH_2 (morpholine)), 4.69 (s, 2H, $C\underline{H}_2CO_2H$), 6.40 (bs, 1H, NH), 7.69 (s, 1H, CH (H-8)); δ_C (100 MHz, DMSO-*d*$_6$) 13.9, 21.9, 28.7, 28.8, 40.9, 43.9, 44.9, 66.2, 112.7, 137.4, 153.3, 153.4, 158.7, 169.7; HRMS (MS-ES), calcd for $C_{16}H_{26}N_6O_3$[M+H] *m/z* = 349.1982, fnd. 349.1974; *rp*HPLC t_R: condition (I) 12.899 (II) 26.385 minutes, purity 94.2 %and 98.1%.



2-(6-(3-nitrophenoxy)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8an)

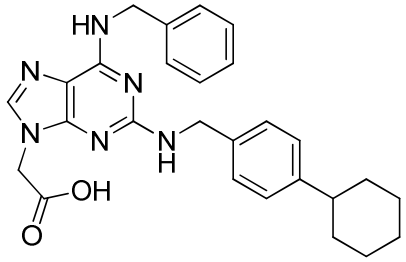
Purine **7an** was treated according to general procedure **F**, to yield final product **8an** as a white lyophilized powder (75 %): m.p. > 130 °C (dec); IR (KBr, cm^{-1}) 3550, 3407, 3336, 2958, 1352, 1200; δ_H (400 MHz, DMSO-d_6) 0.73-0.79 (m, 3H, $(CH_2)_4C\underline{H}_3$), 0.96-1.42 (m, 6H, $CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 2.84-3.10 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.87 (s, 2H, $C\underline{H}_2CO_2H$), 7.14 (bm, 1H, NH), 7.75 (t, J = 8.1 Hz, 1H, CH (Ar)), 7.78-7.81 (m, 1H, CH (Ar)), 8.00 (s, 1H, CH (H-8)), 8.14-8.20 (m, 2H, 2 CH (Ar)); δ_C (100 MHz, DMSO-d_6) 13.8, 21.7, 28.2, 28.5, 41.0, 43.8, 112.7, 117.3, 120.1, 128.9, 130.7, 141.6, 148.2, 152.7, 158.0, 158.5, 158.7, 169.2; HRMS (MS- ES), calcd for $C_{18}H_{21}N_6O_5$ [M+H] m/z = 401.1568, fnd. 401.1567; *rp*HPLC t_R: condition (I) 13.772 (II) 31.491 minutes, purity 92.67 %and 92.5%.



2-(6-(4-nitrophenoxy)-2-(pentylamino)-9H-purin-9-yl)acetic acid (8ao)

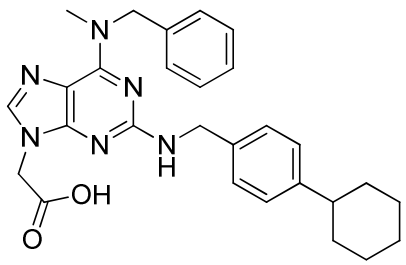
Purine **7ao** was treated according to general procedure **F**, to yield final product **8ao** as a white lyophilized powder (72 %): m.p. > 101 °C (dec); IR (KBr, cm^{-1}) 3571, 3100, 2921, 1582, 1342,

1254; δ_H (400 MHz, DMSO-d_6) 0.78-0.86 (m, 3H, $(CH_2)_4C\underline{H}_3$), 1.00-1.44 (m, 6H, $CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 2.87-2.92 (m, 2H, $C\underline{H}_2(CH_2)_3CH_3$), 4.88 (s, 2H, $C\underline{H}_2CO_2H$), 7.15 (bs, 1H, NH), 7.57 (d, J = 9.2 Hz, 2H, 2 CH (Ar)), 8.01 (s, 1H, CH (H-8)), 8.31 (d, J = 9.2 Hz, 2H, 2 CH (Ar)); δ_C (100 MHz, DMSO-d_6) 13.8, 21.7, 28.6, 41.0, 43.7, 43.8, 52.4, 112.9, 122.8, 125.1, 141.7, 144.3, 155.9, 157.8, 158.4, 158.6, 169.2; HRMS (MS- ES), calcd for $C_{18}H_{21}N_6O_5$ [M+H] m/z = 401.1577, fnd. 401.1567; *rp*HPLC t_R: condition (I) 13.586 (II) 30.762 minutes, purity 97.1 % and 95.7%.



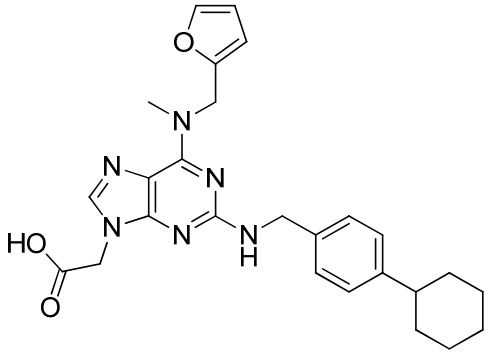
2-(6-(benzylamino)-2-((4-cyclohexylbenzyl)amino)-9*H*-purin-9-yl)acetic acid (8ba)

Purine **7ba** was treated according to general procedure **F**, to yield final product **8ba** as a white lyophilized powder (79 %): m.p. > 182 °C (dec); IR (KBr, cm^{-1}) 3548, 3475, 3414, 2925, 2852, 1733, 1642, 1618, 1425, 1394, 1345, 1244; δ_H (400 MHz, DMSO-d_6) 1.28-1.38 (m, 5H (cyclohexyl)), 1.67-1.78 (m, 5H (cyclohexyl)), 2.42-2.45 (m, 1H, CH), 4.44 (s, 2H, $HNC\underline{H}_2$), 4.63 (bs, 2H, CH_2Ar), 4.88 (s, 2H, $C\underline{H}_2CO_2H$), 7.10-7.29 (m, 9H, 9 CH (Ar)), 7.63 (bs, 1H, NHAr), 7.94 (s, 1H, CH (H-8)), 8.70 (bs, 1H, NHAr); HRMS (MS-ES), calcd for $C_{27}H_{31}N_6O_2$ [M+H] m/z = 471.2514, fnd. 471.2503; *rp*HPLC t_R: condition (I) 18.355 (II) 42.706 minutes, purity 98.0 % and 90.1%.



2-(6-(benzyl(methyl)amino)-2-((4-cyclohexylbenzyl)amino)-9H-purin-9-yl)acetic acid (8bb)

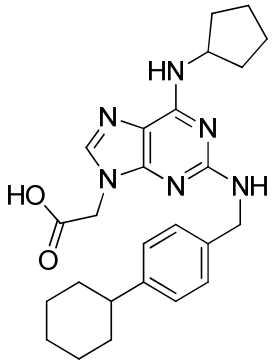
Purine **7bb** was treated according to general procedure **F**, to yield final product **8bb** as a white lyophilized powder (82 %): m.p. > 133 °C (dec); IR (KBr, cm^{-1}) 3318, 2925, 2852, 1735, 1655, 1625, 1558, 1421, 1244, 1199; δ_H (400 MHz, DMSO-d_6) 1.29-1.42 (m, 5H, (cyclohexyl)), 1.67-1.77 (m, 5H (cyclohexyl)), 2.40-2.45 (m, 1H, CH), 2.97-3.71 (bm, 3H, $NC\underline{H}_3$), 4.43 (s, 2H, CH_2Ar), 4.77-5.63 (br m, 2H, $CH_3NC\underline{H}_2$), 4.87 (bs, 2H, $C\underline{H}_2CO_2H$), 7.09-7.30 (m, 9H, 9 CH (Ar)), 7.47 (bs, 1H, NH), 7.82 (s, 1H, CH (H-8)); HRMS (MS-ES), calcd for $C_{28}H_{33}N_6O_2$ [M+H] *m/z* = 485.2676, fnd. 485.2659; *rp*HPLC t_R: condition (I) 18.496 (II) 44.040 minutes, purity 92.6 %and 90.89%.



2-(2-((4-cyclohexylbenzyl)amino)-6-((furan-2-ylmethyl)(methyl)amino)-9H-purin-9-yl)acetic acid (8bd)

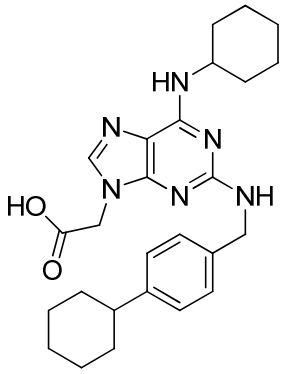
Purine **7bc** was treated according to general procedure **F**, to yield final product **8bc** as a white lyophilized powder (84 %): m.p. > 74 °C (dec); IR (KBr, cm^{-1}) 2925, 2851, 1661, 1555, 1402, 1320, 1201, 1138; δ_H (400 MHz, DMSO-d_6) 1.29-1.40 (m, 5H, 5H (cyclohexyl)), 1.67-1.77 (m,

5H (cyclohexyl)), 2.40-2.45 (m, 1H, CH), 2.98-3.57(bm, 3H, CH_3 (furfuryl)), 4.24 (bm, 2H, CH_2 (furfuryl)), 4.43 (s, 2H, CH_2Ar), 4.84 (s, 2H, $C\underline{H}_2CO_2H$), 6.21-6.40 (m, 2H, 2 CH (furfuryl)), 7.11 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.24 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.20 (bs, 1H, NH), 7.54-7.60 (m, 1H, CH (furfuryl)), 7.80 (s, 1H, CH (H-8)); δ_c (100 MHz, DMSO-*d*$_6$) 25.5, 26.3, 33.9, 41.7, 43.4, 43.9, 44.2, 53.5, 108.0, 110.3, 112.8, 126.2, 127.4, 137.6, 138.1, 142.5, 145.7, 151.3, 153.6, 153.6, 169.3; HRMS (MS-ES), calcd for $C_{26}H_{31}N_6O_3$ [M+H] *m/z* = 475.2445, fnd. 475.2452; *rp*HPLC t_R: condition (I) 16.862 (II) 42.090 minutes, purity 91.9 %and 90.2%.



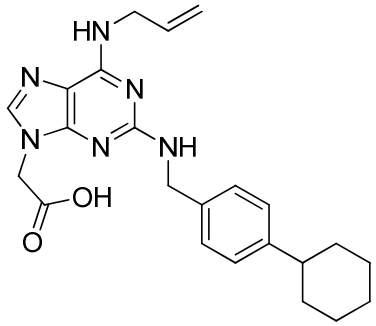
2-(2-((4-cyclohexylbenzyl)amino)-6-(cyclopentylamino)-9H-purin-9-yl)acetic acid (8be)

Purine **7be** was treated according to general procedure **F**, to yield final product **8be** as a white lyophilized powder (91 %): m.p. > 140 °C (dec); IR (KBr, cm^{-1}) 3855, 3508, 3294, 2928, 1388, 1202; δ_H (400 MHz, DMSO-*d*$_6$) 1.28-1.41 (m, 5H, (cyclohexyl)), 1.47-1.59 (m, 4H (cyclopentyl)), 1.65-1.93 (m, 9H, 5H (cyclohexyl) and 4H (cyclopentyl)), 2.40-2.45 (m, 1H, CH), 4.37 (bs, 1H, NC$\underline{H}$), 4.41 (bs, 2H, CH_2Ar), 4.81(s, 2H, $C\underline{H}_2CO_2H$), 7.11 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.22 (bs, 1H, NH), 7.24 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.56 (br s, 1H, NH), 7.78 (bs, 1H, CH (H-8)); HRMS (MS-ES), calcd for $C_{25}H_{33}N_6O_2$ [M+H] *m/z* = 449.2680, fnd. 449.2659; *rp*HPLC t_R: condition (I) 17.193 (II) 43.772 minutes, purity 95.1 %and 91.9%.



2-(6-(cyclohexylamino)-2-((4-cyclohexylbenzyl)amino)-9H-purin-9-yl)acetic acid (8bf)

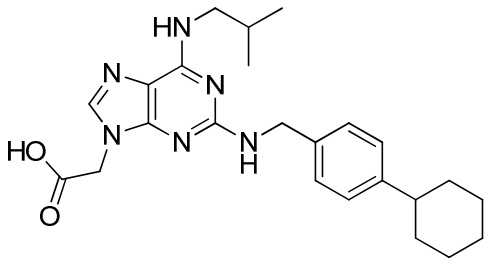
Purine **7bf** was treated according to general procedure **F**, to yield final product **8bf** as a white lyophilized powder (88 %): m.p. = 172-179°C; IR (KBr, cm^{-1}) 2927, 2854, 1448, 1388, 1201, 1142; δ_H (400 MHz, DMSO-d_6) 1.13-1.38 (m, 10H, 5H (cyclohexyl) and 5H (NH-cyclohexyl)), 1.56-1.81 (m, 10H, 5H (cyclohexyl) and 5H (NH-cyclohexyl)), 2.38-2.48 (m, 1H, CH), 3.89 (bs, 1H, HNC<u>H</u>), 4.44 (s, 2H, CH_2Ar), 4.89 (s, 2H, C<u>H</u>$_2CO_2H$), 7.14 (d, J = 7.7 Hz, 2H, 2 CH (Ar)), 7.26 (d, J = 7.7 Hz, 2H, 2 CH (Ar)), 7.75 (bs, 1H, NH), 7.99 (s, 1H, CH (H-8)); HRMS (MS-ES), calcd for $C_{26}H_{35}N_6O_2$ [M+H] m/z = 463.2819, fnd. 463.2816; *rp*HPLC t_R: condition (I) 17.233 (II) 44.956 minutes, purity 95.3 %and 92.2%.



2-(6-(allylamino)-2-((4-cyclohexylbenzyl)amino)-9H-purin-9-yl)acetic acid (8bi).

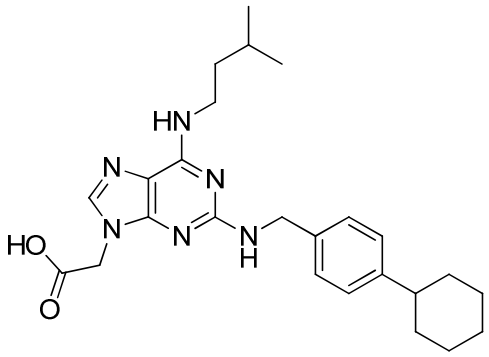
Purine **7bi** was treated according to general procedure **F**, to yield final product **8bi** as a white lyophilized powder (81 %): m.p. > 170 °C (dec); IR (KBr, cm^{-1}) 3550, 3477, 3414, 2924, 2852, 1638, 1618, 1385, 1201; δ_H (400 MHz, DMSO-d_6) 1.27-1.44 (m, 5H (cyclohexyl)), 1.62-1.81

(m, 5H (cyclohexyl)), 2.38-2.48 (m, 1H, CH), 4.04 (bs, 2 H, C<u>H</u>$_2$CHCH$_2$), 4.43 (s, 2H, CH$_2$Ar), 4.84 (s, 2H, CH$_2$CO$_2$H), 5.05 (dd, *J* = 10.1 and 1.5 Hz, 1H, CH$_2$CHC<u>H</u>$_2$), 5.14 (dd, *J* = 17.1 and 1.5 Hz, 1H, CH$_2$CHC<u>H</u>$_2$), 5.81-5.97 (m, 1H, CH$_2$C<u>H</u>CH$_2$), 7.12 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.25 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 7.36 (bs, 1H, NH), 7.85 (s, 1H, CH (H-8)), 8.04 (bs, 1H, NH); HRMS (MS-ES), calcd for $C_{23}H_{29}N_6O_2$ [M+H] *m/z* = 421.2349, fnd. 421.2346; *rp*HPLC t_R: condition (I) 15.403 (II) 40.030 minutes, purity 96.4 %and 93.86%.



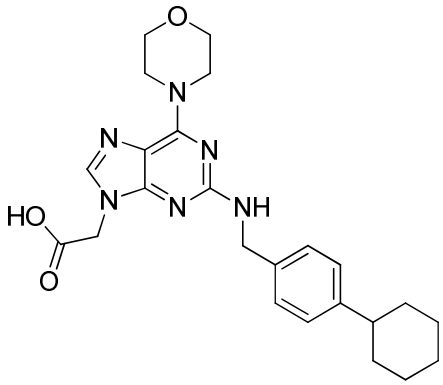
2-(2-((4-cyclohexylbenzyl)amino)-6-(isobutylamino)-9H-purin-9-yl)acetic acid (8bj).

Purine **7bj** was treated according to general procedure **F**, to yield final product **8bj** as a white lyophilized powder (73 %): m.p. > 116 °C (dec); IR (KBr, cm^{-1}) 3549, 3477, 3414, 2920, 1744, 1620, 1449, 1404, 1387, 1367, 1248, 1206; δ_H (400 MHz, DMSO-*d*$_6$) 0.81 (s, 3H, CH$_2$CH(C<u>H</u>$_3$)$_2$), 0.83 (s, 3H, CH$_2$CH(C<u>H</u>$_3$)$_2$), 1.26-1.42 (m, 5H, (cyclohexyl)), 1.62-1.80 (m, 5H, (cyclohexyl)), 1.79-1.92 (m, 1H, CH$_2$C<u>H</u>(CH$_3$)$_2$) 2.33-2.46 (m, 1H, CH), 3.16 (bs, 2H, C<u>H</u>$_2$CH(CH$_3$)$_2$), 4.30-4.43 (m, 2H, CH$_2$Ar), 4.69 (s, 2H, C<u>H</u>$_2$CO$_2$H), 6.90 (bs, 1H, NH), 7.1 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.23 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.27 (bs, 1H, NH), 7.64 (s, 1H, CH (H-8)); δ_C (100 MHz, DMSO-*d*$_6$) 20.1, 25.5, 26.3, 34.0, 43.4, 43.8, 44.3, 46.9, 112.6, 126.1, 127.3, 137.5, 138.9, 145.4, 151.4, 154.7, 159.1, 169.7; HRMS (MS-ES), calcd for $C_{24}H_{33}N_6O_2$ [M+H] *m/z* = 437.2663, fnd. 437.2659; *rp*HPLC t_R: condition (I) 16.906 (II) 45.089 minutes, purity 96.6 %and 97.8%.



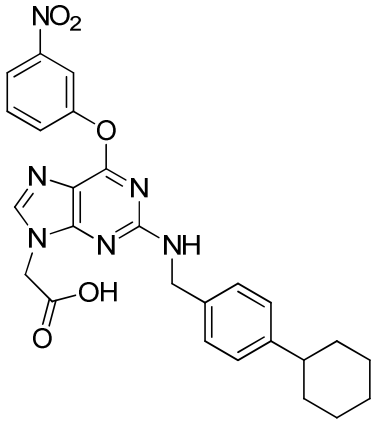
2-(2-((tert-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(isopentylamino)-9H-purin-9-yl)acetic acid (8bl).

Purine **7bl** was treated according to general procedure **F**, to yield final product **8bl** as a white lyophilized powder (69 %): m.p. > 153 °C (dec); IR (KBr, cm^{-1}) 2937, 2851, 1736, 1646, 1528, 1432, 1244, 1201; δ_H (400 MHz, DMSO-*d*$_6$) 0.85 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 0.86 (s, 3H, $(CH_2)_2CH(C\underline{H}_3)_2$), 1.18-1.60 (m, 8H, 5H (cyclohexyl) and $(CH_2)_2C\underline{H}(CH_3)_2$ and $CH_2C\underline{H}_2CH(CH_3)_2$), 1.67-1.77 (m, 5H, (cyclohexyl)), 2.41-2.47 (m, 1H, CH), 3.41 (bs, 2H, $C\underline{H}_2CH_2CH(CH_3)_2$), 4.47 (s, 2H, CH_2Ar), 4.88 (s, 2H, $C\underline{H}_2CO_2H$), 7.14 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 7.25 (d, *J* = 7.7 Hz, 2H, 2 CH (Ar)), 7.58 (bs, 1H, NH), 7.91 (s, 1H, CH (H-8)), 8.32 (bs, 1H, NH); HRMS (MS-ES), calcd for $C_{25}H_{35}N_6O_2$ [M+H] *m/z* = 451.2835, fnd. 451.2816; *rp*HPLC t_R: condition (I) 17.061 (II) 44.519 minutes, purity 91.9 %and 94.2%.



2-(2-((4-cyclohexylbenzyl)amino)-6-morpholino-9H-purin-9-yl)acetic acid (8bm)

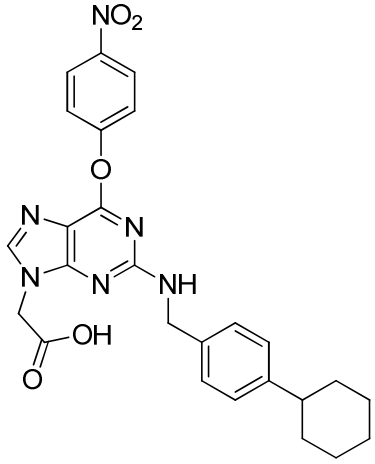
Purine **7bm** was treated according to general procedure **F**, to yield final product **8bm** as a white lyophilized powder (73 %): m.p. > 147 °C (dec); IR (KBr, cm^{-1}) 3422, 2923, 2851, 1603, 1542, 1516, 1446, 1416, 1384, 1314, 1272, 1242, 1207, 1121, 1003; δ_H (400 MHz, DMSO-d_6) 1.17-1.36 (m, 5H, (cyclohexyl)), 1.66-1.77 (m, 5H, (cyclohexyl)), 2.38-2.45 (m, 1H, CH), 3.63 (t, J = 4.4 Hz, 4H, 2 C$\underline{H}_2$, (morpholine)), 4.08 (bs, 4H, 2 C$\underline{H}_2$, (morpholine)), 4.37 (d, J = 5.1 Hz, 2H, CH_2Ar), 4.78 (s, 2H, C$\underline{H}_2CO_2H$), 7.03 (bs, 1H, NH), 7.1 (d, J = 8.1 Hz, 2H, 2 CH (Ar)), 7.23 (d, J = 7.9 Hz, 2H, 2 CH (Ar)), 7.73 (s, 1H, CH, (H-8)); HRMS (MS-ES), calcd for $C_{24}H_{31}N_6O_3$ [M+H] m/z = 451.2463, fnd. 451.2452; *rp*HPLC t_R: condition (I) 14.895 (II) 38.319 minutes, purity 99.9% and 96.6%.



2-(2-((4-cyclohexylbenzyl)amino)-6-(3-nitrophenoxy)-9H-purin-9-yl)acetic acid (8bn)

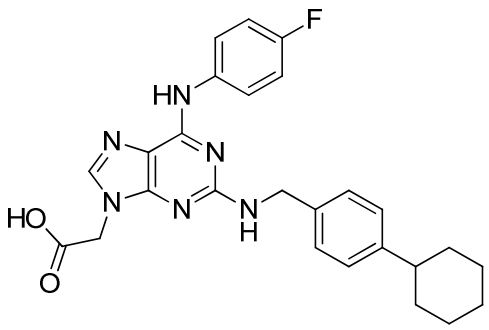
Purine **7bn** was treated according to general procedure **F**, to yield final product **8bn** as a white lyophilized powder (86 %): m.p. > 150 °C (dec); IR (KBr, cm^{-1}) 3434, 2926, 2853, 1587, 1526, 1417, 1352, 1252; δ_H (400 MHz, DMSO-d_6) 1.29-1.37 (m, 5H, (cyclohexyl)), 1.66-1.77 (m, 5H, (cyclohexyl)), 2.35-2.41 (m, 1H, CH), 4.17 (m, 2H, CH_2Ar), 4.89 (s, 2H, C$\underline{H}_2CO_2H$), 6.81-7.20 (m, 4H, 3 CH (Ar) and NH), 7.72-7.75 (m, 3H, 3 CH (Ar)), 8.00 (s, 1H, CH, (H-8)), 8.10-8.17 (m, 2H, 2 CH (Ar)); δ_C (100 MHz, DMSO-d_6) 25.5, 26.3, 33.9, 43.4, 43.9, 44.2, 113.0, 117.3, 120.2, 126.0, 127.6, 129.1, 130.7, 137.5, 141.7, 145.7, 148.3, 152.7, 155.8, 158.3, 158.8, 169.2;

HRMS (MS-ES), calcd for $C_{26}H_{27}N_6O_5$ [M+H] *m/z* = 503.2018, fnd. 503.2037; *rp*HPLC t_R: condition (I) 15.558 (II) 40.643, purity 99.7 %and 99.0%.



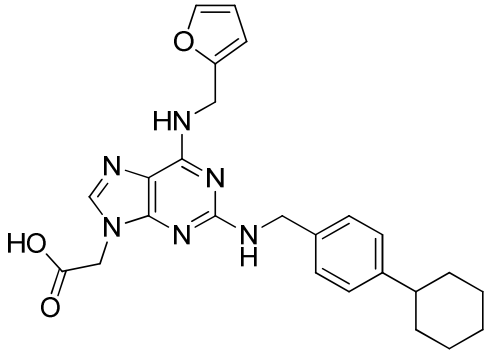
2-(2-((4-cyclohexylbenzyl)amino)-6-(4-nitrophenoxy)-9H-purin-9-yl)acetic acid (8bo).

Purine **7bo** was treated according to general procedure **F**, to yield final product **8bo** as a white lyophilized powder (74 %): m.p. > 170 °C (dec); IR (KBr, cm^{-1}) 3550, 3413, 2924, 2852, 1724, 1636, 1616, 1581, 1552, 1522, 1488, 1449; δ_H (400 MHz, DMSO-d_6) 1.31-1.39 (m, 5H, (cyclohexyl)), 1.67-1.78 (m, 5H, (cyclohexyl)), 2.37-2.44 (m, 1H, CH), 4.07-4.36 (m, 2H, CH_2Ar), 4.89 (s, 2H, $C\underline{H}_2CO_2H$), 6.92-7.26 (m, 4H, 4 CH (Ar)), 7.44-7.53 (m, 2H, 2 CH (Ar)), 7.70 (bs, 1H, NH), 8.01 (s, 1H, CH, (H-8)), 8.23-8.28 (m, 2H, 2 CH (Ar)); δ_C (100 MHz, DMSO-d_6) 25.5, 26.3, 33.9, 43.4, 43.8, 44.2, 113.2, 115.8, 122.6, 125.1, 126.1, 127.4, 127.9, 137.4, 141.9, 144.2, 145.7, 157.6, 158.4, 169.2; HRMS (MS-ES), calcd for $C_{26}H_{27}N_6O_5$ [M+H] *m/z* = 503.2026, fnd. 503.2037; *rp*HPLC t_R: condition (I) 13.824 (II) 41.102 minutes, purity 90.4 %and 90.2%.



2-(2-((4-cyclohexylbenzyl)amino)-6-((4-fluorophenyl)amino)-9H-purin-9-yl)acetic acid (8bp).

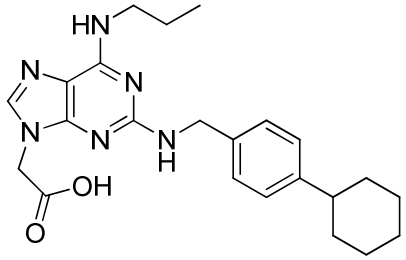
Purine **7bp** was treated according to general procedure **F**, to yield final product **8bp** as a white lyophilized powder (91 %): m.p. > 125 °C (dec); IR (KBr, cm^{-1}) 3429, 3226, 2924, 2851, 1682, 1646, 1509, 1206, 1134; δ_H (400 MHz, DMSO-d_6) 1.31-1.40 (m, 5H, (cyclohexyl)), 1.66-1.76 (m, 5H (cyclohexyl)), 2.40-2.46 (m, 1H, CH), 4.42 (d, J = 6.2 Hz, 2H, CH_2Ar), 4.83 (s, 2H, $C\underline{H}_2CO_2H$), 6.99-7.04 (m, 2H, 2 CH (Ar)), 7.12 (d, J = 8.1 Hz, 2H, 2 CH (Ar)), 7.24 (d, J = 8.1 Hz, 2H, 2 CH (Ar)), 7.29 (bs, 1H, NHAr), 7.75-7.90 (m, 2H, 2 CH (Ar)), 7.83 (s, 1H, CH (H-8)), 9.50 (s, 1H, NHAr), 13.21 (bs, 1H, CO_2H); δ_C (100 MHz, DMSO-d_6) 25.5, 26.3, 34.0, 41.7, 43.4, 44.3, 113.1, 114.4, 114.6, 121.5, 121.6, 126.2, 136.5, 138.3, 138.6 145.5, 151.8, 156.0, 158.9, 169.5; HRMS (MS-ES), calcd for $C_{26}H_{28}N_6O_2F$ [M+H] m/z = 475.2266, fnd. 475.2252; *rp*HPLC t_R: condition (I) 17.250 (II) 43.207 minutes, purity 99.9 %and 95.6%.



2-(2-((4-cyclohexylbenzyl)amino)-6-((furan-2-ylmethyl)amino)-9H-purin-9-yl)acetic acid

(8bq)

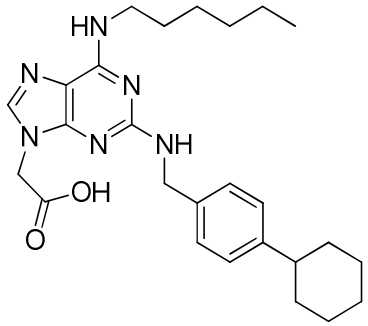
Purine **7bq** was treated according to general procedure **F**, to yield final product **8bq** as a white lyophilized powder (88 %): m.p. > 162 (dec) °C; IR (KBr, cm^{-1}) 3320, 2920, 2855, 1731, 1574, 1530, 1426, 1246, 1201, 1141; δ_H (400 MHz, DMSO-d_6) 1.29-1.42 (m, 5H, 5H (cyclohexyl)), 1.67-1.77 (m, 5H (cyclohexyl)), 2.41-2.47 (m, 1H, CH), 4.46 (s, 2H, CH_2 (furfuryl)), 4.62 (bs, 2H, CH_2Ar), 4.88 (s, 2H, CH_2CO_2H), 6.15-6.26 (m, 1H, CH (furfuryl)), 6.35 (bs, 1H, CH (furfuryl)), 7.12 (d, J = 7.9 Hz, 2H, 2 CH (Ar)), 7.25 (d, J = 7.9 Hz, 2H, 2 CH (Ar)), 7.55 (s, 1H, CH (furfuryl)), 7.61 (bs, 1H, NH), 7.96 (bs, 1H, CH (H-8)), 8.33-8.55 (bm, 1H, NH); HRMS (MS-ES), calcd for $C_{25}H_{29}N_6O_3$ [M+H] m/z = 461.2297, fnd. 461.2295; *rp*HPLC t_R: condition (I) 17.001 (II) 40.686 minutes, purity 96.4 %and 92.2%.



2-(2-((tert-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(propylamino)-9H-purin-9-yl) acetic acid (8bs).

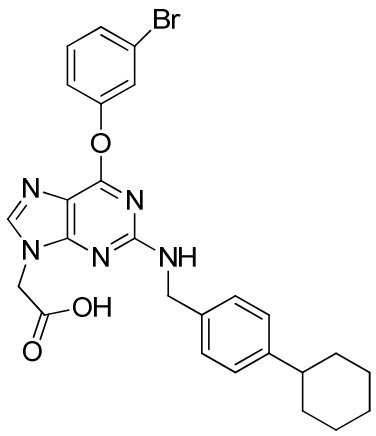
Purine **7bs** was treated according to general procedure **H**, to yield final product **8bs** as a white lyophilized powder (78 %): m.p. > 202 °C (dec); IR (KBr, cm^{-1}) 3677, 3519, 3396, 2922, 1452, 1123; δ_H (400 MHz, DMSO-d_6) 0.85 (m, 3H, $NHCH_2CH_2C\underline{H}_3$), 1.26-1.41 (m, 5H (cyclohexyl)), 1.53 (m, 2H, $NHCH_2C\underline{H}_2CH_3$), 1.65-1.78 (m, 5H (cyclohexyl)), 2.40-2.46 (m, 1H, CH), 3.38 (bs, 2H, $NHC\underline{H}_2CH_2CH_3$), 4.41-4.44 (m, 2H, CH_2Ar), 4.85 (s, 2H, $C\underline{H}_2CO_2H$), 7.11 (d, J = 8.1 Hz,

2H, 2 CH (Ar)), 7.23 (d, J = 7.9 Hz, 2H, 2 CH (Ar)), 7.88 (s, 1H, CH, (H-8)); δ_C (100 MHz, DMSO-d_6) 11.2, 25.5, 26.3, 33.9, 43.5, 43.9, 44.1, 44.2, 112.7, 115.7, 118.6, 121.6, 126.3, 127.6, 157.9, 158.2, 158.5, 158.8, 169.1; HRMS (MS-ES), calcd for $C_{23}H_{31}N_6O_2$ [M+H] m/z = 423.2499, fnd. 423.5203; *rp*HPLC t_R: condition (I) 15.644 (II) 41.468 minutes, purity 90.4 %and 90.2%.



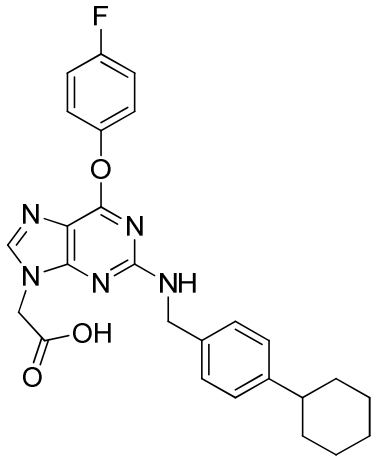
2-(2-((4-cyclohexylbenzyl)amino)-6-(hexylamino)-9H-purin-9-yl)acetic acid (8bt).

Purine **7bt** was treated according to general procedure **F**, to yield final product **8bt** as a white lyophilized powder (85 %): m.p. > 105 °C (dec); IR (KBr, cm^{-1})3549, 3413, 2925, 2853, 1686, 1638, 1618, 1448, 1384, 1303, 1208, 1183; δ_H (400 MHz, $CDCl_3$) 0.84 (t, J = 7.1 Hz, 3H, $(CH_2)_5C\underline{H}_3$), 1.10-1.39 (m, 11H, 5H (cyclohexyl) and $(CH_2)_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.43-1.57 (m, 2H, $CH_2C\underline{H}_2(CH_2)_3CH_3$)), 1.60-1.87 (m, 5H, (cyclohexyl)), 2.37-2.47 (m, 1H, CH), 3.42 (bs, 2H, $C\underline{H}_2(CH_2)_4CH_3$), 4.42 (s, 2H, CH_2Ar), 4.81 (s, 2H, $C\underline{H}_2CO_2H$), 7.11 (d, J = 7.9 Hz, 2H, 2 CH (Ar)), 7.24 (d, J = 8.1 Hz, 2H, 2 CH (Ar)), 7.25 (bs, 1H, NH), 7.76 (bs, 1H, NH), 7.77 (s, 1H, CH, (H-8)); δ_C (100 MHz, DMSO-d_6) 13.8, 18.8, 22.1, 25.5, 26.1, 26.3, 28.9, 31.0, 33.9, 43.4, 43.7, 43.8, 44.2, 112.1, 121.9, 126.2, 127.4, 128.6, 131.5, 145.6, 158.1, 169.3; HRMS (MS-ES), calcd for $C_{26}H_{37}N_6O_2$ [M+H] m/z = 465.2991, fnd. 465.2983; *rp*HPLC t_R: condition (I) 16.366 (II) 30.267 minutes, purity 92.7 %and 95.7%.



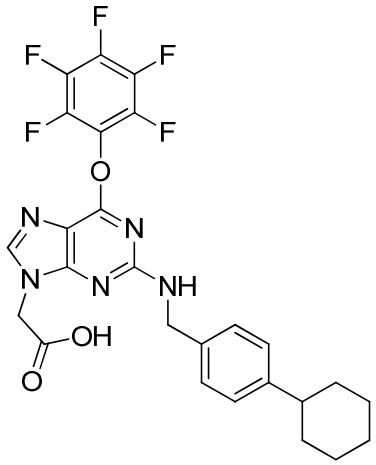
2-(6-(3-bromophenoxy)-2-((4-cyclohexylbenzyl)amino)-9H-purin-9-yl)acetic acid (8bu).

Purine **7bu** was treated according to general procedure **F**, to yield final product **8bu** as a white lyophilized powder (93 %): m.p. > 128 °C (dec); IR (KBr, cm^{-1}) 3462, 2921, 2850, 1729, 1626, 1449, 1349, 1237; δ_H (400 MHz, DMSO-d_6) 1.22-1.38 (m, 5H, (cyclohexyl)), 1.64-1.82 (m, 5H, (cyclohexyl)), 2.35-2.47 (m, 1H, CH), 4.04-4.25 (m, 2H, CH_2, (Ar)), 4.88 (s, 2H, $C\underline{H}_2CO_2H$), 6.71-7.18 (m, 4H, 4 CH (Ar)), 7.22-7.34 (m, 1H, CH (Ar)), 7.42 (t, J = 8.1 Hz, 1H, CH (Ar)), 7.47-7.52 (m, 1H, CH (Ar)), 7.54 (t, J = 2.02 Hz, 1H, CH (Ar)), 7.69 (bs, 1H, NH), 8.00 (s, 1H, CH, (H-8)); δ_C (100 MHz, DMSO-d_6) 25.5, 26.3, 33.9, 43.4, 43.8, 44.2, 112.8, 121.4, 121.5, 125.1, 125.2, 126.2, 127.8, 128.3, 131.1, 137.5, 141.4, 145.7, 153.1, 158.4, 159.1, 169.2; HRMS (MS-ES), calcd for $C_{26}H_{27}N_5O_3Br$ [M+H] m/z = 536.1271, fnd. 536.1291; *rp*HPLC t_R: condition (I) 16.049 (II) 43.812 minutes, purity 99.8 % and 97.32%.



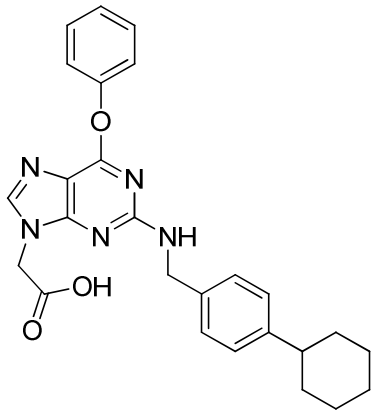
2-(2-((4-cyclohexylbenzyl)amino)-6-(4-fluorophenoxy)-9H-purin-9-yl)acetic acid (8bv).

Purine **7bv** was treated according to general procedure **F**, to yield final product **8bv** as a white lyophilized powder (77 %): m.p. > 100°C (dec); IR (KBr, cm^{-1})3550, 3414, 3235, 2925, 2852, 1619, 1587, 1504, 1450, 1408, 1349, 1256; δ_H (400 MHz, DMSO-d_6) 1.31-1.40 (m, 5H, (cyclohexyl)), 1.67-1.79 (m, 5H, (cyclohexyl)), 2.38-2.44 (m, 1H, CH), 4.01-4.32 (m, 2H, CH_2Ar), 4.88 (s, 2H, $C\underline{H}_2CO_2H$), 6.57-7.14 (m, 4H, 4 CH (Ar)), 7.26 (d, J = 6.8Hz, 4H, 4 CH (Ar)), 7.61 (bs, 1H, NH), 8.00 (s, 1H, CH, (H-8)); δ_C (100 MHz, DMSO-d_6) 25.5, 26.3, 33.9, 43.4, 43.8, 44.2, 112.8, 115.8, 116.0, 123.6, 123.7, 126.1, 127.8, 137.5, 145.7, 148.2, 148.3, 158.1, 158.4, 159.4, 160.5, 169.2; HRMS (MS-ES), calcd for $C_{26}H_{27}FN_5O_3$ [M+H] *m/z* = 476.2073, fnd. 476.2092; *rp*HPLC t_R: condition (I) 15.577 (II) 41.341 minutes, purity 95.7 %and 92.1%.



2-(2-((4-cyclohexylbenzyl)amino)-6-(perfluorophenoxy)-9H-purin-9-yl)acetic acid (8bw).

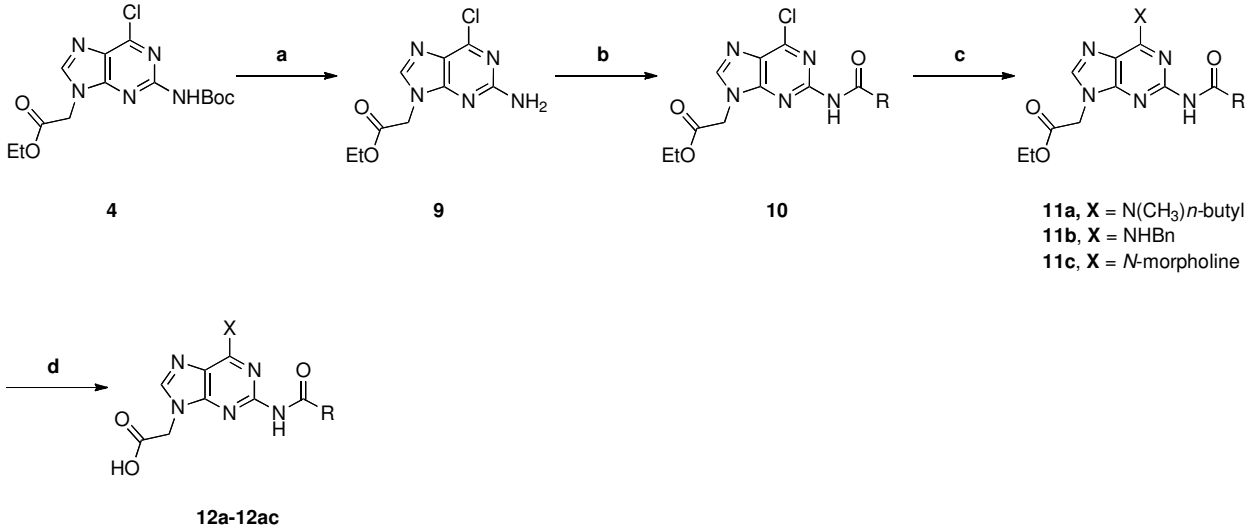
Purine **7bw** was treated according to general procedure **F**, to yield final product **8bw** as a white lyophilized powder (84 %): m.p. > 110 °C (dec); IR (KBr, cm^{-1}) 3550, 3408, 2925, 1637, 1618, 1584, 1558, 1521, 1404, 1227; δ_H (400 MHz, DMSO-d_6) 1.29-1.40 (m, 5H, (cyclohexyl)), 1.67-1.80 (m, 5H, (cyclohexyl)), 2.38-2.45 (m, 1H, CH), 4.02-4.41 (m, 2H, CH_2Ar), 4.91 (s, 2H, $C\underline{H}_2CO_2H$), 6.74-7.31 (m, 4H, 4 CH (Ar)), 8.01 (bs, 1H, NH), 8.07 (s, 1H, CH (H-8)), 13.3 (vbs, 1H, CO_2H); δ_C (100 MHz, DMSO-d_6) 25.5, 26.3, 33.9, 43.4, 43.9, 44.4, 112.0, 126.1, 127.1, 132.9, 138.5, 142.5, 142.9, 145.6, 152.3, 156.1, 158.1, 159.2, 169.1; HRMS (MS-ES), calcd for $C_{26}H_{23}F_5N_5O_3$ [M+H] *m/z* = 548.1704, fnd. 548.1715; *rp*HPLC t_R: condition (I) 16.078 (II) 44.286 minutes, purity 97.2 %and 97.3%.



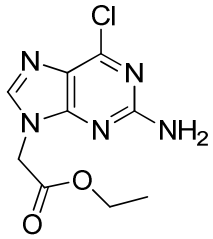
2-(2-((4-cyclohexylbenzyl)amino)-6-(perfluorophenoxy)-9H-purin-9-yl)acetic acid (8bx).

Purine **7bx** was treated according to general procedure **F**, to yield final product **8bx** as a white lyophilized powder (82 %): m.p. > 129°C (dec); IR (KBr, cm^{-1}) 3707, 2925, 2851, 1580, 1546, 1401, 1349, 1254; δ_H (400 MHz, DMSO-d_6) 1.25-1.38 (m, 5H, (cyclohexyl)), 1.66-1.76 (m, 5H, (cyclohexyl)), 2.37-2.43 (m, 1H, CH), 4.01-4.25 (m, 2H, CH_2Ar), 4.60 (s, 2H, $C\underline{H}_2CO_2H$), 7.02-7.05 (m, 3H, 3 CH (Ar)), 7.17-7.28 (m, 4H, 4 CH (Ar)), 7.39-7.46 (m, 3H, 2 CH (Ar) and 1 NH), 7.89 (s, 1H, CH (H-8)); δ_C (100 MHz, DMSO-d_6) 25.5, 26.3, 33.9, 43.4, 44.1, 45.4, 113.2, 121.8, 125.0, 126.2, 127.7, 129.4, 137.8, 141.9, 145.6, 152.4, 155.4, 158.3, 159.3, 170.0; HRMS (MS-ES), calcd for $C_{26}H_{28}N_5O_3$ [M+H] *m/z* = 458.2180, fnd. 458. 2186; *rp*HPLC t_R: condition (I) 15.570 (II) 40.997 minutes, purity 97.8 %and 97.1%.

Scheme 2.

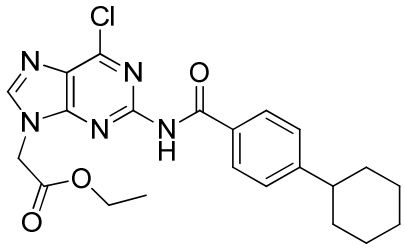


Scheme 2. a) TFA:CH_2Cl_2 (3:1), r.t., 1.5 hrs, 87 %; b) RCOCl, pyridine, r.t., 15 mins, 55 %; c) X (HNR'R"), DIPEA, DMSO, 105 ^oC, 40 mins, microwave assisted, 67-83 %; f) LiOH, THF:H_2O(3:1), r.t., 30 mins, 73-85 %.



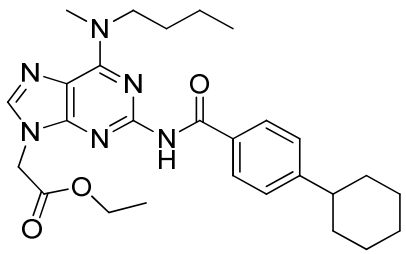
methyl 2-(2-amino-6-chloro-9H-purin-9-yl)acetate (9).

Purine **4** was treated according to general procedure **F**, to yield lyophilized product **9** as an off-white solid (90 %): m.p. = 148–150 °C; IR (KBr, cm^{-1}) 2982, 1761, 1738, 1522, 1473, 1423, 1441, 1380, 1343, 1310, 1286, 1225, 1173, 1143, 1023, 1002; δ_H (400 MHz, $CDCl_3$) 1.30 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 4.26 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.84 (s, 2H, CH_2CO_2Et), 5.15 (bs, 2H, NH_2), 7.83 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_9H_{11}ClN_5O_2$ [M+H] *m/z* = 256.05, fnd. 256.18.



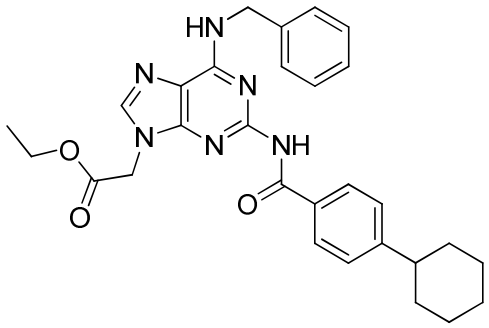
ethyl 2-(6-chloro-2-(4-cyclohexylbenzamido)-9H-purin-9-yl)acetate (10).

Purine **9** was treated with 4-cyclohexylbenzoyl chloride according to general procedure **G**, to yield lyophilized product **10** as a yellow solid (63 %): m.p. = 90-107 °C; IR (KBr, cm^{-1}) 2924, 2850, 1750, 1576, 1493, 1437, 1402, 1285, 1215, 1172; δ_H (400 MHz, $CDCl_3$) 1.32 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.38-1.49 (m, 5H, (cyclohexyl), 1.76-1.92 (m, 5H, (cyclohexyl)), 2.56-2.62 (m, 1H, CH), 4.29 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.06 (s, 2H, CH_2CO_2Et), 7.35 (d, J = 8.3 Hz, 2H, 2 CH (Ar)), 7.87 (d, J = 8.3 Hz, 2H, 2 CH (Ar)), 8.12 (s, 1H, CH (H-8)), 8.71 (bs, 1H, NH); LRMS (MS-ES), calcd for $C_{22}H_{24}ClN_5O_3Na$ [M+Na] *m/z* = 464.16, fnd. 464.32.



ethyl 2-(6-(butyl(methyl)amino)-2-(4-cyclohexylbenzamido)-9H-purin-9-yl)acetate (11a).

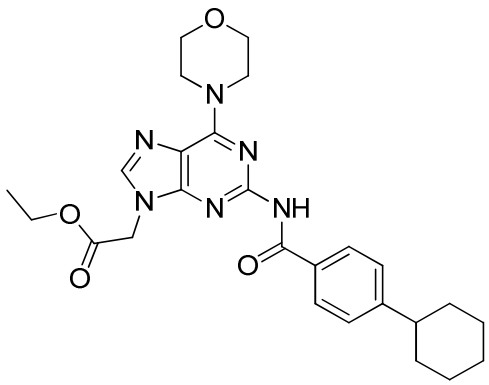
Purine **10** was treated with *N*-butylmethylamine according to general procedure **B**, yielding the final product **11a** as a clear viscous oil (69 %): IR (KBr, cm^{-1}) 3630, 2931, 1752, 1578, 1533, 1449, 1406, 1353, 1275, 1221, 1149; δ_H (400 MHz, $CDCl_3$) 0.95 (t, *J* = 7.4 Hz, 3H, $N(CH_2)_3C\underline{H}_3$), 1.27-1.49 (m, 7H, $N(CH_2)_2C\underline{H}_2CH_3$ and 5H (cyclohexyl)), 1.30 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.63-1.91 (m, 7H, $NCH_2C\underline{H}_2CH_2CH_3$ and 5H (cyclohexyl)), 2.54-2.61 (m, 1H, CH), 3.16-4.34 (bm, 5H, $C\underline{H}_3NC\underline{H}_2(CH_2)_2CH_3$), 4.26 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.92 (s, 2H, CH_2CO_2Et), 7.31 (d, *J* = 8.3 Hz, 2H, 2 CH (Ar)), 7.72 (s, 1H, CH (H-8)), 7.82 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 8.24 (bs, 1H, NH); LRMS (MS-ES), calcd for $C_{27}H_{37}N_6O_3$ [M+H] *m/z* = 493.28, fnd. 493.47.



ethyl 2-(6-(benzylamino)-2-(4-cyclohexylbenzamido)-9H-purin-9-yl)acetate (11b).

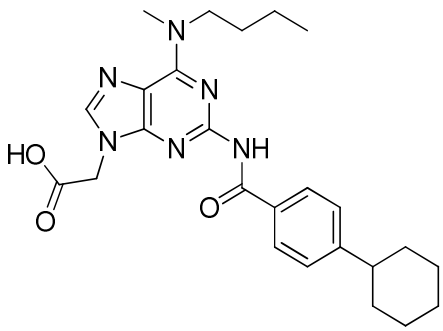
Purine **10** was treated with benzylamine according to general procedure **B**, yielding the final product **11b** as a off-white solid (83 %): m.p. > 100–118 °C; IR (KBr, cm^{-1}) 2924, 1449, 1385, 1245; δ_H (400 MHz, $CDCl_3$) 1.31 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.35-1.50 (m, 5H,

(cyclohexyl)), 1.75-1.89 (m, 5H, (cyclohexyl)), 2.53-2.60 (m, 1H, CH), 4.27 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.83 (bs, 2H, $C\underline{H}_2Ar$), 4.97 (s, 2H, CH_2CO_2Et), 6.32 (bs, 1H, $\underline{H}NCH_2Ar$), 7.28-7.41 (m, 7H, 2 CH (Ar)), 7.79 (s, 1H, CH (H-8)), 7.86 (d, *J* = 7.9 Hz, 2H, 2 CH (Ar)), 8.54 (bs, 1H, NH); LRMS (MS-ES), calcd for $C_{29}H_{33}N_6O_3$ [M+H] *m/z* = 513.25, fnd. 513.50.



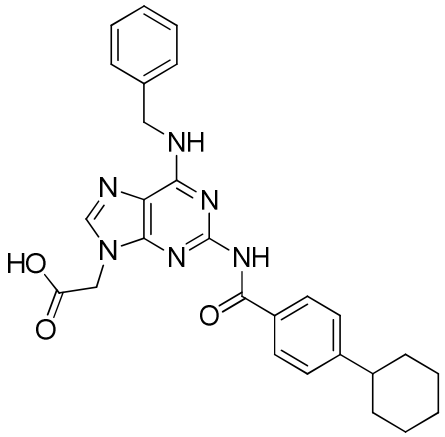
ethyl 2-(2-(4-cyclohexylbenzamido)-6-morpholino-9H-purin-9-yl)acetateacetate (11c).

Purine **10** was treated with morpholine according to general procedure **B**, yielding the final product **11c** as a off-white solid (67 %); m.p, > 70 ^oC (dec); IR (KBr, cm^{-1}) 2958, 2926, 2856, 1752, 1730, 1590, 1458, 1389, 1305, 1267, 1244, 1146, 1113; δ_H (400 MHz, $CDCl_3$) 1.30 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.36-1.50 (m, 5H, (cyclohexyl)), 1.75-1.90 (m, 5H, (cyclohexyl)), 2.54-2.60 (m, 1H, CH), 3.82 (t, *J* = 4.7 Hz, 4H, 2 CH_2 (morpholine)), 4.26 (q, *J* = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.29 (bs, 4H, $2CH_2$ (morpholine)), 4.92 (s, 2H, CH_2CO_2Et), 7.31 (d, J = 8.1 Hz, 2H, 2 CH (Ar)), 7.73 (s, 1H, CH (H-8)), 7.82 (d, J = 7.9 Hz, 2H, 2 CH (Ar)), 8.28 (bs, 1H, NH); LRMS (MS-ES), calcd for $C_{26}H_{33}N_6O_4$ [M+H] *m/z* = 493.25, fnd. 493.41.



2-(6-(butyl(methyl)amino)-2-(4-cyclohexylbenzamido)-9H-purin-9-yl)acetic acid (12a).

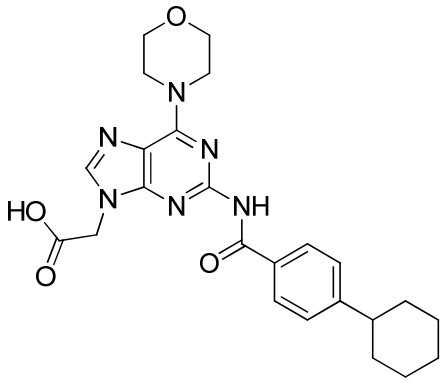
Purine **11a** was treated according to general procedure **E**, to yield final product **12a** as a white lyophilized powder (85 %): m.p. > 124 °C (dec); IR (KBr, cm^{-1})2925, 2852, 1504,1463, 1402, 1314, 1256, 1059; δ_H (400 MHz, DMSO-d_6) 0.89 (t, J = 7.3 Hz, 3H, $N(CH_2)_3C\underline{H}_3$), 1.27-1.49 (m, 7H, $N(CH_2)_2C\underline{H}_2CH_3$ and 5H (cyclohexyl)), 1.52-1.64 (m, 2H, $NCH_2C\underline{H}_2CH_2CH_3$), 1.69-1.80 (m, 5H, (cyclohexyl)), 2.54-2.61 (m, 1H, CH), 2.99-4.34 (bm, 5H, $C\underline{H}_3NC\underline{H}_2(CH_2)_2CH_3$), 4.60 (s, 2H, $C\underline{H}_2CO_2H$), 7.29 (d, J = 7.9 Hz, 2H, 2 CH (Ar)), 7.80 (d, J = 7.9 Hz, 2H, 2 CH (Ar)), 7.95 (s, 1H, CH (H-8)), 10.24 (s, 1H, NH); δ_C (100 MHz, DMSO-d_6) 13.8, 19.3, 25.5, 26.2, 29.2, 33.6, 33.6, 43.6, 46.1, 49.4, 116.0, 126.4, 128.0, 132.6, 140.6, 151.1, 151.5, 153.7, 165.5, 170.3; HRMS (MS-ES), calcd for $C_{25}H_{33}N_6O_3$ [M+H] m/z = 465.2601, fnd. 465.2608; *rp*HPLC t_R: condition (I) 15.259 (II) 39.232 minutes, purity 95.4 % and 96.9 %.



2-(6-(benzylamino)-2-(4-cyclohexylbenzamido)-9H-purin-9-yl)acetic acid (12b).

Purine **11b** was treated according to general procedure **E**, to yield final product **12b** as a white lyophilized powder (78 %): m.p. > 167 °C; IR (KBr, cm^{-1}) 2926, 2851, 1454, 1386, 1352, 1252, 1126; δ_H (400 MHz, DMSO-d_6) 1.32-1.48 (m, 5H, (cyclohexyl)), 1.69-1.84 (m, 5H, (cyclohexyl)), 2.52-2.60 (m, 1H, CH), 4.64 (bs, 4H, $HNC\underline{H}_2$ and $C\underline{H}_2CO_2H$), 7.18-7.21 (m, 1H, 1 CH (Ar)), 7.26-7.32 (m, 4H, CH (Ar)), 7.40 (d, J = 7.3 Hz, 2H, 2 CH (Ar)), 7.84 (d, J = 8.3 Hz,

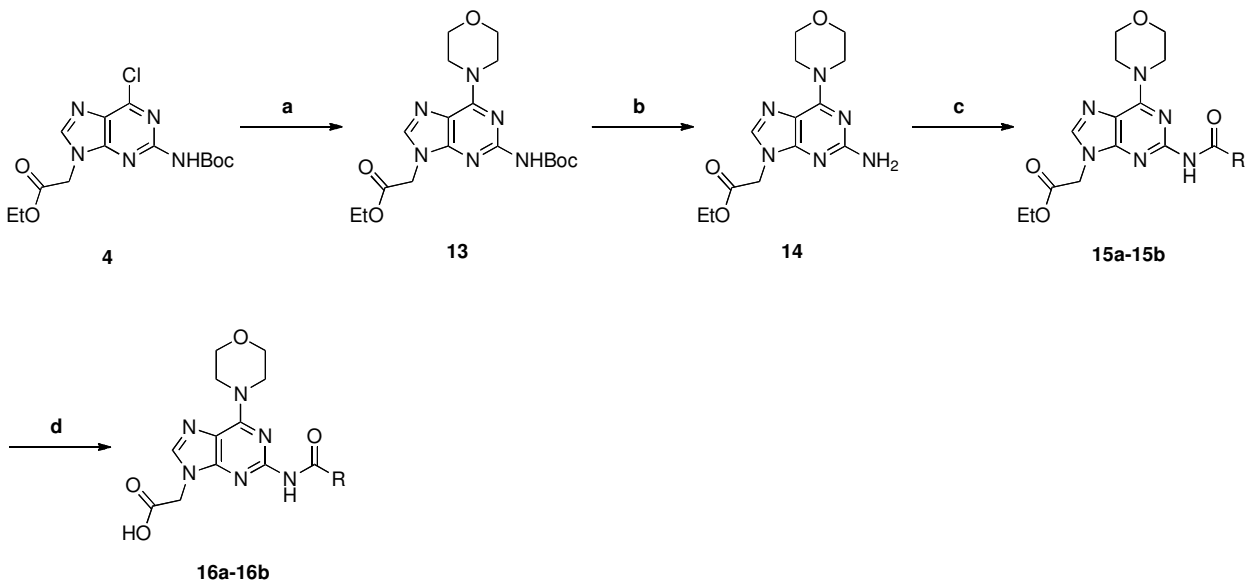
2H, 2 CH (Ar)), 7.98 (s, 1H, CH (H-8)), 8.21 (bs, 1H, NH), 10.30 (s, 1H, CONH); δ_C (100 MHz, DMSO-d_6) 25.5, 26.2, 33.6, 42.7, 43.6, 45.4, 116.0, 126.4, 126.6, 127.6, 128.0, 132.5, 140.3, 141.4, 151.3, 152.8, 154.3, 165.5, 169.8; HRMS (MS-ES), calcd for $C_{27}H_{29}N_6O_3$ [M+H] *m/z* = 485.2286, fnd. 485.2295; *rp*HPLC t_R: condition (I) 14.987 (II) 33.307 minutes, purity 99.0 % and 98.7 %.



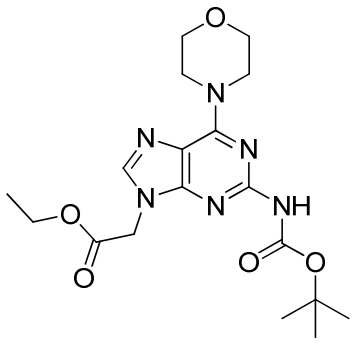
2-(2-(4-cyclohexylbenzamido)-6-morpholino-9H-purin-9-yl)acetic acid (12c).

Purine **11c** was treated according to general procedure **E**, to yield final product **12c** as a white lyophilized powder (73 %): m.p. > 113 °C (dec); IR (KBr, cm^{-1}3672, 2925, 2854, 1720, 1523, 1459, 1384, 1266, 1241, 1194; δ_H (400 MHz, DMSO-d_6) 1.32-1.52 (m, 5H, (cyclohexyl)), 1.69-1.81 (m, 5H, (cyclohexyl)), 2.53-2.59 (m, 1H, CH), 3.67-3.69 (m, 4H, 2 CH_2 (morpholine)), 4.14 (bs, 4H, CH_2 (morpholine)), 4.77 (s, 2H, $C\underline{H}_2CO_2H$), 7.30 (d, *J* = 8.3 Hz, 2H, 2 CH (Ar)), 7.81 (d, *J* = 8.1 Hz, 2H, 2 CH (Ar)), 8.04 (s, 1H, CH (H-8)), 10.37 (s, 1H, NH); δ_C (100 MHz, DMSO-d_6) 25.5, 26.2, 33.6, 43.6, 44.9, 45.0, 66.2, 115.8, 126.4, 128.0, 132.6, 140.6, 151.2, 152.0, 152.3, 152.9, 165.5, 169.3; HRMS (MS-ES), calcd for $C_{24}H_{29}N_6O_4$ [M+H] *m/z* = 465.2246, fnd. 465.2244; *rp*HPLC t_R: condition (I) 14.199 (II) 33.308 minutes, purity 96.2 %and 99.26%.

Scheme 3.



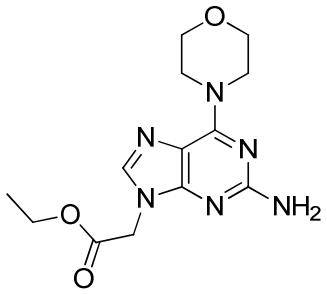
Scheme 3. a) *N*-morpholine, DIPEA, DMSO, 105 °C, 40 mins, microwave assisted, 83 %; b) TFA:CH_2Cl_2 (3:1), r.t., 1.5 hrs, 94 %; c) RCOCl, pyridine, r.t., 15 mins, 72-74 %; d) LiOH, THF:H_2O(3:1), r.t., 30 mins, 68-71 %.



ethyl 2-(2-((tert-butoxycarbonyl)amino)-6-morpholino-9H-purin-9-yl)acetate (13).

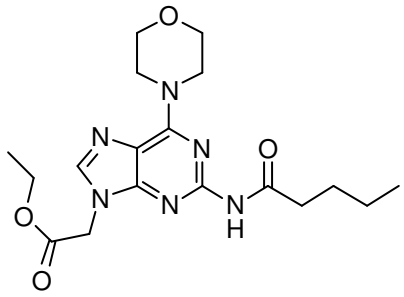
Purine **4** was treated with morpholine according to general procedure **B**, yielding the final product **13** as an off-white solid (83 %): m.p. = 69–85 °C; IR (KBr, cm^{-1}) 3689, 2978, 1750, 1583, 1517, 1472, 1367, 1268, 1221, 1151; δ_H (400 MHz, $CDCl_3$) 1.30 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.52 (s, 9H, $C(CH_3)_3$), 3.82 (t, *J* = 4.9 Hz, 4H, 2 CH_2 (morpholine)), 4.24 (q, *J* = 7.2 Hz, 2H, $COC\underline{H}_2CH_3$), 4.27 (bs, 4H, 2CH_2 (morpholine)), 4.89 (s, 2H, CH_2CO_2Et), 7.13 (s,

1H, NH), 7.69 (s, 1H, CH (H-8));LRMS (MS-ES), calcd for $C_{18}H_{27}N_6O_5$ [M+H] *m/z* = 407.20, fnd. 407.43.



ethyl 2-(2-amino-6-morpholino-9H-purin-9-yl)acetate (14).

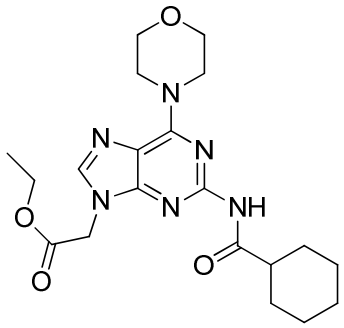
Purine **13** was treated according to general procedure **F**, to yield product **14** as an off-white solid (94%): m.p. = 93-98°C; IR (KBr, cm^{-1}) 3672, 2922, 1736, 1540, 1459, 1312, 1182; δ_H (400 MHz, $CDCl_3$) 1.31 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 3.82 (t, *J* = 4.9 Hz, 4H, 2 CH_2 (morpholine)), 4.26 (q, *J* = 7.2 Hz, 2H, $COC\underline{H}_2CH_3$), 4.29 (bs, 4H, $2CH_2$ (morpholine)), 4.92 (s, 2H, CH_2CO_2Et), 7.48 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{13}H_{19}N_6O_3$ [M+H] *m/z* = 307.14, fnd. 307.28.



ethyl 2-(6-morpholino-2-pentanamido-9H-purin-9-yl)acetate (15a)

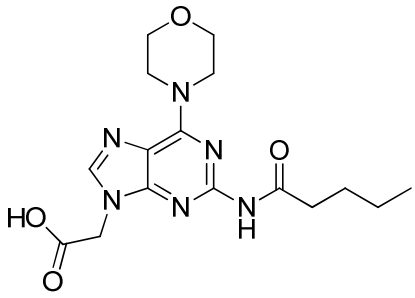
Purine **14** was treated with valeryl chloride according to general procedure **G**, to yield lyophilized product **15a** as a white solid (72%): m.p. > 141°C (dec); IR (KBr, cm^{-1})3551, 3477, 3414, 3228, 3110, 2956, 2930, 2849, 1751, 1670, 1638, 1608; δ_H (400 MHz, $CDCl_3$) 0.94 (t, *J* = 7.3 Hz, 3H, $(CH_2)_3C\underline{H}_3$), 1.30 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.41 (sextet, *J* = 7.4 Hz, 2H, $(CH_2)_2C\underline{H}_2CH_3$), 1.71 (p, *J* = 7.5 Hz, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 2.78 (m, 2H, $C\underline{H}_2(CH_2)_2CH_3$), 3.83

(t, J = 4.9 Hz, 4H, 2 CH_2 (morpholine)), 4.26 (q, J = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.28 (bs, 4H, $2CH_2$ (morpholine)), 4.86 (s, 2H, CH_2CO_2Et), 7.69 (bs, 1H, NH), 7.70 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{18}H_{26}N_6O_4Na$ [M+Na] m/z = 413.20, fnd 413.37.



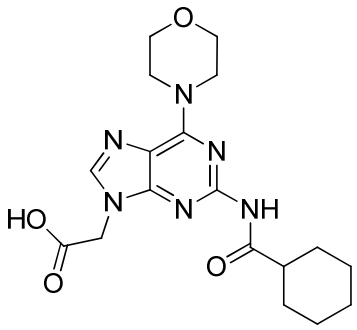
ethyl 2-(2-(cyclohexanecarboxamido)-6-morpholino-9H-purin-9-yl)acetate (15b)

Purine **14** was treated with valeryl chloride according to general procedure **G**, to yield lyophilized product **15b** as an off-white solid (74 %): m.p. = 142-147 °C; IR (KBr, cm^{-1}) 3551, 3415, 3238, 2928, 2852, 1755, 1669, 1604, 1585, 1514, 1448, 1407; δ_H (400 MHz, $CDCl_3$) 1.29 (t, J = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.28-1.32 (m, 2H, CH_2 (cyclohexyl)), 1.49 (m, 3H, (cyclohexyl)), 1.70-1.71 (m, 1H, (cyclohexyl)), 1.82 (m, 2H, (cyclohexyl)), 1.96-1.99 (m, 2H, (cyclohexyl)), 2.88 (m, 1H, CH), 3.82 (t, J = 4.9 Hz, 4H, 2 CH_2 (morpholine)), 4.25 (q, J = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.27 (bs, 4H, $2CH_2$ (morpholine)), 4.87 (s, 2H, CH_2CO_2Et), 7.69 (bs, 1H, NH), 7.70 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for $C_{20}H_{29}N_6O_4$ [M+H] m/z = 417.22, fnd 417.40.



2-(6-morpholino-2-pentanamido-9H-purin-9-yl)acetic acid (16a)

Purine **15a** was treated according to general procedure **E**, to yield final product **16a** as a white lyophilized powder (71 %): m.p. > 138 °C (dec); IR (KBr, cm^{-1}) 3233, 1753, 1516, 1466, 1385, 1311, 1267, 1220, 1114, 1009; δ_H (400 MHz, DMSO-d_6) 0.87 (t, J = 7.3 Hz, 3H, $(CH_2)_3C\underline{H}_3$), 1.29 (sextet, J = 7.5 Hz, 2H, $(CH_2)_2C\underline{H}_2CH_3$), 1.52 (p, J = 7.5 Hz, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 2.47 (t, J = 7.2 Hz, 2H, $C\underline{H}_2(CH_2)_2CH_3$), 3.83 (t, J = 4.3 Hz, 4H, 2 CH_2 (morpholine)), 4.19 (bs, 4H, 2 CH_2 (morpholine)), 4.74 (s, 2H, $C\underline{H}_2CO_2H$), 7.99 (s, 1H, CH (H-8)), 9.92 (s, 1H, NH); δ_C (100 MHz, DMSO-d_6) 13.7, 21.8, 26.8, 35.9, 44.7, 45.0, 66.1, 115.3, 140.2, 151.9, 152.1, 152.9, 169.2, 171.5; HRMS (MS-ES), calcd for $C_{16}H_{23}N_6O_4$ [M+H] m/z = 363.1775, fnd. 363.1775; *rp*HPLC t_R: condition (I) 10.270 (II) 15.079 minutes, purity 98.2 %and 98.0%.



2-(2-(cyclohexanecarboxamido)-6-morpholino-9H-purin-9-yl)acetic acid (16b)

Purine **15b** was treated according to general procedure **E**, to yield final product **16b** as a white lyophilized powder (68 %): m.p. > 122 °C (dec); IR (KBr, cm^{-1}) 3631, 2927, 2856, 1743, 1514, 1466, 1385, 1306, 1265, 1240, 1192, 1116, 1069; δ_H (400 MHz, DMSO-d_6) 1.09-1.38 (m, 5H, (cyclohexyl)), 1.61-1.78 (m, 5H, (cyclohexyl)), 2.61-2.75 (m, 1H, (cyclohexyl)), 3.82 (t, J = 4.6 Hz, 4H, 2 CH_2 (morpholine)), 4.19 (bs, 4H, 2 CH_2 (morpholine)), 4.74 (s, 2H, CH_2CO_2H), 7.99 (s, 1H, CH (H-8)), 9.85 (s, 1H, NH); δ_C (100 MHz, DMSO-d_6) 25.2, 25.4, 29.0, 43.8, 44.7, 45.0, 66.2, 140.2, 151.9, 152.2, 153.0, 169.3, 174.3; HRMS (MS-ES), calcd for $C_{18}H_{25}N_6O_4$ [M+H] m/z = 389.1919, fnd. 389.1931; *rp*HPLC t_R: condition (I) 10.978 (II) 17.891 minutes, purity 97.9 % and 98.0%.

Experimental Procedure

Cells and reagents

Normal mouse fibroblasts (NIH3T3) and counterparts transformed by v-Src (NIH3T3/v-Src) or overexpressing the human epidermal growth factor (EGF) receptor (NIH3T3/hEGFR), the murine thymus epithelial stromal cells, *and* the human breast cancer (MDA-MB-231) and pancreatic cancer (Panc-1) cells have all been previously reported [2, 6]. Antibodies against Stat3, pY705Stat3, Erk1/2, and pErk1/2 are from Cell Signaling Technology (Danvers, MA). Recombinant human epidermal growth factor (rhEGF) was obtained from Invitrogen (Carlsbad, CA).

Cloning and Protein Expression

Coding regions for the murine Stat3 protein and Stat3 SH2 domain were amplified by PCR and cloned into vectors pET-44 Ek/LIC (Novagen) and pET SUMO (Invitrogen), respectively. The primers used for amplification were: Stat3 Forward: GACGACGACAAGATGGCTCAGTGGAACCAGCTGC; Stat3 Reverse: GAGGAGAAGCCCGGTTATCACATGGGGGAGGTAGCACACT; Stat3-SH2 Forward: ATGGGTTTCATCAGCAAGGA; Stat3-SH2 Reverse: TCACCTACAGTACTTTCCAAATGC. Clones were sequenced to verify the correct sequences and orientation. His-tagged recombinant proteins were expressed in BL21(DE3) cells, and purified on Ni-ion sepharose column.

Nuclear extract preparation, gel shift assays, and densitometric analysis

Nuclear extract preparations and electrophoretic mobility shift assay (EMSA) were carried out as previously described [11]. Briefly, nuclear extracts of equal total protein were pre-incubated with increasing concentration of compound for 30 min at room temperature prior to the incubation with the radiolabeled probe for 30 min at 30 ^{o}C before subjecting to EMSA analysis. The ^{32}P-labeled oligonucleotide probe used was hSIE (high affinity sis-inducible element from the *c-fos* gene, m67 variant, 5'-AGCTTCATTTCCCGTAAATCCCTA) that binds Stat1 and Stat3 [12]. Bands corresponding to DNA-binding activities were scanned and quantified for each concentration of compound using ImageQuant and plotted as percent of control (vehicle) against concentration of compound, from which the IC_{50} values were derived, as previously reported [13].

Immunoprecipitation and Immunoblotting assay

Immunoprecipitation, and SDS/PAGE and Western blotting analysis were performed as previously described [2, 6]. Primary antibodies used were anti-Stat3, pY705Stat3, pY416Src, Src, pErk1/2, Erk1/2, pStat1, Stat1, (Cell Signaling), and antiphosphotyrosine, clone 4G10 (Upstate Biotechnology, Lake Placid, NY). Where appropriate, cells were stimulated for 12 min by 9 ng/μl rhEGF (12 μl into 3 ml culture) prior to preparation of whole-cell lysates for immunoprecipitation and/or immunoblotting analysis.

Cell viability and proliferation assay

Cells in culture in 6-well or 96-well plates were treated with or without agents for 24-144 h and subjected to CyQuant cell proliferation assay (Invitrogen Corp/Life Technologies Corp, Carlsbad, CA). IC_{50} values (Table 2) were derived from the plot of viability versus drug concentration.

Surface Plasmon Resonance Analysis

Surface Plasmon resonance analysis was performed to characterize the binding of compounds to Stat3, as previously reported [6]. SensiQ and its analysis software Qdat (ICX Technologies, Oklahoma City, OK) were used to analyze the interaction between agents and the Stat3 protein and to determine the binding affinity. Purified Stat3 was immobilized on a HisCap Sensor Chip by injecting 50 μg/ml of Stat3 onto the chip. Various concentrations of compounds in running buffer (1X PBS, 0.5% DMSO) were passed over the sensor chip to produce response signals. The association and dissociation rate constants were calculated using the Qdat software. The ratio of the association and dissociation rate constants was determined as the affinity (K_D).

References

1. Becker, S.; Groner, B.; Muller, C. W. Three-dimensional structure of the Stat3beta homodimer bound to DNA. *Nature* **1998**, 394, 145-151.

2. Turkson, J.; Ryan, D.; Kim, J. S.; Zhang, Y.; Chen, Z.; Haura, E.; Laudano, A.; Sebti, S.; Hamilton, A. D.; Jove, R. Phosphotyrosyl peptides block Stat3-mediated DNA-binding activity, gene regulation and cell transformation. *J. Biol. Chem.* 2001, **276**, 45443-45455.

3. Gunning, P. T.; Glenn, M. P.; Siddiquee, K. A.; Katt, W. P.; Masson, E.; Sebti, S. M.; Turkson, J.; Hamilton, A. D. Targeting protein-protein interactions: suppression of Stat3 dimerization with rationally designed small-molecule, nonpeptidic SH2 domain binders. *ChemBioChem* **2008**, 9, 2800-2803.

4. Gunning, P. T.; Katt, W. P.; Glenn, M.; Siddiquee, K.; Kim, J. S.; Jove, R.; Sebti, S. M.; Turkson, J.; Hamilton, A. D. Isoform selective inhibition of STAT1 or STAT3 homo-dimerization via peptidomimetic probes: structural recognition of STAT SH2 domains. *Bioorg. Med. Chem. Lett.* **2007**, 17, 1875-1878.

5. Fletcher, S.; Singh, J.; Zhang, X.; Yue, P.; Page, B. D.; Sharmeen, S.; Shahani, V. M.; Zhao, W.; Schimmer, A. D.; Turkson, J.; Gunning, P. T. Disruption of transcriptionally active Stat3 dimers with non-phosphorylated, salicylic acid-based small molecules: potent in vitro and tumor cell activities. *Chembiochem* **2009**, 10, 1959-64.

6. Zhang, X.; Yue, P.; Fletcher, S.; Zhao, W.; Gunning, P. T.; Turkson, J. A novel small-molecule disrupts Stat3 SH2 domain-phosphotyrosine interactions and Stat3-dependent tumor processes. *Biochem Pharmacol* **2010**, 79, 1398-409.

7. Fletcher, S.; Turkson, J.; Gunning, P. T. Molecular approaches towards the inhibition of the signal transducer and activator of transcription 3 (Stat3) protein. *ChemMedChem* **2008**, 3, 1159-68.

8. Fletcher, S.; Shahani, V. M.; Gunning, P. T. Facile and efficient access to 2,6,9-tri-substituted purines through sequential N9, N2 Mitsunobu reactions. *Tet. Lett* 2009, 50, 4258-4261.

9. Fletcher, S.; Shahani, V. M.; Lough, A. J.; Gunning, P. T. Concise access to N9-mono-, N2-mono- and N2,N9-di-substituted guanines via efficient Mitsunobu reactions *Tetrahedron* 2010, 66:4621-32.

10. Siddiquee, K. A. Z.; Gunning, P. T.; Glenn, M.; Katt, W. P.; Zhang, S.; Schroeck, C.; Sebti, S. M.; Jove, R.; Hamilton, A. D.; Turkson, J. An Oxazole-Based Small-Molecule Stat3

Inhibitor Modulates Stat3 Stability and Processing and Induces Antitumor Cell Effects. *ACS Chem. Biol.* **2007**, 2, 787-798.

11. Turkson, J.; Bowman, T.; Garcia, R.; Caldenhoven, E.; De Groot, R. P.; Jove, R. Stat3 activation by Src induces specific gene regulation and is required for cell transformation. *Mol. Cell. Biol.* **1998**, 18, 2545-2552.

12. Wagner, M.; Kleeff, J.; Friess, H.; Buchler, M. W.; Korc, M. Enhanced expression of the type II transforming growth factor-beta receptor is associated with decreased survival in human pancreatic cancer. *Pancreas.* **1999**, 19, 370-6.

13. Turkson, J.; Zhang, S.; Mora, L. B.; Burns, A.; Sebti, S.; Jove, R. A novel platinum compound inhibits constitutive Stat3 signaling and induces cell cycle arrest and apoptosis of malignant cells. *J Biol Chem.* **2005**, 280, 32979-32988.