Supporting Information

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

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Results and Discussion

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

The crystal structure of the Stat3:Stat3-DNA ternary complex \cite{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 \cite{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 \cite{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 \cite{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. 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, 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 $\pi$-$\pi$ 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 = cyclohexylbenzyl, we observed equipotent or moderate increases in affinity for the
different aromatic Y substituents (S3I-V3-27 (X = cyclohexylbenzyl, Y = N(CH$_3$)Bn): $K_D = 4.0 \mu M$ cf. S3I-V2-73 (X = pentyl, Y = N(CH$_3$)Bn): $K_D = 38.4 \mu M$). 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) ($K_D = 0.9 \mu M$) and S3I-S3-41 (7am) ($K_D = 2.0 \mu M$), 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$_2$Cl$_2$, 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 KMnO₄ stain or phosphomolybdic acid stain). \(^1\)H and \(^{13}\)C NMR spectra were recorded on Bruker 400 MHz and a Varian 500 MHz spectrometers in either CDCl₃, CD₃OD or \(d_6\)-DMSO. Chemical shifts (\(\delta\)) 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 CH₃COONH₄ 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 (PPh₃, 1.3 eq). After ~2 min, diisopropylazodicarboxylate (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
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 (3.0 eq) 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 Na₂SO₄, filtered and concentrated under reduced pressure. Resulting residue was adsorbed onto silica gel from CH₂Cl₂ 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 (3.0 eq) 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 Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was dry-loaded onto silica gel from CH₂Cl₂ 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 (1.5 eq) 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$_2$SO$_4$, 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$_2$O (3:1). Reaction was deemed complete after 30 minutes, then diluted with water acidified (pH~5.5) by KH$_2$PO$_4$, and continuously extracted into EtOAc. Organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. Reaction was purified by flash column chromatography using an isocratic solvent system (35:7:1 DCM:MeOH:H$_2$O) on the Biotage Isolera. Dried product was suspended in a mixture of milicule 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$_2$O). 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$_2$SO$_4$ 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$_4$OH) and dried under reduced pressure.

**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$_2$O(3:1), r.t., 15 mins, 75-97 %; g) TFA:CH$_2$Cl$_2$ (1:1), r.t., 1 hr, 63-95 %.
**N⁹-Boc-2-amino-6-chloropurine (2)**

A rapidly stirred solution of 2-amino-6-chloropurine (1 eq) and di-tert-butyl dicarbonate (Boc₂O; 1 eq) in anhydrous DMSO (0.3M) was briefly cooled over ice under an N₂ 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 Na₂SO₄, filtered and concentrated to afford N⁹-Boc-2-amino-6-chloropurine (2) as a white solid (75 %): δ_H (400 MHz, d₆-DMSO) 1.60 (s, 9H, (CH₃)₃), 7.19 (br s, 2H, NH₂), 8.38 (s, 1H, H-8); δ_C (100 MHz, CDCl₃) 27.9, 87.1, 125.4, 140.1, 145.5, 152.3, 153.3, 160.4; LRMS (ES-MS) calcd for C₁₀H₁₂ClN₅O₂Na [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 N₂ 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 NaHCO₃ solution. The organics were extracted into EtOAc, dried on anhydrous Na₂SO₄, filtered and concentrated. The residue was dry-loaded onto silica gel from CH₂Cl₂, then purified by flash column chromatography (92:7:1 CH₂Cl₂:MeOH:NH₄OH) to afford product as a white powder (95%): \( \delta_H \) (400 MHz, \( d_6 \)-DMSO) 1.47 (s, 9H, \((\text{CH}_3)_3\)), 8.46 (s, 1H, H-8), 10.22 (s, 1H, NHBoc), 13.60 (br s, 1H, H-9); \( \delta_C \) (100 MHz, CDCl₃) 28.0, 82.2, 127.8, 145.3, 150.8, 151.1, 151.5, 153.0; LRMS (ES-MS) calcd for C₁₀H₁₂ClN₅O₂Na \([M + Na^+] \ m/z = 292.06\), obsd 291.90.

**ethyl 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 triphenyl phosphine (PPh₃; 1.1 eq) under an N₂ atmosphere. To the homogenous solution, diisopropylazodicarboxylate (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 CH₂Cl₂, 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; \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 1.22 (t, \( J = 7.1 \text{ Hz}, \text{H}, \text{CH}_3 \)), 1.46 (s, 9H, C(\text{CH}_3)_3), 4.18 (q, \( J = 7.1 \text{ Hz}, 2\text{H}, \text{CH}_2\text{CH}_3 \)), 5.11 (s, 2H, CH₂CO₂Et), 8.46 (s, 1H, H-8), 10.33 (s, 1H, NHBoc); \( \delta_C \) (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 C₁₄H₁₈ClN₅O₄Na \([M+Na^+] \ m/z = 378.0939\), 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$_{\text{H}}$ (400 MHz, CDCl$_3$) 0.88 (t, $J = 6.9$ Hz, 3H, (CH$_2$)$_4$CH$_3$), 1.25-1.34 (m, 7H, CO$_2$CH$_2$CH$_3$ and (CH$_2$)$_2$CH$_2$CH$_2$CH$_3$), 1.50 (s, 9H, C(CH$_3$)$_3$), 1.65 (p, $J = 7.4$ Hz, 2H, CH$_2$CH$_2$(CH$_2$)$_2$CH$_3$), 3.89-3.93 (m, 2H, CH$_2$(CH$_3$)CH$_3$), 4.27 (q, $J = 7.1$ Hz, 2H, CO$_2$CH$_2$CH$_3$), 4.96 (s, 2H, CH$_2$CO$_2$Et), 8.07 (s, 1H, CH (H-8)); LRMS (MS-ES) calcd for C$_{19}$H$_{29}$ClN$_5$O$_4$ [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$_{\text{H}}$ (400 MHz, CDCl$_3$) 1.20-1.38 (m, 8H, 5H (cyclohexyl) and CO$_2$CH$_2$CH$_3$), 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$_2$CH$_3$CH$_3$), 4.93 (s, 2H, CH$_2$Ar), 5.15 (s, 2H, CH$_2$CO$_2$Et), 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$_5$O$_4$ [M+H] $m/z = 528.23$, fnd. 528.32.

![Chemical Structure](image)

**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$_2$)$_4$CH$_3$), 1.29-1.33 (m, 7H, CO$_2$CH$_2$CH$_3$ and (CH$_2$)$_2$CH$_2$CH$_3$CH$_3$), 1.48 (s, 9H, C(CH$_3$)$_3$), 1.58-1.65 (m, 2H, (CH$_2$)$_3$CH$_2$CH$_3$), 3.77-3.81 (m, 2H, CH$_2$(CH$_2$)$_2$CH$_3$), 4.25 (q, J = 7.1 Hz, 2H, CO$_2$CH$_2$CH$_3$), 4.83 (bs, 2H, CH$_2$Ar), 4.90 (s, 2H, CH$_2$CO$_2$Et), 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$_6$O$_4$ [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; \(\delta_H\) (400 MHz, CDCl\(_3\)) 0.81-0.85 (t, \(J = 7.0\) Hz, 3H, \(\text{CH}_2\text{CH}_3\)), 1.24-1.32 (m, 7H, \(\text{CO}_2\text{CH}_2\text{CH}_3\) and \(\text{CH}_2\text{CO}_2\text{Et}\)), 1.32 (s, 9H, \(\text{C(CH}_3)_3\)), 1.46 (s, 9H, \(\text{C(CH}_3)_3\)), 1.57-1.67 (m, 2H, \(\text{CH}_2\text{Ar}\)), 3.12-3.69 (bm, 3H, NCH\(_3\)), 3.76-3.80 (m, 2H, \(\text{CH}_2\text{CO}_2\text{Et}\)), 4.25 (q, \(J = 7.1\) Hz, 2H, \(\text{CH}_2\text{CO}_2\text{CH}_3\)), 4.91 (s, 2H, \(\text{CH}_2\text{Ar}\)), 4.99-5.63 (bm, 2H, \(\text{CH}_2\text{Ar}\)), 7.23-7.33 (m, 5H, CH (Ar)), 7.75 (s, 1H, CH (H-8)); LRMS (MS-ES) calcd for \(\text{C}_{27}\text{H}_{39}\text{N}_6\text{O}_4\) [M+H] \(m/z = 511.30\), fnd. 511.39.

ethyl 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; δH (400 MHz, CDCl$_3$) 0.88 (t, $J = 7.0$ Hz, 3H, (CH$_2$)$_4$CH$_3$), 1.29-1.33 (m, 7H, CO$_2$CH$_2$CH$_3$ and (CH$_2$)$_2$CH$_2$CH$_2$CH$_3$), 1.48 (s, 9H, C(CH$_3$)$_3$), 1.66-1.73 (m, 2H, (CH$_2$)$_3$CH$_2$CH$_3$), 3.86-3.90 (m, 2H, CH$_2$(CH$_2$)$_3$CH$_3$), 4.27 (q, $J = 7.1$ Hz, 2H, CO$_2$CH$_2$CH$_3$), 4.94 (s, 2H, CH$_2$CO$_2$Et), 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$_6$O$_4$ [M+H] $m/z = 483.26$, fnd. 483.31.

![Chemical structure of 6ac](image1)

ethyl 2-(2-((tert-butoxycarbonyl)(pentyl)amo-o)-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; δH (400 MHz, CDCl$_3$) 0.86 (t, $J = 6.9$ Hz, 3H, (CH$_2$)$_4$CH$_3$), 1.25-1.34 (m, 7H, CO$_2$CH$_2$CH$_3$ and (CH$_2$)$_2$CH$_2$CH$_2$CH$_3$), 1.48 (s, 9H, C(CH$_3$)$_3$), 1.65 (p, 2H, CH$_2$CH$_2$(CH$_2$)$_2$CH$_3$), 3.56 (vbs, 3H, CH$_3$(furfuryl)), 3.81 (t, $J = 7.6$ Hz, 2H, CH$_2$(CH$_2$)$_3$CH$_3$), 4.25 (q, $J = 7.1$ Hz, 2H, CO$_2$CH$_2$CH$_3$), 4.93 (s, 2H, CH$_2$CO$_2$Et), 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$_6$O$_5$ [M+H] $m/z = 501.27$, fnd. 501.30.
ethyl 2-(2-((tert-butoxycarbonyl)(pentyl)amino)-6-(clopentylamino)-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; δH (400 MHz, CDCl₃) 0.87 (t, J = 7.0 Hz, 3H, (CH₂)₄CH₃), 1.25-1.34 (m, 7H, CO₂CH₂CH₃ and (CH₂)₂CH₂CH₂CH₃), 1.48 (s, 9H, C(CH₃)₃), 1.54-1.84 (m, 8H, CH₂CH₂(CH₂)₂CH₃ and 3 CH₂ (cyclopentyl)), 2.11 (m, 2H, CH₂ (cyclopentyl)), 3.81 (t, J = 7.6 Hz, 2H, CH₂(CH₂)₂CH₃), 4.25 (q, J = 7.0 Hz, 2H, CO₂CH₂CH₃), 4.53 (bs, 1H, CH (cyclopentyl)), 4.89 (s, 2H, CH₂CO₂Et), 5.68 (bs, 1H, NH), 7.76 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C₂₄H₃₉N₆O₄ [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; $\delta_H$ (400 MHz, CDCl$_3$) 0.88 (t, $J = 6.9$ Hz, 3H, (CH$_2$)$_4$CH$_3$), 1.25-1.44 (m, 13H, CO$_2$CH$_2$CH$_3$, (CH$_2$)$_2$CH$_2$CH$_2$CH$_3$ and 3 CH$_2$ (cyclohexyl)), 1.49 (s, 9H, C(CH$_3$)$_3$), 1.62-1.71 (m, 2H, CH$_2$CH$_2$(CH$_2$)$_2$CH$_3$), 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, CH$_2$(CH$_2$)$_2$CH$_3$), 4.10 (bs, 1H, CH (cyclohexyl)), 4.25 (q, $J = 7.1$Hz, 2H, CO$_2$CH$_2$CH$_3$), 4.88 (s, 2H, CH$_2$CO$_2$Et), 5.62 (bs, 1H, NH), 7.76 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C$_{25}$H$_{41}$N$_6$O$_4$ [M+H] $m/z = 489.31$, fnd. 489.34.

![Structure](image)

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; $\delta_H$ (400 MHz, CDCl$_3$) 0.87 (t, $J = 7.0$ Hz, 3H, (CH$_2$)$_4$CH$_3$), 1.24-1.33 (m, 10H, CO$_2$CH$_2$CH$_3$, (CH$_2$)$_2$CH$_2$CH$_2$CH$_3$ and NCH$_2$CH$_3$), 1.47 (s, 9H, C(CH$_3$)$_3$), 1.67 (p, 2H, CH$_2$CH$_2$(CH$_2$)$_2$CH$_3$), 3.42 (bm, 3H, NCH$_3$), 3.79 (t, $J = 7.7$ Hz, 2H, CH$_2$(CH$_2$)$_2$CH$_3$), 4.04 (bm, 2H, NCH$_2$CH$_3$), 4.24 (q, $J = 7.1$ Hz, 2H, CO$_2$CH$_2$CH$_3$), 4.89 (s, 2H, CH$_2$CO$_2$Et), 7.74 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C$_{22}$H$_{37}$N$_6$O$_4$ [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; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 0.87 (t, \(J = 7.0\) Hz, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 1.24-1.33 (m, 13H, CO\(_2\)CH\(_2\)CH\(_3\), (CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CH\(_3\) and CH(CH\(_3\))\(_2\)), 1.48 (s, 9H, C(CH\(_3\))\(_3\)), 1.66 (p, 2H, CH\(_2\)CH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 3.80 (t, \(J = 7.6\) Hz, 2H, CH\(_2\)(CH\(_2\))\(_3\)CH\(_3\)), 4.25 (q, \(J = 7.1\) Hz, 2H, CO\(_2\)CH\(_2\)CH\(_3\)), 4.45 (bs, 1H, CH(CH\(_3\))\(_2\)), 4.89 (s, 2H, CH\(_2\)CO\(_2\)Et), 5.56(bs, 1H, NH), 7.76 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C\(_{22}\)H\(_{37}\)N\(_6\)O\(_4\) [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; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 0.87 (t, \(J = 6.8\) Hz, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 1.25-1.33 (m, 7H, CO\(_2\)CH\(_2\)CH\(_3\) and (CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.49 (s, 9H, C(CH\(_3\))\(_3\)),
1.65 (p, 2H, CH$_2$CH$_2$(CH$_2$)$_2$CH$_3$), 3.82 (t, $J = 7.6$ Hz, 2H, CH$_2$(CH$_2$)$_3$CH$_3$), 4.25 (q, $J = 7.1$ Hz, 2H, CO$_2$CH$_2$CH$_3$), 4.27 (vbs, 2H, CH$_2$CHCH$_2$), 4.90 (s, 2H, CH$_2$CO$_2$Et), 5.18 (d, $J = 9.9$Hz, 1H, CH$_2$CHCH$_2$), 5.31 (d, $J = 17.4$ Hz, 1H, CH$_2$CHCH$_2$), 5.85(bs, 1H, NH), 5.94-6.04 (m, 1H, CH$_2$CHCH$_2$), 7.80 (s, 1H, CH (H-8)). LRMS (MS-ES), calcd for C$_{22}$H$_{35}$N$_6$O$_4$ [M+H] $m/z$ = 447.26, fnd. 447.36.

![Image of chemical structure]

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 white solid (83 %): m.p. = 89-93 °C; IR (KBr, cm$^{-1}$) 3425, 3290, 2960, 2925, 2885, 1760, 1670, 1630, 1580, 1380, 1249, 1200; $\delta_H$ (400 MHz, CDCl$_3$) 0.87 (t, $J = 6.8$ Hz, 3H, (CH$_2$)$_3$CH$_3$), 0.99 (s, 3H, CH(CH$_3$)$_3$), 1.00 (s, 3H, CH(CH$_3$)$_3$), 1.25-1.34 (m, 7H, CO$_2$CH$_2$CH$_3$ and (CH$_2$)$_2$CH$_2$CH$_2$CH$_3$), 1.48 (s, 9H, C(CH$_3$)$_3$), 1.66 (p, 2H, CH$_2$CH$_2$(CH$_2$)$_2$CH$_3$), 1.97 (septet, $J = 6.6$ Hz, 1H, CH(CH$_3$)$_3$), 3.43 (bs, 2H, CH$_2$CH(CH$_3$)$_3$), 3.81 (t, $J = 7.6$ Hz, 2H, CH$_2$(CH$_2$)$_3$CH$_3$), 4.25 (q, $J = 7.1$ Hz, 2H, CO$_2$CH$_2$CH$_3$), 4.89 (s, 2H, CH$_2$CO$_2$Et), 5.79 (bs, 1H, NH), 7.76 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C$_{23}$H$_{39}$N$_6$O$_4$ [M+H] $m/z$ = 463.30, fnd. 463.41.
2ethyl 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; δH (400 MHz, CDCl₃) 0.88 (t, J = 7.0 Hz, 3H, (CH₂)₄CH₃), 0.96 (t, J = 7.3 Hz, 3H, (CH₂)₃CH₃), 1.26-1.45 (m, 9H, CO₂CH₂CH₃, CH₂CH₂CH₂CH₃ and (CH₂)₂CH₂CH₂CH₃), 1.49 (s, 9H, C(CH₃)₃), 1.62-1.73 (4H, CH₂CH₂CH₂CH₃ and CH₂CH₂(CH₂)₂CH₃), 3.20-4.24 (m, 5H, CH₂(CH₂)₂CH₃ and CH₃(CH₂)₃CH₃), 3.79 (t, J = 7.6 Hz, 2H, CH₂(CH₂)₃CH₃), 4.25 (q, J = 7.1 Hz, 2H, CO₂CH₂CH₃), 4.91 (s, 2H, CH₂CO₂Et), 7.74 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C₂₄H₄₁N₆O₄ [M+H] m/z = 477.31, fnd. 477.38.

ethyl 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; \(\delta_H\) (400 MHz, CDCl\(_3\)) 0.87 (t, \(J = 6.9\) Hz, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 0.95 (s, 3H, (CH\(_2\))\(_2\)CH(CH\(_3\))\(_2\)), 0.96 (s, 3H, (CH\(_2\))\(_2\)CH(CH\(_3\))\(_2\)), 1.25-1.34 (m, 7H, CO\(_2\)CH\(_2\)CH\(_3\), and (CH\(_2\))\(_2\)CH\(_2\)CH\(_3\)), 1.49 (s, 9H, C(CH\(_3\))\(_3\)), 1.53-1.78 (m, 5H, CH\(_2\)CH\(_2\)(CH\(_3\))\(_2\)CH\(_3\) and CH\(_2\)CH\(_2\)CH(CH\(_3\))\(_2\)), 3.62 (bs, 2H, CH\(_2\)(CH\(_2\))\(_2\)(CH\(_3\))\(_2\)), 4.25 (q, \(J = 7.6\) Hz, 2H, CH\(_2\)(CH\(_2\))\(_2\)(CH\(_3\))\(_2\)), 4.89 (s, 2H, CH\(_2\)CO\(_2\)Et) 5.76 (bs, 1H, NH), 7.77 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C\(_{24}\)H\(_{41}\)N\(_6\)O\(_4\) [M+H] \(m/z\) = 477.3, fnd 477.32.

**ethyl 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; \(\delta_H\) (400 MHz, CDCl\(_3\)) 0.87 (t, \(J = 6.9\) Hz, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 1.25-1.31 (m, 7H, CO\(_2\)CH\(_2\)CH\(_3\) and (CH\(_2\))\(_2\)CH\(_2\)CH\(_3\)CH\(_3\)), 1.47 (s, 9H, C(CH\(_3\))\(_3\)), 1.65 (p, \(J = 7.4\) Hz, 2H, CH\(_2\)CH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 3.78-3.84 (m, 6H, CH\(_2\)(CH\(_2\))\(_3\)CH\(_3\) and 2 CH\(_2\) (morpholine)), 4.25 (q, \(J = 7.2\) Hz, 2H, CO\(_2\)CH\(_2\)CH\(_3\)), 4.26 (bs, 4H, 2 CH\(_2\) (morpholine)), 4.89 (s, 2H, CH\(_2\)CO\(_2\)Et), 7.75 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C\(_{23}\)H\(_{36}\)N\(_6\)O\(_4\)Na [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, 1651, 1578, 1533, 1448, 1407, 1354, 1276, 1222, 1149; $\delta_H$ (400 MHz, CDCl$_3$) 0.82 (t, $J = 7.3$ Hz, 3H, (CH$_2$)$_2$CH$_3$), 1.04-1.21 (m, 4H, (CH$_2$)$_2$CH$_2$CH$_3$), 1.32 (t, $J = 7.2$ Hz, 3H, CO$_2$CH$_2$CH$_3$), 1.40 (s, 9H, C(CH$_3$)$_3$), 1.44-1.52 (m, 2H, CH$_2$CH$_2$(CH$_2$)$_2$CH$_3$), 3.65-3.69 (m, 2H, CH$_2$(CH$_2$)$_2$CH$_3$), 4.28 (q, $J = 7.2$ Hz, 2H, CO$_2$CH$_3$), 4.98 (s, 2H, CH$_2$CO$_2$Et), 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), caleld for C$_{24}$H$_{33}$N$_6$O$_7$ [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, CDCl₃) 0.82 (t, J = 7.1 Hz, 3H, (CH₂)₄CH₃), 1.01-1.26 (m, 4H, (CH₂)₂CH₂CH₂CH₂CH₃), 1.32 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 1.43 (s, 9H, C(CH₃)₃), 1.51 (p, J = 7.6 Hz, 2H, CH₂CH₂(CH₂)₂CH₃), 3.68-3.72 (m, 2H, CH₂(CH₂)(CH₂)₃CH₃), 4.28 (q, J = 7.6 Hz, 2H, CO₂CH₂CH₃), 4.98 (s, 2H, CH₂CO₂Et), 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 C₂₅H₃₂N₆O₇Na [M+Na] m/z = 528.23, fnd. 551.27.

![Chemical structure of 6ao](image)

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-2H-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, CDCl₃) 0.87 (t, J = 6.9 Hz, 3H, (CH₂)₄CH₃), 1.25-1.34 (m, 7H, CO₂CH₂CH₃, and (CH₂)₂CH₂CH₃CH₃), 1.48 (s, 9H, C(CH₃)₃), 1.58-1.73 (m, 4H, 2H, CH₂, (tetrahydropyran) and CH₂CH₂(CH₂)₂CH₃), 2.04-2.08 (m, 2H, CH₂, (tetrahydropyran)), 3.48-3.60 (m, 2H, CH₂, (tetrahydropyran)), 3.79 (t, J = 7.6 Hz, 2H, CH₂(CH₂)₃CH₃), 3.95-4.07 (m, 2H, CH₂, (tetrahydropyran)), 4.25 (q, J = 7.1 Hz,
2H, CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 4.33 (bs, 1H, CH), 4.89 (s, 2H, CH\textsubscript{2}CO\textsubscript{2}Et) 6.01 (bs, 1H, NH), 7.77 (s, 1H, CH (H-8)); LRMS (MS- ES), calcd for C\textsubscript{24}H\textsubscript{38}N\textsubscript{6}O\textsubscript{5}Na \[M+Na\] \textit{m/z} = 513.29, fnd. 513.44.

![Image of chemical structure]

**ethyl 2-(6-(benzylamino)-2-((\textit{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\textsuperscript{-1}) 3325, 3140, 2990, 2925, 2850, 1750, 1697, 1625, 1600, 1390, 1370, 1225; \(\delta\text{H} \text{ (400 MHz, CDCl}_3\text{)} 1.21-1.40 \text{ (m, 8H, 5H (cyclohexyl) and CO}_2\text{CH}_2\text{CH}_3\text{)}, 1.46 \text{ (s, 9H, C(CH}_3)_3\text{)}, 1.71-1.85 \text{ (m, 5H (cyclohexyl)), 2.41-} \\
2.46 \text{ (m, 1H, CH)}, 4.25 \text{ (q, } J = 7.2 \text{ Hz, 2H, CO}_2\text{CH}_3\text{CH}_3\text{)}, 4.75 \text{ (bs, 2H, HNCH}_2\text{)}, 4.90 \text{ (bs, 2H, CH}_2\text{Ar)}, 5.06 \text{ (s, 2H, CH}_2\text{CO}_2\text{Et)}, 7.08 \text{ (m, 2H, 2 CH (Ar))}, 7.21-7.32 \text{ (m, 7H, 7 CH (Ar)), 7.43} \\
\text{ (bs, 1H, NH), 7.87 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C}_{34}H_{43}N_6O_4 \ [M+H] \textit{m/z} = 599.33, fnd. 599.49.

![Image of chemical structure]

**ethyl 2-(6-(benzyl(methyl)amino)-2-((\textit{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; δH (400 MHz, CDCl3) 1.29 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 1.33 - 1.41 (m, 5H, (cyclohexyl)), 1.41 (s, 9H, C(CH₃)₃), 1.71-1.82 (m, 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 3.06-3.71 (bm, 3H, NCH₃), 4.24 (q, J = 7.2Hz, 2H, CO₂CH₂CH₃), 4.89 (s, 2H, CH₂Ar), 5.03 (bs, 2H, CH₂CO₂Et), 5.17-5.61 (bm, 2H, CH₃NCH₂), 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 C₃₅H₄₅N₆O₄ [M+H] m/z = 613.34, fnd. 613.50.

![Chemical Structure](image)

**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; δH (400 MHz, CDCl3) 1.26-1.39 (m, 8H, 5H (cyclohexyl) and CO₂CH₂CH₃), 1.41 (s, 9H, C(CH₃)₃), 1.71-1.83 (m, 5H (cyclohexyl)), 2.40-2.46 (m, 1H, CH), 3.14-3.75 (vbs, 3H, NCH₃), 4.23 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.88 (s, 2H, CH₂Ar), 5.05 (s, 2H, CH₂CO₂Et), 5.17 (vbs, 2H, CH₂ (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 =
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; δH (400 MHz, CDCl₃) 1.18-1.46 (m, 14H, 5H (cyclohexyl) and C(CH₃)₃), 1.28 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 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, CO₂CH₂CH₃), 4.44 (bs, 1H, NCH), 4.87 (s, 2H, CH₂Ar), 5.05 (s, 2H, CH₂CO₂Et), 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 C₃₂H₄₅N₆O₄ [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; δH (400 MHz, CDCl₃) 1.15-1.40 (m, 13H, 5H, (cyclohexyl)), 1.42 (s, 9H, C(CH₃)₃), 1.57-1.86 (m, 10H, 5H, (cyclohexyl) and 5H, (NH-cyclohexyl)), 2.38-2.48 (m, 1H, CH), 4.02 (bs, 1H, HNCH), 4.24 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.87 (s, 2H, CH₂Ar), 5.03 (s, 2H, CH₂CO₂Et), 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 C₃₃H₄₇N₆O₄ [M+H] m/z = 591.36, fnd. 591.54.

ethyl 2-(6-(allylamino)-2-((tert-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-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; δH (400 MHz, CDCl₃) 1.15-1.40 (m, 13H, 5H, (cyclohexyl)), 1.42 (s, 9H, C(CH₃)₃), 1.57-1.86 (m, 10H, 5H, (cyclohexyl) and 5H, (NH-cyclohexyl)), 2.38-2.48 (m, 1H, CH), 4.02 (bs, 1H, HNCH), 4.24 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.87 (s, 2H, CH₂Ar), 5.03 (s, 2H, CH₂CO₂Et), 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 C₃₃H₄₇N₆O₄ [M+H] m/z = 591.36, fnd. 591.54.
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; δH (400 MHz, CDCl₃) 1.25-1.40 (m, 8H, 5H (cyclohexyl) and CO₂CH₂CH₃), 1.41 (s, 9H, C(CH₃)₃), 1.70-1.86 (m, 5H (cyclohexyl)), 2.40-2.48 (m, 1H, CH), 4.25 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.26 (bs, 2 H, CH₂CHCH₂), 4.88 (s, 2H, CH₂Ar), 5.05 (s, 2H, CH₂CO₂Et), 5.15 (dd, J = 10.3 and 1.5 Hz, 1H, CH₂CHCH₂), 5.25 (dd, J = 17.1 and 1.5 Hz, 1H, CH₂CHCH₂), 5.70 (bs, 1H, NH), 5.89-5.99 (m, 1H, CH₂CHCH₂), 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 C₃₀H₄₁N₆O₄ [M+H] m/z = 549.31, fnd. 549.45.

ethyl 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; δH (400 MHz, CDCl₃) 0.93 (s, 3H, CH₂CH(CH₃)₂), 0.95 (s, 3H, CH₂CH(CH₃)₂), 1.21-1.40 (m, 8H, 5H (cyclohexyl) and CO₂CH₂CH₃), 1.42 (s, 9H, C(CH₃)₃), 1.67-1.84 (m, 5H (cyclohexyl)), 1.86-1.96 (m, 1H, CH₂CH(CH₃)₂), 2.40-2.47 (m, 1H, CH(CH₃)₂), 3.37 (bs, 2H, CH₂CH(CH₃)₂), 4.24 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.88 (s, 2H, CH₂Ar), 5.04 (s, 2H, CH₂CO₂Et), 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_{6}O_{4}Na [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; δH (400 MHz, CDCl₃) 0.91 (s, 3H, (CH₂)₂CH(CH₃)₂), 0.93 (s, 3H, (CH₂)₂CH(CH₃)₂), 1.25-1.39 (m, 8H, 5H (cyclohexyl) and CO₂CH₂CH₃), 1.41 (s, 9H, C(CH₃)₃), 1.49-1.55 (m, 1H, (CH₂)₂CH(CH₃)₂), 1.65-1.83 (m, 7H, CH₂CH₂CH(CH₃)₂ and 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 3.58 (bs, 2H, CH₂CH₂CH(CH₃)₂), 4.24 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.87 (s, 2H, CH₂Ar), 5.06 (s, 2H, CH₂CO₂Et), 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_{6}O_{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; δH (400 MHz, CDCl₃) 1.21-1.40 (m, 8H, 5H (cyclohexyl) and CO₂CH₂CH₃), 1.41 (s, 9H, C(CH₃)₃), 1.75-1.84 (m, 5H (cyclohexyl)), 2.40-2.45 (m, 1H, CH), 3.77 (t, J = 4.7 Hz, 4H, 2 CH₂ (morpholine)), 4.19 (bs, 4H, 2 CH₂ (morpholine)), 4.24 (q, J = 7.1 Hz, 2H, CO₂CH₂CH₃), 4.88 (s, 2H, CH₂Ar), 5.03 (s, 2H, CH₂CO₂Et), 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 C₃₁H₄₂N₆O₅Na [M+Na] m/z = 601.32, fnd. 601.49.

ethyl 2-((tert-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(3-nitrophenoxy)-9H-purin-9-ylacetate (6nm).
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; \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.19-1.41 (m, 8H, 5H (cyclohexyl) and CO\(_2\)CH\(_2\)CH\(_3\)), 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\(_2\)CH\(_2\)CH\(_3\)), 4.92 (s, 2H, CH\(_2\)Ar), 4.97 (s, 2H, CH\(_2\)CO\(_2\)Et), 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\(_6\)O\(_7\)Na \([M+Na]\) \(m/z = 653.28\), fnd. 653.39.

![Structure of ethyl 2-((tert-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(4-nitrophenoxy)-9H-purin-9-yl)acetate (6bo).](image)

ethyl 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; \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.20-1.33 (m, 8H, 5H (cyclohexyl) and CO\(_2\)CH\(_2\)CH\(_3\)), 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\(_2\)CH\(_2\)CH\(_3\)), 4.94 (s, 2H, CH\(_2\)Ar), 4.99 (s, 2H, CH\(_2\)CO\(_2\)Et), 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,
ethyl 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; δH (400 MHz, CDCl₃) 1.20-1.38 (m, 8H, 5H (cyclohexyl) and CO₂CH₂CH₃), 1.41 (s, 9H, C(CH₃)₃), 1.70-1.85 (m, 5H (cyclohexyl)), 2.43-2.48 (m, 1H, CH), 4.25 (q, J = 7.1 Hz, 2H, CO₂CH₂CH₃), 4.91 (s, 2H, CH₂Ar), 5.10 (s, 2H, CH₂CO₂Et), 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 C₃₃H₃₉F₆N₆O₄Na [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; δH (400 MHz, CDCl₃) 1.25-1.40 (m, 8H, 5H (cyclohexyl) and CO₂CH₂CH₃), 1.41 (s, 9H, C(CH₃)₃), 1.71-1.82 (m, 5H (cyclohexyl)), 2.41-2.47 (m, 1H, CH), 4.23 (q, J = 7.1 Hz, 2H, CO₂CH₂CH₃), 4.76 (bs, 2H, CH₂ (furfuryl)), 4.88 (s, 2H, CH₂Ar), 5.07 (s, 2H, CH₂CO₂Et), 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 C₃₂H₄₁N₆O₅ [M+H] m/z = 589.31, fnd. 589.43.
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, CDCl₃) 0.95 (t, J = 7.4 Hz, 3H, NHCH₂CH₂CH₃), 1.20-1.33 (m, 8H, 5H (cyclohexyl) and CO₂CH₂CH₃), 1.42 (s, 9H, C(CH₃)₃), 1.64 (m, 2H, NHCH₂CH₂CH₃) 1.7-1.83 (m, 5H (cyclohexyl)), 2.40-2.46 (m, 1H, CH), 3.52 (bs, 2H, NHCH₂CH₂CH₃), 4.24 (q, J = 7.1 Hz, 2H, CO₂CH₂CH₃), 4.87 (s, 2H, CH₂Ar), 5.05 (s, 2H, CH₃CO₂Et), 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 C₃₀H₄₃N₆O₄ [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).](image)

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, CDCl₃) 0.88 (t, J = 7.2 Hz, 3H, NH(CH₂)₂CH₃), 1.16-1.34 (m, 14H, 5H (cyclohexyl) and 6H NH(CH₂)₂CH₂CH₂CH₂CH₃ and CO₂CH₂CH₃), 1.42 (s, 9H, C(CH₃)₃), 1.51-1.76 (m, 7H, 5H (cyclohexyl) and NHCH₂CH₃(CH₂)₂CH₃), 2.40-2.46 (m, 1H, CH), 3.54 (bs, 2H, NHCH₂(CH₂)₄CH₃), 4.24 (q, J =
7.1 Hz, 2H, CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 4.87 (s, 2H, CH\textsubscript{2}Ar), 5.05 (s, 2H, CH\textsubscript{2}CO\textsubscript{2}Et), 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\textsubscript{33}H\textsubscript{49}N\textsubscript{6}O\textsubscript{4} [M+H] m/z = 593.37, fnd. 593.51.

![Chemical structure](image)

ethyl 2-(6-(3-bromophenoxy)-2-((\textit{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\textsuperscript{-1}) 3546, 3480, 3425, 3230, 2930, 2840, 1750, 1710, 1625, 1580, 1470, 1400; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.14-1.34 (m, 8H, 5H (cyclohexyl) and CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.35 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 1.67-1.86 (m, 5H, (cyclohexyl)), 2.38-2.49 (m, 1H, CH), 4.26 (q, J = 7.1 Hz, 2H, CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 4.93 (s, 2H, CH\textsubscript{2}Ar), 4.95 (s, 2H, CH\textsubscript{2}CO\textsubscript{2}Et), 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\textsubscript{33}H\textsubscript{35}BrN\textsubscript{5}O\textsubscript{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; δH (400 MHz, CDCl₃) 1.14-1.32 (m, 8H, 5H (cyclohexyl) and CO₂CH₂CH₃), 1.35 (s, 9H, C(CH₃)₃), 1.70-1.84 (m, 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 4.26 (q, J = 7.1 Hz, 2H, CO₂CH₂CH₃), 4.90 (s, 2H, CH₂Ar), 4.95 (s, 2H, CH₂CO₂Et), 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 C₃₃H₃₉FN₅O₅ [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; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 1.21-1.34 (m, 8H, 5H (cyclohexyl) and CO\(_2\)CH\(_2\)CH\(_3\)), 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\(_2\)CH\(_2\)CH\(_3\)), 4.88 (s, 2H, CH\(_2\)Ar), 4.98 (s, 2H, CH\(_2\)CO\(_2\)Et), 6.98 (d, \(J=8.2\) Hz, 2H, 2 CH (Ar)), 7.04 (d, \(J=8.2\)Hz, 2H, 2 CH (Ar)), 8.04 (s, 1H, CH, (H-8)); LRMS (MS-ES), calcd for C\(_{33}\)H\(_{34}\)F\(_5\)N\(_5\)O\(_5\)Na \([M+Na]\) \(m/z = 698.25\), fnd. 698.34.

![Structure of 6bw](image)

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; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 1.11-1.40 (m, 8H, 5H (cyclohexyl) and CO\(_2\)CH\(_2\)CH\(_3\)), 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\(_2\)CH\(_2\)CH\(_3\)), 4.91 (s, 2H, CH\(_2\)Ar), 4.95 (s, 2H, CH\(_2\)CO\(_2\)Et), 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\(_5\)O\(_5\) [M+H] \(m/z = 586.30\),
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; δH (400 MHz, DMSO-d₆) 0.77 (t, J = 7.0 Hz, 3H, (CH₂)₄CH₃), 1.09-1.23 (m, 4H, (CH₂)₂CH₂CH₂CH₃), 1.35 (s, 9H, C(CH₃)₃), 1.52-1.59 (m, 2H, CH₂CH₂(CH₂)₂CH₃), 3.59 (t, J = 6.9 Hz, 2H, CH₂(CH₂)₂CH₃), 4.65 (bs, 2H, CH₂Ar), 4.89 (s, 2H, CH₂CO₂H), 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, CH₂CO₂H); δC (100 MHz, DMSO-d₆) 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 C₂₄H₃₃N₆O₄ [M+H] m/z = 469.2562, fnd. 469.2557; rpHPLC tᵣ: condition (I) 14.246 (II) 39.742 minutes, purity 91.2 % and 93.4%. 

fnd. 586.43.
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; δH (400 MHz, DMSO-d6) 0.82 (m, 3H, (CH₂)₄CH₃), 1.21-1.29 (m, 4H, (CH₂)₂CH₂CH₂CH₃), 1.38 (s, 9H, C(CH₃)₃), 1.43-1.58 (m, 2H, (CH₂)₂CH₂CH₂CH₃), 3.15-3.60 (bm, 3H, NCH₃), 3.60-3.70 (m, 2H, CH₂CH₂(CH₂)₃CH₃), 4.78 (s, 2H, CH₂CO₂H), 4.86-5.55 (bm, 2H, CH₂Ar), 7.24-7.31 (m, 5H, 2 CH (Ar)), 7.71 (s, 1H, CH (H-8)), 13.23 (vbs, 1H, CH₂CO₂H); HRMS (MS- ES), calcd for C₂₅H₃₅N₆O₄ [M+H] m/z = 483.2701, fnd. 483.2714; rpHPLC tR: 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<sub>H</sub> (400 MHz, DMSO-<sup>d6</sup>) 0.81 (t, J = 7.0 Hz, 3H, (CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>), 1.23-1.27 (m, 4H, (CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.39 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.52-1.59 (m, 2H, (CH<sub>2</sub>)<sub>3</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.72 (t, J = 7.4 Hz, 2H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 4.90 (s, 2H, CH<sub>2</sub>CO<sub>2</sub>H), 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<sub>C</sub> (100 MHz, DMSO-<sup>d6</sup>) 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<sub>23</sub>H<sub>31</sub>N<sub>6</sub>O<sub>4</sub> [M+H] m/z = 455.2387, fnd. 455.2401; rpHPLC <i>t</i>: condition (I) 14.988 (II) 38.416 minutes, purity 93.1 %and 98.2%.

<chemistry>
\[
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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<sup>-1</sup>) 3549, 3471, 3415, 3120, 2958, 2925, 2855, 1703, 1637, 1618, 1591, 1460; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 0.83-0.88 (m, 3H, (CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>), 1.25-1.34 (m, 4H, (CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.48 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.56-1.69 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>), 3.50 (vbs, 3H, CH<sub>3</sub>(furanyl)), 3.80 (t, J = 7.6 Hz, 2H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 4.86 (s, 2H, CH<sub>2</sub>CO<sub>2</sub>H), 5.22 (vbs, 2H, CH<sub>3</sub>(furanyl)), 6.29-6.33 (m, 2H, CH (furanyl)), 7.35-7.36 (m, 1H, CH (furanyl)), 7.81 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C<sub>23</sub>H<sub>31</sub>N<sub>6</sub>O<sub>5</sub> [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; δH (400 MHz, CDCl₃) 0.82-0.90 (m, 3H, (CH₂)₄CH₃), 1.23-1.32 (m, 4H, (CH₂)₂CH₂CH₂CH₂CH₃), 1.49 (s, 9H, C(CH₃)₃), 1.56-1.80 (m, 8H, CH₂CH₂(CH₂)₂CH₃ and 3 CH₂ (cyclopentyl)), 2.00-2.11 (m, 2H, CH₂ (cyclopentyl)), 3.80-3.86 (m, 2H, CH₂(CH₂)₃CH₃), 4.45 (bs, 1H, CH (cyclopentyl)), 4.89 (s, 2H, CH₂CO₂H), 7.10 (s, 1H, NH), 7.90 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C₂₂H₃₃N₆O₄ [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; \(\delta_H\) (400 MHz, CDCl\(\text{3}\)) 0.82-0.90 (m, 3H, (CH\(_2\))\(_4\)CH\(\text{3}\)), 1.17-1.42 (m, 10H, (CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CH\(_3\) and 3 CH\(_2\)(cyclohexyl)), 1.49 (s, 9H, C(CH\(_3\))\(_3\)), 1.60-1.72(m, 2H, CH\(_2\)CH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 1.75-1.83 (m, 2H, CH\(_2\) (cyclohexyl)), 2.00-2.07 (m, 2H, CH\(_2\) (cyclohexyl)), 3.78-3.85 (m, 2H, CH\(_2\)(CH\(_2\))\(_3\)CH\(_3\)), 4.03 (bs, 1H, CH (cyclohexyl)), 4.89 (s, 2H, CH\(_3\)CO\(\text{2H}\)), 6.90 (bs, 1H, NH), 7.89 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C\(_{23}\)H\(_{35}\)N\(_6\)O\(_4\) [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 \(6\text{ag}\) was treated according to general procedure \(E\), to yield product \(7\text{ag}\) as a clear oil (94 \%): IR (KBr, cm\(^{-1}\)) 3414, 2961, 2931, 2859, 1723, 1596, 1492, 1456, 1433, 1418, 1380, 1296; \(\delta_H\) (400 MHz, CDCl\(\text{3}\)) 0.89 (t, \(J = 6.9\) Hz, 3H, (CH\(_2\))\(_4\)CH\(\text{3}\)), 1.25-1.36 (m, 7H, (CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CH\(_3\) and NCH\(_2\)CH\(_3\)), 1.52 (s, 9H, C(CH\(_3\))\(_3\)), 1.68 (p, 7.4 Hz, 2H, CH\(_2\)CH\(_3\)(CH\(_2\))\(_2\)CH\(_3\)), 3.21-3.76 (bm, 3H, NCH\(_3\)), 3.85-3.91 (m, 2H, CH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 4.28 (bs, 2H, NCH\(_2\)CH\(_3\)), 5.00 (s, 2H, CH\(_3\)CO\(\text{2H}\)), 7.74 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C\(_{20}\)H\(_{31}\)N\(_6\)O\(_4\) [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; \(\delta_H\) (400 MHz, CDCl\(_3\)) 0.82-0.91 (m, 3H, \((\text{CH}_2)_4\text{CH}_3\)), 1.20-1.41 (m, 10H, \((\text{CH}_2)_2\text{CH}_2\text{CH}_2\text{CH}_3\) and \(\text{CH}(\text{CH}_3)_2\)), 1.52 (s, 9H, \(\text{C}(\text{CH}_3)_3\)), 1.58-1.72 (m, 2H, \(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 3.80-3.90 (m, 2H, \(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 4.33 (bs, 1H, \(\text{CH}(\text{CH}_3)_2\)), 4.92 (s, 2H, \(\text{CH}_2\text{CO}_2\text{H}\)), 7.26 (bs, 1H, \(\text{NH}\)), 7.96 (bs, 1H, \(\text{CH}(\text{H}-8)\)); LRMS (MS-ES), calcd for C\(_{20}\)H\(_{31}\)N\(_6\)O\(_4\) [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; \(\delta_H\) (400 MHz, CDCl\(_3\)) 0.86 (t, \(J = 6.8\) Hz, 3H, \((\text{CH}_2)_4\text{CH}_3\)), 1.26-1.34 (m, 4H, \(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 1.49 (s, 9H, \(\text{C}(\text{CH}_3)_3\)), 1.64 (p, \(J = 7.3\) Hz, 2H,
\( \text{CH}_2\text{CH}_2(\text{CH}_2)_2\text{CH}_3 \), 3.82 (t, \( J = 7.6 \text{ Hz} \), 2H, \( \text{CH}_3(\text{CH}_2)_3\text{CH}_3 \)), 4.24 (bs, 2H, \( \text{CH}_2\text{CHCH}_2 \)), 4.89 (s, 2H, \( \text{CH}_2\text{CO}_2\text{H} \)), 5.16 (d, \( J = 10.1 \text{ Hz} \), 1H, \( \text{CH}_2\text{CHCH}_2 \)), 5.30 (d, \( J = 17.4 \text{ Hz} \), 1H, \( \text{CH}_2\text{CHCH}_2 \)), 5.91-6.03 (m, 1H, \( \text{CH}_2\text{CHCH}_2 \)), 7.86 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for \( \text{C}_{20}\text{H}_{29}\text{N}_6\text{O}_4 \) [M-H] \( m/\epsilon = 417.23 \), fnd. 417.37.

\[ \text{2-(2-((t\text{e}r\text{-butoxy}c\text{arbonyl})(p\text{entyl})a\text{mino})-6-(isobutylamino)-9\text{H-purin-9-yl})acetic acid (7aj)} \]

Purine \( \text{6aj} \) was treated according to general procedure E, to yield product \( \text{7aj} \) 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; \( \delta_H \) (400 MHz, CDCl\(_3\)) 0.82-0.91 (m, 3H, \( \text{CH}_2\text{CH}_3 \)), 0.96-1.02 (m, 6H, \( \text{CH}(\text{CH}_3)_2 \)), 1.20-1.35 (m, 4H, \( \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)), 1.51 (s, 9H, C(\( \text{CH}_3 \)_3)), 1.61-1.73 (m, 2H, \( \text{CH}_2\text{CH}_2(\text{CH}_2)_2\text{CH}_3 \)), 1.94-2.08 (m, 1H, \( \text{CH}(\text{CH}_3)_2 \)), 3.36-3.44 (m, 2H, \( \text{CH}_2\text{CH}(\text{CH}_3)_2 \)), 3.78-3.92 (m, 2H, \( \text{CH}_2(\text{CH}_2)_3\text{CH}_3 \)), 4.92 (s, 2H, \( \text{CH}_2\text{CO}_2\text{H} \)), 7.94 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for \( \text{C}_{21}\text{H}_{33}\text{N}_6\text{O}_4 \) [M-H] \( m/\epsilon = 433.26 \), 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; \(\delta_H\) (400 MHz, CDCl\(_3\)) 0.84-0.89 (m, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 0.94 (t, \(J = 7.3\) Hz, 3H, (CH\(_2\))\(_3\)CH\(_3\)), 1.25-1.43 (m, 6H, CH\(_2\)CH\(_2\)CH\(_3\)CH\(_3\) and (CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.47 (s, 9H, C(CH\(_3\))\(_3\)), 1.59-1.70 (m, 4H, CH\(_2\)CH\(_2\)CH\(_3\)CH\(_3\) and CH\(_2\)CH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 3.14-3.86 (bm, 4H, CH\(_2\)CO\(_2\)H and CH\(_2\)CH\(_2\)(CH\(_2\))\(_3\)CH\(_3\)), 3.79 (t, \(J = 7.6\) Hz, 2H, CH\(_2\)(CH\(_2\))\(_3\)CH\(_3\)), 4.84 (s, 2H, CH\(_2\)CO\(_2\)H), 7.78 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C\(_{22}\)H\(_{35}\)N\(_6\)O\(_4\) [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; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 0.82-0.90 (m, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 0.92 (s, 3H, (CH\(_2\))\(_2\)CH(CH\(_3\))\(_2\)), 0.94 (s, 3H, (CH\(_2\))\(_2\)CH(CH\(_3\))\(_2\)), 1.19-1.35 (m, 4H, (CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.50 (s, 9H, C(CH\(_3\))\(_3\)), 1.54-1.76 (m, 5H, CH\(_2\)CH\(_2\)(CH\(_2\))\(_2\)CH\(_3\) and CH\(_2\)CH\(_2\)CH(CH\(_3\))\(_2\)), 3.57 (bs, 2H, CH\(_2\)(CH\(_2\))\(_2\)(CH\(_3\))\(_2\)), 3.80-3.89 (m, 2H, CH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 4.05 (bs, 1H, NH), 4.91 (s, 2H, CH\(_2\)(CH\(_2\))\(_2\)(CH\(_3\))\(_2\)), 7.92 (bs, 1H, CH (H-8)); LRMS (MS-ES), calcd for C\(_{22}\)H\(_{35}\)N\(_6\)O\(_4\) [M-H] \(m/z = 447.28\), fnd. 447.38.

![Chemical structure](image)

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, 1388, 1304, 1266, 1241, 1137; \(\delta\)\(_H\) (400 MHz, DMSO-d\(_6\)) 0.87 (t, \(J = 6.9\) Hz, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 1.17-1.26 (m, 4H, (CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.38 (s, 9H, C(CH\(_3\))\(_3\)), 1.52 (p, \(J = 7.3\) Hz, 2H, CH\(_2\)CH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 3.64-3.75 (m, 6H, CH\(_3\)(CH\(_2\))\(_3\)CH\(_3\) and 2 CH\(_2\) (morpholine)), 4.17 (bs, 4H, 2 CH\(_2\) (morpholine)), 4.76 (s, 2H, CH\(_2\)CO\(_2\)H), 8.07 (s, 1H, CH (H-8)); \(\delta\)\(_C\) (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\(_{22}\)H\(_{35}\)N\(_6\)O\(_4\) [M+H] \(m/z = 449.2506\), fnd. 449.2497; \textit{rpHPLC} \(t_R\): condition (I) 13.883 (II) 32.404 minutes, purity 90.8 %and 90.9%.
2-(2-((tert-butoxycarbonyl)(pentyl)amino)-6-(3-nitrophenoxo)-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-d₆) 0.75 (t, J = 7.2 Hz, 3H, (CH₂)₄CH₃), 0.97-1.13 (m, 4H, (CH₂)₂CH₂CH₂CH₃), 1.29 (s, 9H, C(CH₃)₃), 1.31-1.38 (m, 2H, (CH₂)₃CH₂CH₃), 3.52 (t, J = 7.4 Hz, 2H, CH₂(CH₂)₃CH₃), 5.03 (s, 2H, CH₂CO₂H), 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, CH₂CO₂H); δ_C (100 MHz, DMSO-d₆) 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 C₂₃H₂₉N₆O₇ [M+H] m/z = 501.2095, fnd. 501.2092; rpHPLC t_R: condition (I) 14.230 (II) 36.038 minutes, purity 98.3% and 97.16%.

2-(2-((tert-butoxycarbonyl)(pentyl)amino)-6-(4-nitrophenoxo)-9H-purin-9-yl)acetic acid
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; \(\delta\)\(_H\) (400 MHz, DMSO-\(d_6\)) 0.74 (t, \(J = 7.2\) Hz, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 0.99-1.17 (m, 4H, (CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.31 (s, 9H, C(CH\(_3\))\(_3\)), 1.34-1.39 (m, 2H, CH\(_2\)CH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 2.81-3.03 (m, 2H, CH\(_2\)(CH\(_2\))\(_3\)CH\(_3\)), 5.04 (s, 2H, CH\(_2\)CO\(_2\)H), 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)); \(\delta\)\(_C\) (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\(_6\)O\(_7\) [M+H] \(m/z = 501.2110\), fnd. 501.2092; rpHPLC \(t_R\): condition (I) 14.647 (II) 36.729 minutes, purity 98.2 % and 98.3%. (Decomposed- remaking)
7.1 Hz, 2H, CH₂(CH₂)₃CH₃), 3.85-3.96 (m, 2H, CH₂ (tetrahydropyran)), 4.22 (bs, 1H, CH), 4.77 (s, 2H, CH₂CO₂Et) 7.74 (bs, 1H, NH), 8.02 (s, 1H, CH (H-8)); δC (100 MHz, DMSO-d₆); 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 C₂₂H₃₅N₆O₅ [M+H] m/z = 463.2666, fnd. 463.2663; rpHPLC tR: 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; δH (400 MHz, CDCl₃) 1.20-1.42 (m, 14H, 5H (cyclohexyl) and C(CH₃)₃), 1.69-1.81 (m, 5H (cyclohexyl)), 2.39-2.45 (m, 1H, CH), 4.72 (bs, 2H, HNCH₂), 4.87 (bs, 2H, CH₂Ar), 5.04 (s, 2H, CH₂CO₂H), 6.94-7.27 (m, 10H, NH and 9 CH (Ar)), 7.88 (bs, 1H, CH (H-8)); LRMS (MS-ES), calcd for C₃₂H₃₇N₆O₄ [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; \(\delta\)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, NCH\(_3\)), 4.94 (s, 2H, CH\(_2\)Ar), 5.03 (bs, 2H, CH\(_2\)CO\(_2\)H), 5.39-5.62 (bm, 2H, CH\(_3\)NCH\(_2\)), 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\(_6\)O\(_4\) [M-H] \(m/z\) = 583.31, fnd. 583.38.

![Molecular Structure of 9-yl)acetic acid (7bb)](image)

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; \(\delta\)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\(_2\)Ar), 5.12 (s, 2H, CH\(_2\)CO\(_2\)H), 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\(_6\)O\(_5\) [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; δH (400 MHz, CDCl₃) 1.18-1.46 (m, 14H, 5H (cyclohexyl) and C(CH₃)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, CH₂Ar), 5.05 (s, 2H, CH₂CO₂H), 7.00 (bs, 1H, 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 C₃₀H₃₉N₆O₄ [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; δH (400 MHz, CDCl₃) 1.16-1.38 (m, 10H, 5H (cyclohexyl) and 5H (NH-cyclohexyl)), 1.35 (s, 9H, C(CH₃)₃), 1.59-1.94 (m, 10H, 5H (cyclohexyl) and 5H (NH-cyclohexyl)), 2.38-2.48 (m, 1H, CH), 3.90 (bs, 1H, HNCH), 4.79 (s, 2H, CH₂Ar), 5.00 (s, 2H, CH₃CO₂H), 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 C₃₁H₄₁N₆O₄ [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; δH (400 MHz, CDCl₃) 1.17-1.30 (m, 5H, (cyclohexyl)), 1.36 (s, 9H, C(CH₃)₃), 1.68-1.87 (m, 5H (cyclohexyl)), 2.36-2.49 (m, 1H, CH), 4.15 (bs, 2 H, CH₂CHCH₂), 4.88 (s, 2H, CH₂Ar), 5.06 (s, 2H, CH₃CO₂H), 5.12 (dd, J = 10.6 and 1.5 Hz, 1H, CH₂CHCH₂), 5.21 (dd, J = 17.2 and 1.5 Hz, 1H, CH₂CHCH₂), 5.79-5.97 (m, 1H, CH₂CHCH₂), 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
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; $\delta_H$ (400 MHz, CDCl$_3$) 0.93 (s, 3H, CH$_2$CH(CH$_3$)$_2$), 0.95 (s, 3H, CH$_2$CH(CH$_3$)$_2$), 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$_2$CH(CH$_3$)$_2$) 2.40-2.47 (m, 1H, CH), 3.37 (bs, 2H, CH$_2$CH(CH$_3$)$_2$), 4.88 (s, 2H, CH$_2$Ar), 5.04 (s, 2H, CH$_2$CO$_2$H), 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$_6$O$_4$ [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
9%); m.p. > 128 °C (dec); IR (KBr, cm⁻¹) 2925, 2852, 1707, 1485, 1440, 1400, 1379, 1246; δH (400 MHz, CDCl₃) 0.87 (s, 3H, (CH₂)₂CH(CH₃)₂), 0.88 (s, 3H, (CH₂)₂CH(CH₃)₂), 1.25-1.39 (m, 5H, (cyclohexyl)), 1.39 (s, 9H, C(CH₃)₃), 1.46-1.66 (m, 3H, CH₂CH₂CH(CH₃)₂), 1.67-1.84 (m, 5H, (cyclohexyl)), 2.39-2.47 (m, 1H, CH), 3.50 (bs, 2H, CH₂CH₂CH(CH₃)₂), 4.88 (s, 2H, CH₂Ar), 5.08 (s, 2H, CH₂CO₂H), 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 C₃₀H₄₁N₆O₄ [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; δH (400 MHz, DMSO-d₆) 1.17-1.36 (m, 5H, (cyclohexyl)), 1.37 (s, 9H, C(CH₃)₃), 1.66-1.77 (m, 5H, (cyclohexyl)), 2.38-2.44 (m, 1H, CH), 3.68 (t, J = 4.5 Hz, 4H, 2 CH₂ (morpholine)), 4.12 (bs, 4H, 2 CH₂ (morpholine)), 4.85 (s, 2H, CH₂Ar), 4.91 (s, 2H, CH₂CO₂H), 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)); δC (100 MHz, DMSO-d₆) 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 C₂₉H₃₉N₆O₅ [M+H] m/z = 551.2962, fnd. 551.2976; rpHPLC tR: 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; \(\delta\)\(\text{H}(400\text{ MHz, CDCl}_3)\) 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\(_2\)Ar), 4.88 (s, 2H, CH\(_2\)CO\(_2\)H), 6.92 (d, \(J = 8.1\text{ Hz}, 2\text{ H}, 2\text{ CH (Ar)}\)), 6.97 (d, \(J = 8.1\text{ Hz}, 2\text{ H}, 2\text{ CH (Ar)}\)), 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\(_6\)O\(_7\) [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; \(\delta\)\(_H\) (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\(_2\)Ar), 5.02 (s, 2H, CH\(_2\)CO\(_2\)H), 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\(_6\)O\(_7\) [M-H] \(m/z\) = 601.25, fnd. 601.31.

![Structure of 7bo](image)

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; \(\delta\)\(_H\) (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\(_2\)Ar), 5.10 (s, 2H, CH\(_2\)CO\(_2\)H), 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\(_6\)O\(_4\) [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; δH (400 MHz, CDCl₃) 1.19-1.38 (m, 5H, 5H (cyclohexyl)), 1.40 (s, 9H, C(CH₃)₃), 1.79-1.81 (m, 5H (cyclohexyl)), 2.39-2.45 (m, 1H, CH), 4.73 (bs, 2H, CH₂(furfuryl)), 4.85 (s, 2H, CH₂Ar), 5.06 (s, 2H, CH₂CO₂H), 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 C₃₀H₃₅FN₆O₅ [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; $\delta_H$ (400 MHz, CDCl$_3$) 0.91 (t, $J = 7.3$ Hz, 3H, NHCH$_2$CH$_2$CH$_3$), 1.21 (s, 9H, C(CH$_3$)$_3$), 1.28-1.43 (m, 5H (cyclohexyl)), 1.59 (m, 2H, NHCH$_2$CH$_2$CH$_3$), 1.7-1.83 (m, 5H (cyclohexyl)), 2.40-2.46 (m, 1H, CH), 3.42 (bs, 2H, NHCH$_2$CH$_2$CH$_3$), 4.81 (s, 2H, CH$_2$Ar), 5.00 (s, 2H, CH$_2$CO$_2$H), 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$_6$O$_4$ [M-H] $m/\zeta$ = 521.30, fnd. 521.42.

![](image)

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; $\delta_H$ (400 MHz, CDCl$_3$) 0.88 (t, $J = 7.2$ Hz, 3H, NH(CH$_2$)$_3$CH$_3$), 1.11-1.23 (m, 11H, 5H (cyclohexyl), 6H, NH(CH$_2$)$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.25 (s, 9H, C(CH$_3$)$_3$), 1.53-1.76 (m, 7H, 5H, (cyclohexyl) and NH(CH$_2$)$_4$CH$_2$CH$_3$)), 2.36-2.47 (m, 1H, CH), 3.40 (bs, 2H, NHCH$_2$CH$_2$CH$_3$), 4.53-4.75 (m, 2H, CH$_2$Ar), 4.95 (s, 2H, CH$_2$CO$_2$H), 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$_6$O$_4$ [M-H] $m/\zeta$ = 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; δH (400 MHz, CDCl₃) 1.10-1.33 (m, 5H, (cyclohexyl)), 1.37 (s, 9H, C(CH₃)₃), 1.67-1.85 (m, 5H, (cyclohexyl)), 2.37-2.47 (m, 1H, CH), 4.90 (s, 2H, CH₂ (Ar)), 4.99 (s, 2H, CH₂CO₂H), 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_{5}O_{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 (7bu).
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; δH (400 MHz, CDCl₃) 1.11-1.34 (m, 5H, (cyclohexyl)), 1.36 (s, 9H, C(CH₃)₃), 1.70-1.84 (m, 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 4.87 (s, 2H, CH₂Ar), 4.99 (s, 2H, CH₂CO₂H), 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 C₃₁H₃₃FN₅O₅ [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; δH (400 MHz, CDCl₃) 1.18-1.28 (m, 5H (cyclohexyl)), 1.36 (s, 9H, C(CH₃)₃), 1.71-1.85 (m, 5H (cyclohexyl)), 2.40-2.47 (m, 1H, CH), 4.85 (s, 2H, CH₂Ar), 5.06 (s, 2H, CH₂CO₂H) 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 C₃₁H₂₉F₅N₅O₅ [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; \(\delta_H\) (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\(_2\)Ar), 4.99 (s, 2H, CH\(_2\)CO\(_2\)H), 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\(_5\)O\(_5\) [M-H] \(m/\ell = 556.26\), 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; $\delta_H$ (400 MHz, DMSO-$d_6$) 0.84 (m, 3H, (CH$_2$)$_4$CH$_3$), 1.19-1.34 (m, 4H, (CH$_2$)$_2$CH$_2$CH$_2$CH$_3$), 1.42-1.54 (m, 2H, CH$_2$CH$_3$(CH$_2$)$_2$CH$_3$), 3.26 (t, $J = 6.9$ Hz, 2H, CH$_2$(CH$_2$)$_3$CH$_3$), 4.67 (bs, 2H, CH$_2$Ar), 4.89 (s, 2H, CH$_2$CO$_2$H), 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$_6$O$_2$ [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%.

![Chemical Structure](image)

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; $\delta_H$ (400 MHz, DMSO-$d_6$) 0.82-0.87 (m, 3H, (CH$_2$)$_4$CH$_3$), 1.12-1.30 (m, 4H, CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.49-1.53 (m, 2H, CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 3.04-3.67 (m, 3H, NCH$_3$), 3.23-3.31 (m, 2H, CH$_2$(CH$_2$)$_3$CH$_3$), 4.67-5.59 (bm, 2H, CH$_2$Ar), 4.87 (s, 2H, CH$_2$CO$_2$H), 7.22(bs, 1H, NH), 7.24-7.35 (m, 5H, CH (Ar)), 7.83 (s, 1H, CH (H-8)); $\delta_C$ (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$_6$O$_2$ [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%. 

61
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; δH (400 MHz, DMSO-d₆) 0.87 (t, J = 7.0 Hz, 3H, (CH₂)₄CH₃), 1.22-1.32 (m, 4H, (CH₂)₂CH₂CH₂CH₃), 1.52-1.59 (m, 2H, (CH₂)₃CH₂CH₃), 3.27 (t, J = 7.2 Hz, 2H, CH₂(CH₂)₃CH₃), 4.85 (s, 2H, CH₃CO₂H), 6.95 (bs, 1H, NHCH₂), 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); δC (100 MHz, DMSO-d₆) 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 C₁₈H₂₃N₆O₂ [M+H] m/z = 355.1870, fnd. 355.1877; rpHPLC tR: 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; δH (400 MHz, DMSO-d₆) (0.85, t, J = 6.9 Hz, 3H, (CH₂)₄CH₃), 1.22-1.30 (m, 4H,
(CH$_2$)$_2$CH$_2$CH$_2$CH$_3$), 1.50 (p, $J = 7.1$ Hz, 2H, CH$_2$CH$_3$(CH$_2$)$_2$CH$_3$), 3.21 (q, $J = 6.7$ Hz, 2H, CH$_2$(CH$_2$)$_3$CH$_3$), 3.32 (vbs, 3H, NCH$_3$), 4.55 (s, 2H, CH$_2$CO$_2$H), 5.26 (vbs, 2H, CH$_2$(fururyl)), 6.27-6.29 (m, 1H, CH (fururyl)), 6.33 (bs, 1H, NH), 6.37-6.39 (m, 1H, CH (fururyl)), 7.55-7.57 (m, 1H, CH (fururyl)), 7.66 (s, 1H, CH (H-8)); $\delta$$_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$_6$O$_3$ [M+H]$^+$ m/z = 373.1994, fnd. 373.1982; rpHPLC $t_R$: 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; $\delta$$_H$ (400 MHz, DMSO-$d_6$) 0.87 (t, $J = 6.8$ Hz, 3H, (CH$_2$)$_4$CH$_3$), 1.21−1.35 (m, 4H, (CH$_2$)$_2$CH$_2$CH$_2$CH$_3$), 1.50-1.77 (m, 8H, CH$_2$CH$_3$(CH$_2$)$_2$CH$_3$ and 3 CH$_2$ (cyclopentyl)), 1.92-2.04 (m, 2H, CH$_2$ (cyclopentyl)), 3.27-3.33 (m, 2H, CH$_2$(CH$_2$)$_3$CH$_3$), 4.35 (vbs, 1H, CH (cyclopentyl)), 4.88 (s, 2H, CH$_2$CO$_2$H), 7.30 (vbs, 1H, NH), 7.96 (bs, 1H, NH), 8.32 (s, 1H, CH (H-8)), 13.34 (br s, 1H, CH$_2$CO$_2$H); HRMS (MS-ES), calcd for C$_{17}$H$_{27}$N$_6$O$_2$ [M+H]$^+$ m/z = 347.2192, fnd. 347.2190; rpHPLC $t_R$: condition (I) 14.582 (II) 34.685 minutes, purity 90.1 % and 97.6%.

63
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; \(\delta\_H\) (400 MHz, DMSO-\(d_6\)) 0.87 (t, \(J = 6.8\) Hz, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 1.10-1.45 (m, 10H, (CH\(_2\))\(_2\)CH\(_2\)CH\(_3\)CH\(_3\) and 3 CH\(_2\)(cyclohexyl)), 1.53 (p, \(J = 6.8\) Hz, 2H, CH\(_2\)CH\(_2\)(CH\(_2\))\(_3\)CH\(_3\)), 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, CH\(_3\)(CH\(_2\))\(_2\)CH\(_3\)), 3.95 (bs, 1H, CH (cyclohexyl)), 4.84 (s, 2H, CH\(_3\)CO\(_2\)H), 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\(_6\)O\(_2\) [M+H] \(m/z = 361.2356\), fnd. 361.2346; \(r_p\)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; \(\delta\_H\) (400 MHz, DMSO-\(d_6\)) 0.85 (t, \(J = 6.9\) Hz, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 1.13 (t, 7.0 Hz, 3H,
NCH$_2$CH$_3$), 1.22-1.33 (m, 4H, (CH$_2$)$_2$CH$_2$CH$_2$CH$_3$), 1.49 (p, $J = 7.0$ Hz, 2H, CH$_2$CH$_2$(CH$_2$)$_2$CH$_3$), 3.20 (q, $J = 6.7$ Hz, 2H, CH$_2$(CH$_2$)$_3$CH$_3$), 3.30 (vbs, 3H, NCH$_3$), 3.97 (vbs, 2H, NCH$_2$CH$_3$), 4.59 (s, 2H, CH$_2$CO$_2$H), 6.26 (bs, 1H, NH), 7.63 (s, 1H, CH (H-8)); HRMS (MS-ES), calcd for C$_{15}$H$_{25}$N$_6$O$_2$ [M+H] m/z = 321.2034, fnd. 321.2033; rpHPLC $t_R$: 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; $\delta$H (400 MHz, DMSO-d$_6$) 0.86 (t, $J = 6.7$ Hz, 3H, (CH$_2$)$_4$CH$_3$), 1.20 (s, 3H, CH(CH$_3$)$_3$), 1.22 (s, 3H, CH(CH$_3$)$_3$), 1.25-1.34 (m, 4H, (CH$_2$)$_2$CH$_2$CH$_2$CH$_3$), 1.51 (p, $J = 6.8$ Hz, 2H, CH$_2$CH$_2$(CH$_2$)$_2$CH$_3$), 3.22-3.28 (m, 2H, CH$_2$(CH$_2$)$_3$CH$_3$), 4.35 (bs, 1H, CH(CH$_3$)$_2$), 4.79 (s, 2H, CH$_2$CO$_2$H), 6.65 (bs, 1H, NH), 7.40 (bs, 1H, NH), 7.75 (s, 1H, CH (H-8)) 13.15 (vbs, 1H CH$_2$CO$_2$H); HRMS (MS-ES), calcd for C$_{15}$H$_{25}$N$_6$O$_2$ [M+H] m/z = 321.2039, fnd. 321.2033; rpHPLC $t_R$: 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; \(\delta_H\) (400 MHz, DMSO-\(d_6\)) 0.85 (t, J = 6.9, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 1.22-1.33 (m, 4H, (CH\(_2\))\(_2\)CH\(_2\)CH\(_3\)), 1.49 (p, J = 7.0 Hz, 2H, CH\(_2\)CH\(_3\)(CH\(_2\))\(_2\)CH\(_3\)), 3.20 (q, J = 6.6 Hz, 2H, CH\(_2\)(CH\(_2\))\(_3\)CH\(_3\)), 4.07 (bs, 2H, CH\(_2\)CHCH\(_2\)), 4.47 (s, 2H, CH\(_2\)CO\(_2\)H), 5.02 (dd, 1H, J = 10.3 Hz and 1.7 Hz, CH\(_2\)CHCH\(_2\)), 5.14 (dd, 1H, J = 17.2 Hz and 1.8 Hz, CH\(_2\)CHCH\(_2\)), 5.88-5.99 (m, 1H, CH\(_2\)CHCH\(_2\)), 6.20 (bs, 1H, NH), 7.24 (bs, 1H, NH), 7.59 (s, 1H, CH (H-8)); \(\delta_C\) (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\(_6\)O\(_2\) [M+H] \(m/z = 319.1869\), fnd. 319.1877; rpHPLC \(t_R\): 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)](image)

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; \(\delta_H\) (400 MHz, DMSO-\(d_6\)) 0.81-0.86 (m, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 0.87-0.92 (m, 6H, CH(CH\(_3\))\(_2\)), 1.13-1.31 (m, 4H, (CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.52 (p, J = 7.1 Hz, 2H, CH\(_2\)CH\(_2\)(CH\(_2\))\(_2\)CH\(_3\)), 1.89-1.98 (m, 1H, CH(CH\(_3\))\(_2\)), 3.23-3.31 (m, 4H, CH\(_2\)(CH\(_2\))\(_3\)CH\(_3\) and CH\(_2\)CH(CH\(_3\))\(_2\)), 4.76 (s, 2H, CH\(_2\)CO\(_2\)H), 7.63 (bs, 1H, NH), 7.90 (s, 2H, CH (H-8) and NH); HRMS (MS-ES), calcd for C\(_{16}\)H\(_{27}\)N\(_6\)O\(_2\) [M+H] \(m/z = 335.2201\), fnd. 335.2190; rpHPLC \(t_R\): 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; δH (400 MHz, DMSO-d₆) 0.87 (t, J = 6.7 Hz, 3H, (CH₂)₄CH₃), 0.91 (t, 3H, J = 7.3 Hz, (CH₂)₃CH₃), 1.22-1.36 (m, 6H, CH₂CH₂CH₂CH₃ and (CH₂)₂CH₂CH₂CH₃), 1.53 (p, J = 6.9 Hz, 2H, CH₂CH₂(CH₂)₂CH₃), 1.61 (p, 2H, CH₂CH₂CH₂CH₃), 3.23-4.17 (bm, 5H, CH₂(CH₂)₂CH₃ and NCH₃), 3.27 (t, J = 7.3 Hz, 2H, CH₂CH₂(CH₂)₂CH₃), 4.84 (s, 2H, CH₃CO₂H), 6.90 (vbs, 1H, NH), 7.80 (s, 1H, CH (H-8)); HRMS (MS-ES), calcd for C₁₇H₂₉N₆O₂ [M+H] m/z = 349.2342, fnd. 349.2346; rpHPLC tₚ: 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; \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 0.79-0.86 (m, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 0.87 (s, 3H, (CH\(_2\))\(_2\)CH(CH\(_3\))\(_2\)), 0.89 (s, 3H, (CH\(_2\))\(_2\)CH(CH\(_3\))\(_2\)), 1.10-1.30 (m, 4H, (CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.45-1.55 (m, 4H, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.59-1.67 (m, 1H, CH\(_2\)CH\(_2\)CH(CH\(_3\))\(_2\)), 3.25-3.33 (m, 2H, CH\(_2\)(CH\(_2\))\(_3\)CH\(_3\)), 3.41-3.53 (m, 2H, CH\(_2\)(CH\(_2\))\(_3\)CH\(_3\)), 4.77 (s, 2H, CH\(_2\)CO\(_2\)H), 7.63 (bs, 1H, NH), 7.86 (s, 1H, CH (H-8)), 7.87 (bs, 1H, NH); \( \delta_C \) (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\(_6\)O\(_2\) [M+H] \( m/z \) = 349.2339, fnd. 349.2346; \( r_p \)HPLC \( t_R \): condition (I) 14.864 (II) 36.430 minutes, purity 90.3% and 96.1%.

![Image of a molecule](image-url)

**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; \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 0.85 (t, \( J = 6.9 \) Hz, 3H, (CH\(_2\))\(_4\)CH\(_3\)), 1.22-1.31 (m, 4H, (CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.49 (p, \( J = 6.9 \) Hz, 2H, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 3.63-3.76 (m, 4H, 2 CH\(_2\) (morpholine)), 4.11 (bs, 4H, 2 CH\(_2\) (morpholine)), 4.69 (s, 2H, CH\(_2\)CO\(_2\)H), 6.40 (bs, 1H, NH), 7.69 (s, 1H, CH (H-8)); \( \delta_C \) (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\(_6\)O\(_3\) [M+H] \( m/z \) = 349.1982, fnd. 349.1974; \( r_p \)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; \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 0.73-0.79 (m, 3H, (CH₂)₄CH₃), 0.96-1.42 (m, 6H, CH₂CH₂CH₂CH₂CH₃), 2.84-3.10 (m, 2H, CH₂(CH₂)₃CH₃), 4.87 (s, 2H, CH₂CO₂H), 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)); \( \delta_C \) (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 C₁₈H₂₁N₆O₅ [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; $\delta_H$ (400 MHz, DMSO-$d_6$) 0.78-0.86 (m, 3H, (CH$_2$)$_3$CH$_3$), 1.00-1.44 (m, 6H, CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 2.87-2.92 (m, 2H, CH$_2$(CH$_2$)$_3$CH$_3$), 4.88 (s, 2H, CH$_2$CO$_2$H), 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)); $\delta_C$ (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$_6$O$_5$ [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%.

![Chemical Structure](image)

2-(6-(benzylamino)-2-((4-cyclohexylbenzyl)amino)-9H-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; $\delta_H$ (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, HNCH$_2$), 4.63 (bs, 2H, CH$_2$Ar), 4.88 (s, 2H, CH$_2$CO$_2$H), 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$_6$O$_2$ [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-d₆) 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, NCH₃), 4.43 (s, 2H, CH₂Ar), 4.77-5.63 (br m, 2H, CH₂NCH₂), 4.87 (bs, 2H, CH₂CO₂H), 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 C₂₈H₃₃N₆O₂ [M+H] m/z = 485.2676, fnd. 485.2659; rpHPLC 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-d₆) 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, CH₃ (furfuryl)), 4.24 (bm, 2H, CH₂ (furfuryl)), 4.43 (s, 2H, CH₂Ar), 4.84 (s, 2H, CH₂CO₂H), 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)); δc (100 MHz, DMSO-d₆) 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 C₂₆H₃₁N₆O₃ [M+H] m/z = 475.2445, fnd. 475.2452; rpHPLC tR: 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; δH (400 MHz, DMSO-d₆) 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, NCH), 4.41 (bs, 2H, CH₂Ar), 4.81(s, 2H, CH₂CO₂H), 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 C₂₅H₃₃N₆O₂ [M+H] m/z = 449.2680, fnd. 449.2659; rpHPLC tR: 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; $\delta_H$ (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, HNCH), 4.44 (s, 2H, CH$_2$Ar), 4.89 (s, 2H, CH$_2$CO$\_2$H), 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$_6$O$_2$ [M+H] $m/z$ = 463.2819, fnd. 463.2816; rpHPLC $t_R$: 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; $\delta_H$ (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, CH₂CHCH₂), 4.43 (s, 2H, CH₂Ar), 4.84 (s, 2H, CH₂CO₂H), 5.05 (dd, J = 10.1 and 1.5 Hz, 1H, CH₂CHCH₂), 5.14 (dd, J = 17.1 and 1.5 Hz, 1H, CH₂CHCH₂), 5.81-5.97 (m, 1H, CH₂CHCH₂), 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 C₂₃H₂₉N₆O₂ [M+H] m/z = 421.2349, fnd. 421.2346; rpHPLC tₘ: 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; δH (400 MHz, DMSO-d₆) 0.81 (s, 3H, CH₂CH(CH₃)₂), 0.83 (s, 3H, CH₂CH(CH₃)₂), 1.26-1.42 (m, 5H, (cyclohexyl)), 1.62-1.80 (m, 5H, (cyclohexyl)), 1.79-1.92 (m, 1H, CH₂CH(CH₃)₂) 2.33-2.46 (m, 1H, CH), 3.16 (bs, 2H, CH₂CH(CH₃)₂), 4.30-4.43 (m, 2H, CH₂Ar), 4.69 (s, 2H, CH₂CO₂H), 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)); δC (100 MHz, DMSO-d₆) 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 C₂₄H₃₃N₆O₂ [M+H] m/z = 437.2663, fnd. 437.2659; rpHPLC tₘ: condition (I) 16.906 (II) 45.089 minutes, purity 96.6 % and 97.8%.
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; δH (400 MHz, DMSO-d₆) 0.85 (s, 3H, (CH₂)₂CH(CH₃)₂), 0.86 (s, 3H, (CH₂)₂CH(CH₃)₂), 1.18-1.60 (m, 8H, 5H (cyclohexyl) and (CH₂)₂CH(CH₃)₂ and CH₂CH₂CH(CH₃)₂), 1.67-1.77 (m, 5H, (cyclohexyl)), 2.41-2.47 (m, 1H, CH), 3.41 (bs, 2H, CH₂CH₂CH(CH₃)₂), 4.47 (s, 2H, CH₂Ar), 4.88 (s, 2H, CH₃CO₂H), 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 C₂₅H₃₅N₆O₂ [M+H] m/z = 451.2835, fnd. 451.2816; rpHPLC tR: condition (I) 17.061 (II) 44.519 minutes, purity 91.9 % and 94.2%.

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

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; \(\delta_H\) (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 CH\(_2\), (morpholine)), 4.08 (bs, 4H, 2 CH\(_2\), (morpholine)), 4.37 (d, \(J = 5.1\) Hz, 2H, CH\(_2\)Ar), 4.78 (s, 2H, CH\(_2\)CO\(_2\)H), 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\(_6\)O\(_3\) [M+H] \(m/z = 451.2463\), fnd. 451.2452; \(r p\)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; \(\delta_H\) (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\(_2\)Ar), 4.89 (s, 2H, CH\(_2\)CO\(_2\)H), 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)); \(\delta_C\) (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_{6}O_{5} [M+H] m/z = 503.2018, fnd. 503.2037; rpHPLC $t_R$: condition (I) 15.558 (II) 40.643, purity 99.7% and 99.0%.

![Image of a chemical structure](image)

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; $\delta_H$ (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$_2$Ar), 4.89 (s, 2H, CH$_2$CO$_2$H), 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)); $\delta_C$ (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$_6$O$_5$ [M+H] m/z = 503.2026, fnd. 503.2037; rpHPLC $t_R$: 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; δH (400 MHz, DMSO-δ6) 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, CH₂Ar), 4.83 (s, 2H, CH₂CO₂H), 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, CO₂H); δC (100 MHz, DMSO-δ6) 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 C₂₆H₂₈N₆O₂F [M+H] m/z = 475.2266, fnd. 475.2252; 

*rpHPLC t<sub>R</sub>*: 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
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; \(\delta_H\) (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\(_2\)Ar), 4.88 (s, 2H, CH\(_2\)CO\(_2\)H), 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\(_6\)O\(_3\) [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%.

\[
\text{2-(2-((tert-butoxycarbonyl)(4-cyclohexylbenzyl)amino)-6-(propylamino)-9H-purin-9-yl)acetic acid (8bs).}
\]

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; \(\delta_H\) (400 MHz, DMSO-\(d_6\)) 0.85 (m, 3H, NHCH\(_2\)CH\(_2\)CH\(_3\)), 1.26-1.41 (m, 5H (cyclohexyl)), 1.53 (m, 2H, NHCH\(_2\)CH\(_2\)CH\(_3\)), 1.65-1.78 (m, 5H (cyclohexyl)), 2.40-2.46 (m, 1H, CH), 3.38 (bs, 2H, NHCH\(_2\)CH\(_2\)CH\(_3\)), 4.41-4.44 (m, 2H, CH\(_2\)Ar), 4.85 (s, 2H, CH\(_2\)CO\(_2\)H), 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)); $\delta_C$ (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$_6$O$_2$ [M+H] $m/z$ = 423.2499, fnd. 423.5203; rpHPLC $t_R$: 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; $\delta_H$ (400 MHz, CDCl$_3$) 0.84 (t, $J = 7.1$ Hz, 3H, (CH$_2$)$_2$CH$_3$), 1.10-1.39 (m, 11H, 5H (cyclohexyl) and (CH$_2$)$_2$CH$_2$CH$_2$CH$_3$), 1.43-1.57 (m, 2H, CH$_2$CH$_2$(CH$_2$)$_3$CH$_3$), 1.60-1.87 (m, 5H, (cyclohexyl)), 2.37-2.47 (m, 1H, CH), 3.42 (bs, 2H, CH$_2$(CH$_2$)$_4$CH$_3$), 4.42 (s, 2H, CH$_2$Ar), 4.81 (s, 2H, CH$_2$CO$_2$H), 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)); $\delta_C$ (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$_6$O$_2$ [M+H] $m/z$ = 465.2991, fnd. 465.2983; rpHPLC $t_R$: 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; \(\delta_H\) (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, CH\(_3\)CO\(_2\)H), 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)); \(\delta_C\) (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\(_5\)O\(_3\)Br [M+H] \(m/z = 536.1271\), fnd. 536.1291; \(rpHPLC\) \(t_R\): 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-d₆) 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, CH₂Ar), 4.88 (s, 2H, CH₂CO₂H), 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-d₆) 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 C₂₆H₂₇FN₅O₃ [M+H] m/z = 476.2073, fnd. 476.2092; rpHPLC 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; δH (400 MHz, DMSO-d6) 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, CH₂Ar), 4.91 (s, 2H, CH₂CO₂H), 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, CO₂H); δC (100 MHz, DMSO-d6) 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 C₂₆H₂₃F₅N₅O₃ [M+H] m/z = 548.1704, fnd. 548.1715; rpHPLC tR: 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; δH (400 MHz, DMSO-d6) 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, CH₂Ar), 4.60 (s, 2H, CH₃CO₂H), 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)); δC (100 MHz, DMSO-d6) 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 C₂₆H₂₈N₅O₃ [M+H] m/z = 458.2180, fnd. 458.2186; rpHPLC tR: condition (I) 15.570 (II) 40.997 minutes, purity 97.8 % and 97.1%.

**Scheme 2.**

\[4 \xrightarrow{a} 9 \xrightarrow{b} 10 \xrightarrow{c} 11a, X = \text{N(CH₃)}₃\text{n-butyl}\]

\[11b, X = \text{NHBn}\]

\[11c, X = \text{N-morpholine}\]

\[12a-12ac\]

**Scheme 2.** a) TFA:CH₂Cl₂ (3:1), r.t., 1.5 hrs, 87 %; b) RCOCl, pyridine, r.t., 15 mins, 55 %; c) X (HNR'R") DIPEA, DMSO, 105 °C, 40 mins, microwave assisted, 67-83 %; f) LiOH, THF:H₂O(3:1), r.t., 30 mins, 73-85 %.

84
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; \( \delta_H \) (400 MHz, CDCl₃) 1.30 (t, \( J = 7.2 \) Hz, 3H, CO₂CH₂CH₃), 4.26 (q, \( J = 7.2 \) Hz, 2H, CO₂CH₂CH₃), 4.84 (s, 2H, CH₂CO₂Et), 5.15 (bs, 2H, NH₂), 7.83 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C₉H₁₁ClN₅O₂ [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; \( \delta_H \) (400 MHz, CDCl₃) 1.32 (t, \( J = 7.2 \) Hz, 3H, CO₂CH₂CH₃), 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, CO₂CH₂CH₃), 5.06 (s, 2H, CH₂CO₂Et), 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 C₂₂H₂₄ClN₅O₃Na [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, CDCl₃) 0.95 (t, J = 7.4 Hz, 3H, N(CH₂)₃CH₃), 1.27-1.49 (m, 7H, N(CH₂)₂CH₂CH₃ and 5H (cyclohexyl)), 1.30 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 1.63-1.91 (m, 7H, NCH₂CH₂CH₂CH₃ and 5H (cyclohexyl)), 2.54-2.61 (m, 1H, CH), 3.16-4.34 (bm, 5H, CH₃NCH₂(CH₂)₂CH₃), 4.26 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.92 (s, 2H, CH₂CO₂Et), 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 C₂₇H₃₇N₆O₃ [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, CDCl₃) 1.31 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 1.35-1.50 (m, 5H,
ethyl 2-(2-(4-cyclohexylbenzamido)-6-morpholino-9H-purin-9-yl)acetate acetate (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 °C (dec); IR (KBr, cm⁻¹) 2958, 2926, 2856, 1752, 1730, 1590, 1458, 1389, 1305, 1267, 1244, 1146, 1113; δH (400 MHz, CDCl₃) 1.30 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 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 CH₂ (morpholine)), 4.26 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.29 (bs, 4H, 2CH₂ (morpholine)), 4.92 (s, 2H, CH₂CO₂Et), 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 C₂₆H₃₃N₆O₄ [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; δH (400 MHz, DMSO-d6) 0.89 (t, J = 7.3 Hz, 3H, N(CH₂)₃CH₃), 1.27-1.49 (m, 7H, N(CH₂)$_2$CH₂CH₃ and 5H (cyclohexyl)), 1.52-1.64 (m, 2H, NCH₂CH₂CH₂CH₃), 1.69-1.80 (m, 5H, (cyclohexyl)), 2.54-2.61 (m, 1H, CH), 2.99-4.34 (bm, 5H, CH₃NCH₂(CH₂)₂CH₃), 4.60 (s, 2H, CH₂CO₂H), 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); δC (100 MHz, DMSO-d₆) 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$_6$O$_3$ [M+H] m/z = 465.2601, fnd. 465.2608; rpHPLC tR: 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; δH (400 MHz, DMSO-d₆) 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, HNCH₂ and CH₂CO₂H), 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); δC (100 MHz, DMSO-d₆) 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 C₂₇H₂₉N₆O₃ [M+H] m/z = 485.2286, fnd. 485.2295; rpHPLC tᵣ: 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; δH (400 MHz, DMSO-d₆) 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 CH₂ (morpholine)), 4.14 (bs, 4H, CH₂ (morpholine)), 4.77 (s, 2H, CH₂CO₂H), 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); δC (100 MHz, DMSO-d₆) 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 C₂₄H₂₉N₆O₄ [M+H] m/z = 465.2246, fnd. 465.2244; rpHPLC tᵣ: condition (I) 14.199 (II) 33.308 minutes, purity 96.2 % and 99.26%.

89
Scheme 3.

ethyl 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; δH (400 MHz, CDCl₃) 1.30 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 1.52 (s, 9H, C(CH₃)₃), 3.82 (t, J = 4.9 Hz, 4H, 2 CH₂ (morpholine)), 4.24 (q, J = 7.2 Hz, 2H, COCH₂CH₃), 4.27 (bs, 4H, 2CH₂ (morpholine)), 4.89 (s, 2H, CH₂CO₂Et), 7.13 (s,
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; δH (400 MHz, CDCl₃) 1.31 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 3.82 (t, J = 4.9 Hz, 4H, 2 CH₂ (morpholine)), 4.26 (q, J = 7.2 Hz, 2H, COCH₂CH₃), 4.29 (bs, 4H, 2CH₂ (morpholine)), 4.92 (s, 2H, CH₂CO₂Et), 7.48 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C₁₃H₁₉N₂O₃ [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; δH (400 MHz, CDCl₃) 0.94 (t, J = 7.3 Hz, 3H, (CH₂)₃CH₃), 1.30 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 1.41 (sextet, J = 7.4 Hz, 2H, (CH₂)₂CH₂CH₃), 1.71 (p, J = 7.5 Hz, 2H, CH₂CH₂CH₂CH₃), 2.78 (m, 2H, CH₂(CH₂)₂CH₃), 3.83
(t, J = 4.9 Hz, 4H, 2 CH₂ (morpholine)), 4.26 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.28 (bs, 4H, 2CH₂ (morpholine)), 4.86 (s, 2H, CH₂CO₂Et), 7.69 (bs, 1H, NH), 7.70 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C₁₈H₂₆N₆O₄Na [M+Na] m/z = 413.20, fnd 413.37.

![chemical_structure](image)

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; δH (400 MHz, CDCl₃) 1.29 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 1.28-1.32 (m, 2H, CH₂ (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 CH₂ (morpholine)), 4.25 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.27 (bs, 4H, 2CH₂ (morpholine)), 4.87 (s, 2H, CH₂CO₂Et), 7.69 (bs, 1H, NH), 7.70 (s, 1H, CH (H-8)); LRMS (MS-ES), calcd for C₂₀H₂₉N₆O₄ [M+H] m/z = 417.22, fnd 417.40.

![chemical_structure](image)

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; δH (400 MHz, DMSO-d₆) 0.87 (t, J = 7.3 Hz, 3H, (CH₂)₃CH₃), 1.29 (sextet, J = 7.5 Hz, 2H, (CH₂)₂CH₂CH₃), 1.52 (p, J = 7.5 Hz, 2H, CH₂CH₂CH₂CH₃), 2.47 (t, J = 7.2 Hz, 2H, CH₂(CH₂)₂CH₃), 3.83 (t, J = 4.3 Hz, 2H, 2 CH₂ (morpholine)), 4.19 (bs, 4H, 2 CH₂ (morpholine)), 4.74 (s, 2H, CH₂CO₂H), 7.99 (s, 1H, CH (H-8)), 9.92 (s, 1H, NH); δC (100 MHz, DMSO-d₆) 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 C₁₆H₂₃N₆O₄ [M+H] m/z = 363.1775, fnd. 363.1775; rpHPLC tR: 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; δH (400 MHz, DMSO-d₆) 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 CH₂ (morpholine)), 4.19 (bs, 4H, 2 CH₂ (morpholine)), 4.74 (s, 2H, CH₂CO₂H), 7.99 (s, 1H, CH (H-8)), 9.85 (s, 1H, NH); δC (100 MHz, DMSO-d₆) 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 C₁₈H₂₅N₆O₄ [M+H] m/z = 389.1919, fnd. 389.1931; rpHPLC tR: 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. 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. 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 °C before subjecting to EMSA analysis. The 32P-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. 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 IC50 values were derived, as previously reported.

**Immunoprecipitation and Immunoblotting assay**

Immunoprecipitation, and SDS/PAGE and Western blotting analysis were performed as previously described. 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). IC50 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. 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 ($K_D$).

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