

Article

Development of bicyclo[3.1.0]hexane-based A₃ receptor ligands – closing the gaps in the structure-affinity relationships

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Abstract: In this paper, a series of bicyclo[3.1.0]hexane-based nucleosides was synthesized and evaluated for their P1 receptor affinities in radioligand binding studies. The most potent derivative **30** displayed moderate A₃AR affinity (*K_i* of 0.38 μM) and high A₃R selectivity. A subset of compounds varied at 5'-position was further evaluated in functional P2Y₁R assays displaying no off-target activity.

Keywords: Adenosine receptors; methanocarba; bicyclo[3.1.0]hexane; A₃ receptors.

1. Introduction

The G protein-coupled adenosine (P1) receptors A₁, A_{2A}, A_{2B} and A₃ play a central role in the complex mechanisms of purinergic signaling. In general, adenosine, the endogenous agonist at P1 receptors, exhibits protective functions as a response to organ stress and release of damage-associated-molecular pattern (DAMP) molecules such as e.g. ATP and S100 proteins [1-3]. Various P1 receptor agonists have been in clinical trials, to name a few capadenoson (A₁AR agonist) for the treatment of atrial fibrillation (NCT00568945) [4], apadenoson (A_{2A}AR agonist) for the SPECT-myocardial perfusion imaging (NCT01313572), the A₃ receptor agonists namodenoson in phase III for liver cancer (NCT04697810) [5,6] and piclidenoson (IB-MECA) for the treatment of psoriasis (NCT03168256), rheumatoid arthritis and most recently of COVID-19 infections (NCT04333472) [7]. We are particularly interested in targeting the A₃ receptor due to its high overexpression in inflammatory and cancer cells compared to its low expression levels in healthy cells, thus making it a potentially promising therapeutic and diagnostic target [8-10]. The introduction of the bicyclo[3.1.0]hexane scaffold, also known as (*N*)-methanocarba (*N* for North), in place of the furanose ring of nucleoside agonists is known to increase the A₃ receptor (A₃AR) potency and selectivity in comparison to other adenosine receptor subtypes [11,12]. In 2005 Jacobson et al. reported compounds **1a** and **1b** as highly potent A₃ receptor agonists [13] and, most recently the synthesis of S-thioether (*N*)-methanocarba adenosine derivatives such as compound **2** (Figure 1) [14]. We were interested in exploring these scaffolds further through various substitutions at 6-position of the purine

ring (purine numbering), the introduction of the 1-deazapurine scaffold, and variations of the 5'-position (ribose numbering) at the methanocarba moiety (Figure 1, general structure I). Jacobson et al. have already established the methyl- and ethyl carboxamides being highly efficient substituents at the 5'-position. There are only a few reports on introducing other functional moieties at the 5'-position of adenosine receptor ligands, one of them being the tetrazole compound **3** as a highly potent dual A₁AR and A₃AR ligand [15]. However, the introduction of other, in particular acidic, functional groups at the 5'-position was never investigated. Therefore, we decided to combine the (*N*)-methanocarba moiety (providing A₃AR preference[12]) with various functional groups at the 5'-position to develop novel adenosine receptor ligands.

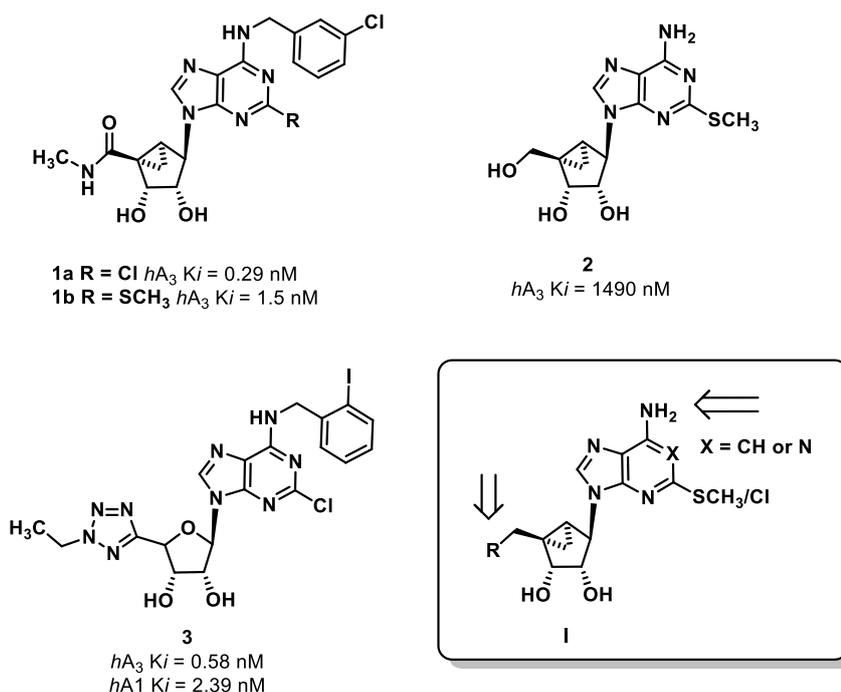


Figure 1. (*N*)-methanocarba-based A₃ receptor antagonists **1a**, **1b**, **2**, the tetrazole derivative **3** and general structure **I**.

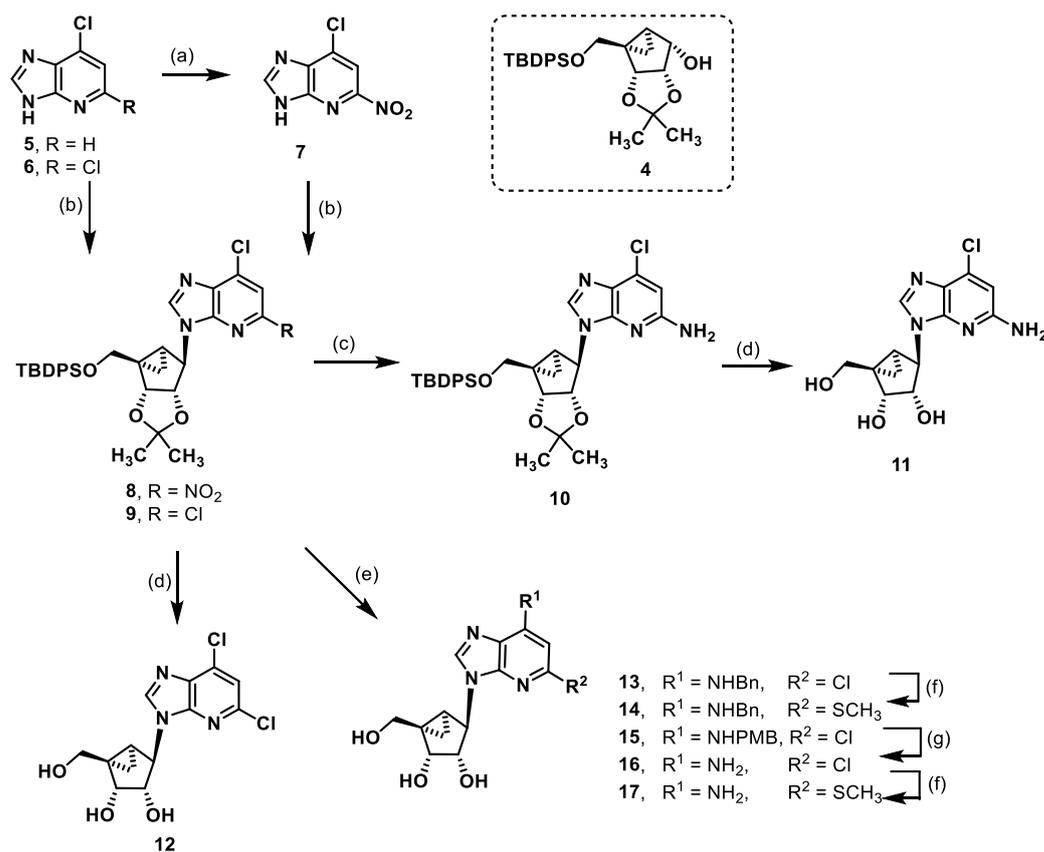
2. Results and Discussion

The synthesis of the bicyclo[3.1.0]hexane scaffold followed the reported procedure by Michel et al.[16], starting with D-ribose and leading to the TBDPS-protected bicyclo[3.1.0]hexane alcohol **4** as a central building block in 9 consecutive steps (see Supporting Information Scheme S1). First, we decided to explore the role of the nitrogen atom at the 1-position of the purine ring. Nitration of 6-chloro-1-deazapurine has led selectively to the formation of 2-nitro derivative **7**. Mitsunobu reaction of either 2,6-dichloro-1-deazapurine (**6**) or 6-chloro-2-nitro-1-deazapurine (**7**) with the methanocarba building block **4** had led to the formation of the protected nucleoside derivatives **8** and **9**, respectively, that were subsequently varied further at the 2-position of the purine ring through the introduction of either amino or methylthio groups (Scheme 1). The exocyclic amine at 6-position was introduced in a reaction of the 6-chloro derivative **9** and benzylamine (for compounds **13** and **14**) or para-methoxybenzyl amine (PMB, for compound **15**). Cleavage of the PMB group led to the derivatives **16** and **17** bearing a free exocyclic amine.

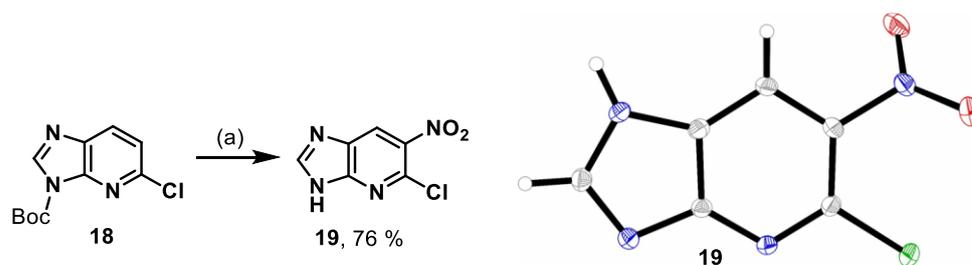
The attempt of introducing the nitro group at the Boc-protected 2-chloro-1-deazapurine (**18**), in order to introduce the electron-withdrawing nitro group at 6-position has led to the formation of one single compound, the 2-chloro-1-nitro-1-deazapurine (**19**), in 76 % yield and not the desired 6-nitro derivative (purine numbering). The position of the nitration was additionally proven by an X-ray structure of compound **19** (Scheme 2).

The reaction of the protected 6-chloro-2-nitro nucleoside **8** with dibenzylamine was sluggish, therefore to synthesize the *N,N*-dibenzyl-1-deaza derivatives, we envisaged the

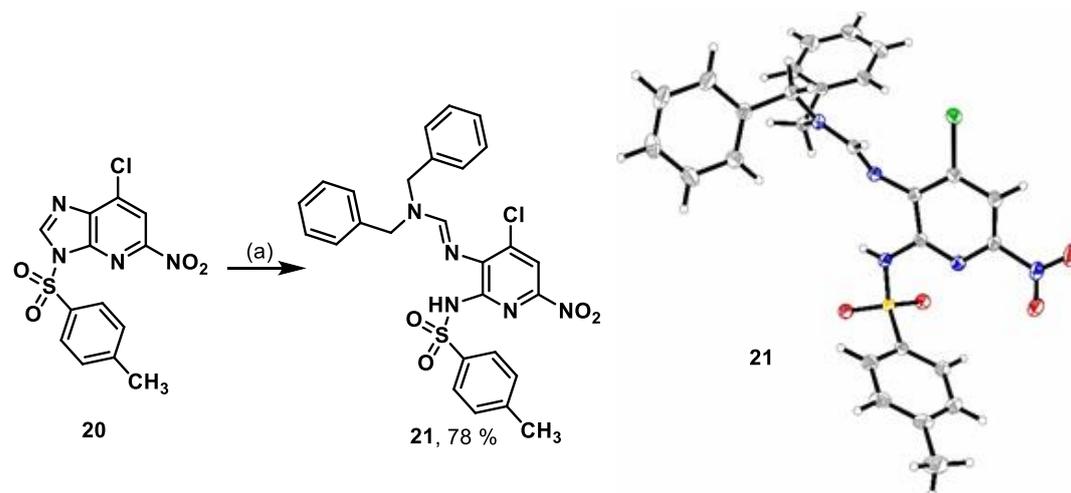
introduction of the dibenzyl group at the tosyl-protected 6-chloro-2-nitro-1-deazapurine **20** followed by subsequent cleavage of the tosyl group and a Mitsunobu reaction with compound **4**. Interestingly the reaction of dibenzylamine with deazapurine **20** provided selectively the ring-opened product **21** in 78 % yield. Due to the strong electron-withdrawing effect of the tosyl group, the dibenzylamine was able to perform a nucleophilic attack at the 8-position of the purine scaffold. The structure of compound **21** was additionally confirmed by X-ray crystal structure analysis (Scheme 3). Since the reaction of nucleoside **8** bearing a nitro group at the 2-position with dibenzylamine has led to the formation of various side-products, the synthesis of dibenzyl derivatives was skipped, and the nitro group was subsequently reduced to the primary amine function leading subsequently to the nucleoside **11**.



Scheme 1: Synthesis of 1-deazapurine derivatives **11-17**. Reagents and conditions: (a) 1) Boc₂O, DMAP, CH₂Cl₂, RT. 2) TBAN, TFAA, CH₂Cl₂, CH₃OH, rt → reflux. (b) compound **4**, DIAD, PPh₃, THF, rt → 70 °C. (c) Na₂S₂O₄, CH₃OH, H₂O, rt. (d) TFA, CH₃OH, H₂O, 70 °C. (e) Benzylamine, DIPEA, NMP, 200 °C, then TFA, CH₃OH, H₂O, 70 °C. or *p*-methoxybenzylamine, DIPEA, NMP, 200 °C, then TFA, CH₃OH, H₂O, 70 °C. (f) NaSCH₃, DMF, 90 °C, then TFA, CH₃OH, H₂O, 70 °C. (g) DDQ, H₂O, CH₂Cl₂, rt, then TFA, CH₃OH, H₂O, 70 °C.

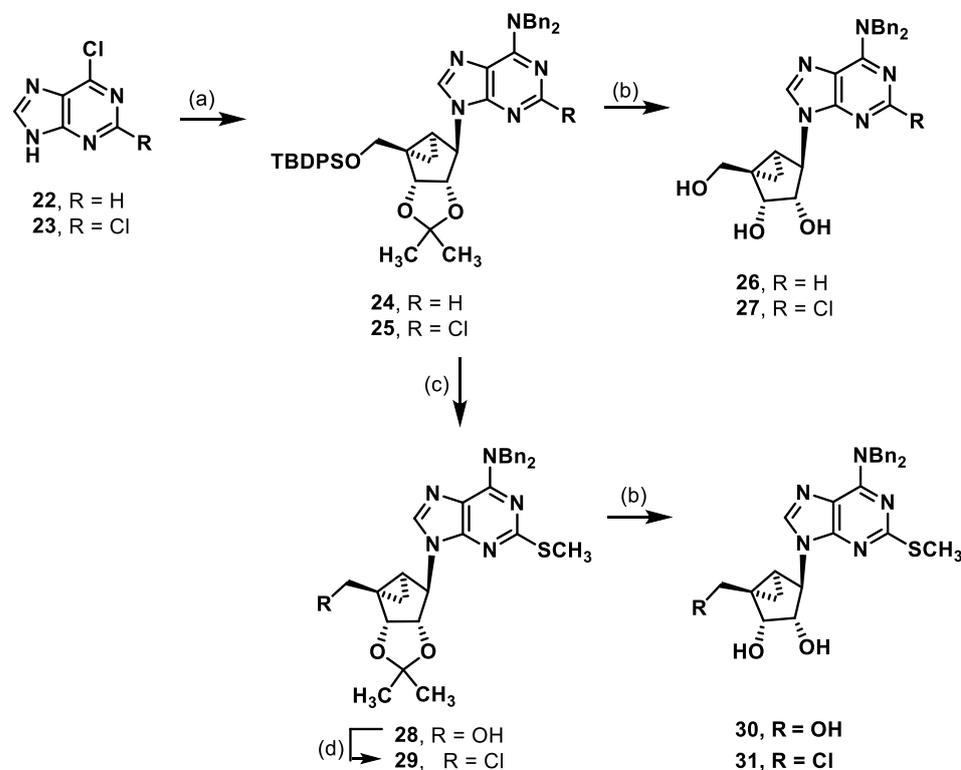


Scheme 2: Nitration of Boc-protected 2-chloro-1-deazapurine (**18**) Reagents and conditions: (a) TBAN, TFAA, CH₂Cl₂, rt → reflux. Molecular structure of compound **19**. Thermal ellipsoids are depicted at 30% probability. CCDC number: 2157452.



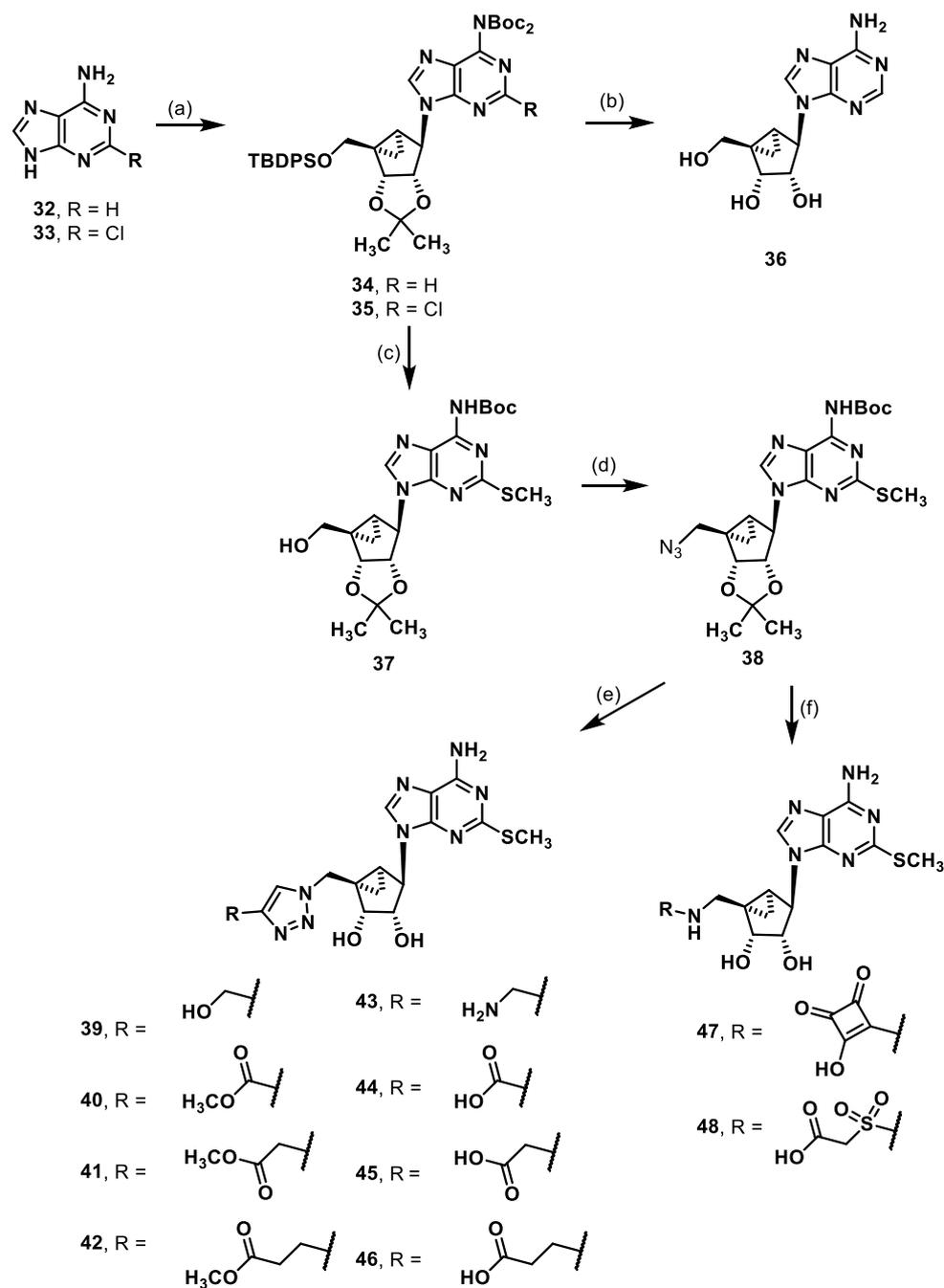
Scheme 3: Reaction of dibenzyl amine with compound **20**. Reagents and conditions: (a) Dibenzylamine, CH_2Cl_2 , RT. Molecular structure of compound **21**. Thermal ellipsoids are depicted at 30% probability. CCDC number: 2157453.

The purine derivatives **24** and **25**, bearing two benzyl groups, were prepared through the reaction of 6-chloropurines **22** and **23** with dibenzyl amine and subsequent Mitsunobu reaction of the methanocarba building block **4**, respectively. The methylthio group was introduced by reacting the protected 2-chloropurine nucleoside **25** with NaSCH_3 . Additionally, the 5'-hydroxy group was replaced by a chloride using cyanuric chloride. Cleavage of the acetonide and TBDPS groups has led to the formation of the respective nucleosides **26**, **27**, **30** and **31** in high yields (Scheme 4).



Scheme 4: Synthesis of dibenzyl derivatives **26**, **27**, **30** and **31**. Reagents and conditions: (a) 1) Dibenzylamine, isopropanol, $90\text{ }^\circ\text{C}$. 2) compound **4**, DIAD, PPh_3 THF, $0\text{ }^\circ\text{C}$ \rightarrow RT. (b) TFA, CH_3OH , H_2O , $70\text{ }^\circ\text{C}$. (c) NaSCH_3 , DMF, $90\text{ }^\circ\text{C}$. (d) Cyanuric chloride, DMF, CH_2Cl_2 , rt.

Intrigued by the high A₃AR affinity of compound **1b** and moderate affinity of compound **2**, we selected the 2-methylthio substituted adenine scaffold for the evaluation of the modifications at the 5'-position. Also, (N)-methanocarba adenine **36** should be prepared as a reference compound for the SAR studies. Hereby adenine (**32**) or 2-chloro adenine (**33**) were subjected to the Mitsunobu reaction. Subsequent cleavage of the protecting groups of compound **34** furnished (N)-methanocarba adenosine **36**, while the protected nucleoside **35** was used for the introduction of the methylthio group at the 2-position. Selective cleavage of the TBDPS protecting group and subsequent tosylation of the free alcohol and nucleophilic substitution of the tosylate led to the formation of the azide **38** as a central intermediate. Huisgen cycloaddition of the azide **38** with various alkynes and subsequent cleavage of the acetonide provided the triazole nucleosides **39-46** bearing neutral (**39-42**) basic (**43**), or acidic (**44-46**) functional groups. While reduction of the azide function using Pd/C, H₂ has led to the formation of the amine suitable for the reaction with squaric acid dimethyl ester or ethyl-2-(chlorosulfonyl)acetate to provide compounds **47** and **48**, respectively.



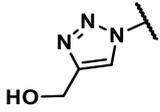
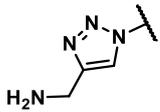
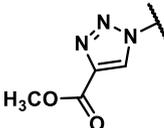
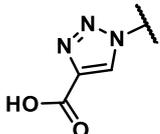
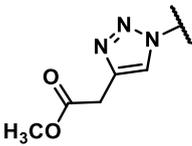
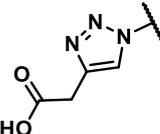
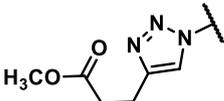
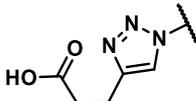
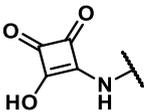
Scheme 5: Synthesis of (*N*)-methanocarba adenosine **33** and derivatives modified at the 5'-position **36-45**. (a) 1) Boc_2O , DMAP, THF, rt., then sat. NaHCO_3 solution, CH_3OH , 50°C . 2) Compound **4**, DIAD, PPh_3 , THF, $0^\circ\text{C} \rightarrow \text{rt}$. (b) TFA, CH_3OH , H_2O , 70°C . (c) NaSCH_3 , DMF, 90°C . (d) 1) Tosyl chloride, Et_3N , DMAP, CH_2Cl_2 , RT. 2) NaN_3 , DMF, 70°C . (e) appropriate alkyne, Cu(II) acetylacetonate, sodium ascorbate, *tert*-butanol, H_2O , rt, then TFA, CH_3OH , H_2O , 70°C . (f) 1) Pd/C , H_2 5 bar, CH_3OH , rt. 2) for **47**: squaric acid dimethyl ester, Et_3N , CH_2Cl_2 , rt., then TFA, CH_3OH , H_2O , 70°C . for **48**: 1) Methyl-2-(chlorosulfonyl)acetate, Et_3N DMAP, CH_2Cl_2 , RT, then TFA, CH_3OH , H_2O , 70°C . 2) NaOH , CH_3CN , H_2O , 70°C

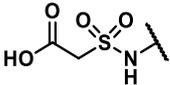
The compounds were evaluated for their P1 receptor affinity in A_1 , $\text{A}_{2\text{A}}$, $\text{A}_{2\text{B}}$ and A_3 receptor binding studies (Table 1). From all synthesized compounds, the (*N*)-methanocarba adenosine **36** is the only derivative displaying affinity to more than one P1 receptor. Compound **36** shows a preference for the A_3 receptor subtype with a K_i of 960 nM, 2- to 6-fold lower affinity towards $\text{A}_{2\text{A}}$ and A_1 receptors, respectively, and no affinity at the $\text{A}_{2\text{B}}$ subtype. The nitrogen atom at 1-position is not required for A_3 receptor affinity, as receptor binding appears to highly depend on substituents at 2- and 6-position. The derivatives **11**

and **12** bearing a chloro substituent at 6-position show no P1 receptor affinity. The introduction of an amino group at the 6-position of the adenine ring as in compound **16** significantly increases the A₃ receptor affinity ($K_i = 1.60 \mu\text{M}$) while not showing any binding at other subtypes. Replacing the chloro with a methylthio group as in **17** leads to a loss of P1 receptor affinity. Interestingly, benzylation of the exocyclic amine as in compounds **13** and **14** restores the A₃R affinity irrespective of the substituent at the 2-position. Extending the benzyl to a para-methoxybenzyl group as in **15** has no effect on A₃R binding ($K_i = 0.50 \mu\text{M}$). In the purine series, the dibenylation of the exocyclic amine appears to work only in combination with the methylthio group (**30**, K_i (A₃R) = $0.38 \mu\text{M}$); derivatives **26**, **27** and **31** were not potent at the A₃ receptor. Most variations at the 5'-position were not tolerated. Only the triazole ester **42** displays a low A₃R affinity of K_i $6.35 \mu\text{M}$. Considering the potential of the introduced moieties in compounds **39-48** to serve as potential bioisosteres of mono- and diphosphate groups, the compounds **39-48** were tested for their functional activity (agonistic and antagonistic) at P2Y₁ receptors; none of the derivatives displayed any functional activity at P2Y₁ receptors up to a concentration of $10 \mu\text{M}$.

Table 1. Inhibitory activities of the novel compounds in human adenosine receptor binding assays ($n = 3$), % displacement by the test compound at a concentration of $10 \mu\text{M}$, or at $1 \mu\text{M}$ ^a. Bn = benzyl, PMB = *p*-methoxybenzyl.

Cmpd.	R ¹	R ²	R ³	X	K _i ± SEM [μM] or displacement [%] at 10 μM, unless noted			
					A ₁	A _{2A}	A _{2B}	A ₃
11	Cl	NH ₂	OH	CH	5 %	4 %	> 10	4 %
12	Cl	Cl	OH	CH	> 10	> 10	> 10	> 10
13	NHBn	Cl	OH	CH	25 %	13 %	> 10	0.46 ± 0.02
14	NHBn	SCH ₃	OH	CH	20 %	4 %	> 10	1.51 ± 0.03
15	NHPMB	Cl	OH	CH	12 %	2 %	> 10	0.50 ± 0.01
16	NH ₂	Cl	OH	CH	32 %	42 %	> 10	1.60 ± 0.11
17	NH ₂	SCH ₃	OH	CH	23 %	3 %	> 10	45 %
26	NBn ₂	H	OH	N	25 %	9 %	12 %	8 %

27	NBn ₂	Cl	OH	N	15 %	> 10	> 10	4 %
30	NBn ₂	SCH ₃	OH	N	30 %	13 %	> 10	0.38 ± 0.01
31	NBn ₂	SCH ₃	Cl	N	21 %	> 10	> 10	26 %
36	NH ₂	H	OH	N	6.10 ± 0.46	1.81 ± 0.11	> 10	0.96 ± 0.05
39	NH ₂	SCH ₃		N	5 %	11 %	> 10	37 %
43	NH ₂	SCH ₃		N	5 %	3 %	> 10	13 %
40	NH ₂	SCH ₃		N	7 %	3 %	> 10	8 %
44	NH ₂	SCH ₃		N	> 1 ^a	> 1 ^a	2 % ^a	> 1 ^a
41	NH ₂	SCH ₃		N	2 % ^a	> 1 ^a	> 1 ^a	3 % ^a
45	NH ₂	SCH ₃		N	> 1 ^a	> 1 ^a	5 % ^a	> 1 ^a
42	NH ₂	SCH ₃		N	19 %	29 %	> 10	6.35 ± 0.23
46	NH ₂	SCH ₃		N	> 1 ^a	> 1 ^a	1 % ^a	> 1 ^a
47	NH ₂	SCH ₃		N	1 % ^a	> 1 ^a	> 1 ^a	6 % ^a

48	NH ₂	SCH ₃		N	3 % ^a	> 1 ^a	> 1 ^a	5 % ^a
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3. Conclusion

With the aim to further explore the SAR of (*N*)-methanocarba nucleosides at A₃ receptor, a series of derivatives **11-17**, **26**, **27**, **30**, **31**, **36**, **39-48** varied at 1-, 2-, 6- and 5'-positions were prepared and evaluated for their affinity across all P1 receptor subtypes. (*N*)-Methanocarba adenosine **36** displayed affinity at A₁, A_{2A} and A₃ receptors combined with only moderate A₃AR preference. The most potent compound **30**, bearing dibenzylamino group at the 6-position and methylthio at the 2-position, displayed high A₃R selectivity. The presence of the nitrogen atom at the 1-position of the purine ring was not required for the A₃AR affinity, consistent with a recent report on hypermodified (*N*)-methanocarba derivatives [15]. The introduction of larger moieties at the 5'-position led to a complete loss of A₃AR affinity, except for the triazole ester **42** displaying low A₃AR affinity. Further structural modifications such as e.g. benzylation of the exocyclic amine function might restore the affinity of the 5'-triazoles at the A₃ receptor.

In conclusion, based on the multiple potential applications of (*N*)-methanocarba nucleosides as therapeutic agents [17,18], we have introduced new lead compounds that bind to the A₃AR and can be further elaborated to increase affinity and selectivity.

4. Materials and Methods

Experimental section

Chemistry General

Unless otherwise noted, moisture-sensitive reactions were conducted under dry nitrogen. Flash column chromatography (fc): Silica gel 60, 40–64 μm; parentheses include: diameter of the column, length of the column, fraction size, eluent, R_f value. Melting point: melting point apparatus Stuart Scientific® SMP 3, uncorrected. IR: IR spectrophotometer FT-ATR-IR (Jasco®). ¹H NMR (400 MHz): Unity Mercury Plus 400 spectrometer (Varian®), AV400 (Bruker®), JEOL JNM-ECA-400. ¹³C NMR (100 MHz): Unity Mercury plus 400 spectrometer (Varian®) JEOL JNM-ECA-400; δ in ppm relative to tetramethylsilane; coupling constants are given with 0.5 Hz resolution, the assignments of ¹³C and ¹H NMR signals were supported by 2D NMR techniques; MS: APCI = atmospheric pressure chemical ionization, EI = electron impact, ESI = electro-spray ionization: MicroTof (Bruker Daltonics, Bremen), calibration with sodium formate clusters before measurement. All solvents were of analytical grade quality and demineralized water was used. HPLC solvents were of gradient grade quality, and ultrapure water was used. All HPLC eluents were degassed by sonication prior to use. Thin-layer chromatography was conducted with silica gel F₂₅₄ on aluminum plates in a saturated chamber at room temperature. The spots were visualized using UV light (254 nm) or reagents such as cerium molybdate dipping bath with additional heating using a standard heat gun. Hence the retention factor values strongly depend on the temperature, the chamber saturation and exact ratio of components of the eluent (highly volatile); the given retention factor values represent just approximate values. Flash column chromatography was conducted with silica gel 600 (40 – 63 μm, Macherey-Nagel). X-ray crystal structures: Equipment: Bruker APEX II CCD diffractometer: four circle diffractometer, Cu X-ray tube, graphite monochromator, APEX II CCD surface detector, Oxford Cryosystem 700 series (N₂ flow: 100-300 K).

X-Ray diffraction Measurements

Data sets for compounds **19** and **21** were collected with a Nonius Kappa CCD rotating anode diffractometer. Programs used: data collection, COLLECT^{xx} (R. W. W. Hooft, Bruker AXS, 2008, Delft, The Netherlands); data reduction Denzo-SMN[19]; absorption

correction, Denzo[20]; structure solution SHELXS-97[21]; structure refinement SHELXL-97[22]. Last step refinement was done with the new software: APEX3 V2019.1.0^{xx} (Bruker AXS (2019) APEX3 Version 2019.1-0, Bruker AXS Inc., Madison, Wisconsin, USA); structure refinement SHELXL-2015[23] and graphics, XP (Version 5.1, Bruker AXS Inc., Madison, Wisconsin, USA, 1998). *R*-values are given for observed reflections, and *wR*² values are given for all reflections.

X-ray crystal structure analysis of 19: A colorless, plate-like specimen of C₆H₃CIN₄O₂, approximate dimensions 0.060 mm x 0.200 mm x 0.260 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a rotating anode Nonius FR591 system equipped with a Mo rotating anode Mo rotating anode (Mo K α , λ = 0.71073 Å) and a Montel mirror monochromator. The integration of the data using an orthorhombic unit cell yielded a total of 3297 reflections to a maximum θ angle of 28.13° (0.75 Å resolution), of which 1804 were independent (average redundancy 1.828, completeness = 99.1%, *R*_{int} = 1.94%, *R*_{sig} = 2.27%) and 1633 (90.52%) were greater than 2 σ (*F*²). The final cell constants of *a* = 11.3385(3) Å, *b* = 6.5407(2) Å, *c* = 20.0740(7) Å, volume = 1488.72(8) Å³, are based upon the refinement of the XYZ-centroids of reflections above 20 σ (*I*). Data were corrected for absorption effects using the multi-scan method (SADABS). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8850 and 0.9720. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group *Pbca*, with *Z* = 8 for the formula unit, C₆H₃CIN₄O₂. The final anisotropic full-matrix least-squares refinement on *F*² with 122 variables converged at *R*₁ = 3.16%, for the observed data and *wR*₂ = 8.40% for all data. The goodness-of-fit was 1.101. The largest peak in the final difference electron density synthesis was 0.293 e/Å³ and the largest hole was -0.263 e/Å³ with an RMS deviation of 0.050 e/Å³. On the basis of the final model, the calculated density was 1.772 g/cm³ and *F*(000), 800 e⁻. The hydrogen at N2 atom was refined freely.

X-ray crystal structure analysis of 21: A pale yellow, prism-like specimen of C₂₇H₂₄CIN₅O₄S, approximate dimensions 0.070 mm x 0.160 mm x 0.200 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a rotating anode Nonius FR591 system equipped with a Mo rotating anode Mo rotating anode (Mo K α , λ = 0.71073 Å) and a Montel mirror monochromator. The integration of the data using a monoclinic unit cell yielded a total of 9321 reflections to a maximum θ angle of 26.73° (0.79 Å resolution), of which 5490 were independent (average redundancy 1.698, completeness = 98.2%, *R*_{int} = 2.98%, *R*_{sig} = 3.82%) and 4655 (84.79%) were greater than 2 σ (*F*²). The final cell constants of *a* = 13.4033(2) Å, *b* = 9.4786(2) Å, *c* = 20.9689(4) Å, β = 98.6230(10)°, volume = 2633.87(8) Å³, are based upon the refinement of the XYZ-centroids of reflections above 20 σ (*I*). Data were corrected for absorption effects using the multi-scan method (SADABS). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9480 and 0.9810. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group *P2₁/n*, with *Z* = 4 for the formula unit, C₂₇H₂₄CIN₅O₄S. The final anisotropic full-matrix least-squares refinement on *F*² with 348 variables converged at *R*₁ = 4.71%, for the observed data and *wR*₂ = 10.64% for all data. The goodness-of-fit was 1.076. The largest peak in the final difference electron density synthesis was 0.214 e/Å³ and the largest hole was -0.339 e/Å³ with an RMS deviation of 0.047 e/Å³. On the basis of the final model, the calculated density was 1.387 g/cm³ and *F*(000), 1144 e⁻. The hydrogen atom at N1 was refined freely.

CCDC-2157452 (compound 19) and -2157453 (compound 21) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

HPLC Purity Measurements

Equipment: UV-detector: UltiMate 3000 variable Wavelength Detector; autosampler: UltiMate 3000; pump: Ultimate 3000; degasser: Ultimate 3000; data acquisition: Chromeleon Client 8.0.0 (Dionex Corpor.). Method: column: guard column: Zorbax SB-Aq 12.5x4.6 mm cartridge, column: Zorbax SB-Aq StableBond analytical 150x4.6 mm, flow

rate: 1.00 mL/min; injection volume: 5.0 μ L; detection at $\lambda = 210$ nm; Method A: solvents: A: Tetrabutylammonium phosphate buffer (5 mM) in H₂O, B: CH₃CN, gradient elution: (A %): 0-20 100 to 90%, 20-30 min: gradient from 90 % to 100 %. Method B: solvents: A: Tetrabutylammonium phosphate buffer (5 mM) in H₂O, B: CH₃CN, gradient elution: (A %): 0-20 min 80 to 20%, 20-30 min: gradient from 20 % to 80 %. Method C: solvents: A: Tetrabutylammonium phosphate buffer (5 mM) in H₂O, B: CH₃CN, gradient elution: (A %): 40-100%, 20-30 min: gradient from 100 % to 40 %. Method D:HPLC method for determination of the product purity: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; Method: column: LiChrospher® 60 RP-select B (5 μ m), 250x4 mm² column; flow rate: 1.00 mL/min; injection volume: 5.0 μ L; detection at $\lambda = 210$ nm; solvents: A: water with 0.05 % (v/v) trifluoroacetic acid; B: acetonitrile with 0.05 % (v/v) trifluoroacetic acid: gradient elution: (A %): 0-4 min: 90 %, 4-29 min: gradient from 90 % to 0 %, 29-31 min: 0 %, 31-31.5 min: gradient from 0 % to 90 %, 31.5-40 min: 90 %.

Data analysis

NMR spectra were processed with MestReNova 12.0 (Mestrelab Research).

Receptor binding studies

Adenosine-receptor binding studies

Cell culture and membrane preparation

Chinese hamster ovary (CHO) cells stably expressing the human adenosine A₁ receptor (CHOhA₁R) were kindly provided by Prof. S. J. Hill and CHO cells stably expressing the human adenosine A₃ receptor (CHOhA₃R) were a gift from Dr. K.-N. Klotz (University of Würzburg, Germany). Chinese hamster ovary cells stably expressing the human A₁-receptor (CHOhA₁R) or the human A₃-receptor (CHOhA₃R) were grown in Dulbecco's Modified Eagle's Medium (DMEM) and Ham's F12 medium (1:1) supplemented with 10 % (v/v) newborn calf serum, 50 μ g/mL streptomycin, 50 IU/mL penicillin, and 200 μ g/mL G418 at 37 °C and 5 % CO₂. CHOhA₁R cells were subcultured twice a week at a ratio of 1:20 on 10 cm \emptyset plates and 15 cm \emptyset plates. CHOhA₃R cells were subcultured twice a week at a ratio of 1:8 on 10 cm \emptyset plates and 15 cm \emptyset plates.

Human embryonic kidney 293 cells stably expressing the human adenosine A_{2A} receptor (HEK293hA_{2A}R) were kindly provided by Dr. J. Wang (Biogen/IDEC, Cambridge, MA), CHO-spap cells stably expressing the wild-type (WT) hA_{2B} receptor (CHO-spap-hA_{2B}R) were kindly provided by S. J. Dowell (GlaxoSmithKline, U.K.). Human embryonic kidney cells from the cell line 293 stably expressing the human A_{2A}-receptor (HEK₂₉₃hA_{2A}R) were grown in culture medium consisting of DMEM supplemented with 10 % (v/v) newborn calf serum, 50 μ g/mL streptomycin, 50 IU/mL penicillin, and 500 μ g/mL G418 at 37 °C and 7 % CO₂. Cells were subcultured twice a week at a ratio of 1:8 on 10 cm \emptyset plates and 15 cm \emptyset plates.

Chinese hamster ovary cells stably expressing the human A_{2A}-receptor and a reporter gene, the secreted placental alkaline phosphatase, (CHO-spap-hA_{2B}R) were grown in DMEM and Ham's F12 medium (1:1) supplemented with 10 % (v/v) newborn calf serum, 100 μ g/mL streptomycin, 100 IU/mL penicillin, 1 mg/mL G418, and 0.4 mg/mL hygromycin at 37 °C and 5 % CO₂. Cells were subcultured at a ratio of 1:20 twice a week.

All cells were grown to 80-90 % confluency and detached from plates by scraping them into 5 mL phosphate-buffered saline. Detached cells were collected and centrifuged at 200 g for 5 min. Pellets derived from 100 15 cm \emptyset plates were pooled and resuspended in 70 mL of ice-cold 50 mM tris(hydroxymethyl)aminomethane (Tris)-HCl buffer, pH 7.4. A Heidolph DiAx 900 homogenizer was used to homogenize the cell suspension. Membranes and the cytosolic fraction were separated by centrifugation at 100,000 g in a Beckman Optima LE-80 K ultracentrifuge (Beckman Coulter, Fullerton, CA) at 4 °C for 20 min. The pellet was resuspended in 35 mL of the Tris-HCl buffer, and the homogenization and centrifugation steps were repeated. Tris-HCl buffer (25 mL) was used to resuspend the pellet, and adenosine deaminase (ADA) was added (0.8 U/mL) to break down endogenous adenosine. Membranes were stored in 250 μ L and 500 μ L aliquots at -80 °C. Total protein concentrations were measured using the bicinchoninic acid (BCA) method.

Radioligand displacement assay

A₁ receptor

Membrane aliquots containing 5 µg (CHO_{hA₁R}) protein were incubated in a total volume of 100 µL assay buffer (50 mM Tris-HCl, pH 7.4) at 25 °C for 1 h. Radioligand displacement experiments were performed using six concentrations of competing ligand in the presence of 1.6 nM [³H]8-cyclopentyl-1,3-dipropylxanthine ([³H]DPCPX). At these concentrations, total radioligand binding did not exceed 10 % of that added to prevent ligand depletion. Nonspecific binding was determined in the presence of 100 µM *N*-cyclopentyladenosine (CPA). Incubations were terminated by rapid vacuum filtration to separate the bound and free radioligand through prewetted 96-well GF/B filter plates using a PerkinElmer Filtermate-harvester (Perkin Elmer, Groningen, the Netherlands). Filters were subsequently washed 12 times with ice-cold 50 mM Tris-HCl, pH 7.4.

A_{2A} receptor

Membrane aliquots containing 30 µg (HEK_{293hA_{2A}R}) total protein were incubated in a total volume of 100 µL assay buffer (50 mM Tris-HCl, pH 7.4) at 25 °C for 1 h. Radioligand displacement experiments were performed using six concentrations of competing ligand in the presence of 5.5 nM [³H]4-[2-[7-amino-2-(2-furyl)-1,2,4-triazolo[1,5-a][1,3,5]triazin-5-yl-amino]ethyl]phenol ([³H]ZM241385). At these concentrations, total radioligand binding did not exceed 10 % of that added to prevent ligand depletion. Nonspecific binding was determined in the presence of 100 µM adenosine-5'-*N*-ethyluronamide (NECA). Incubations were terminated by rapid vacuum filtration to separate the bound and free radioligand through prewetted 96-well GF/B filter plates using a PerkinElmer Filtermate-harvester (Perkin Elmer, Groningen, the Netherlands). Filters were subsequently washed 12 times with ice-cold 50 mM Tris-HCl, pH 7.4.

A_{2B} receptor

Membrane aliquots containing 30 µg (CHO-spap-hA_{2B}R) total protein were incubated in a total volume of 100 µL assay buffer (0.1 % CHAPS in 50 mM Tris-HCl, pH 7.4) at 25 °C for 2 h. Radioligand displacement experiments were performed using six concentrations of competing ligand in the presence of 1.5 nM [³H]8-[4-[4-(4-chlorophenyl)piperazine-1-sulfonyl]phenyl]-1-propylxanthine ([³H]PSB-603). At these concentrations total radioligand binding did not exceed 10 % of that added to prevent ligand depletion. Nonspecific binding was determined in the presence of 10 µM ZM241385. Incubations were terminated by rapid vacuum filtration to separate the bound and free radioligand through prewetted 96-well GF/B filter plates using a PerkinElmer Filtermate-harvester (Perkin Elmer, Groningen, the Netherlands). Filters were subsequently washed 12 times with ice-cold 0.1 % BSA in 50 mM Tris-HCl, pH 7.4.

A₃ receptor

Membrane aliquots containing 15 µg (CHO_{hA₃R}) total protein were incubated in a total volume of 100 µL assay buffer (50 mM Tris-HCl, pH 8.0, supplemented with 10 mM MgCl₂, 1 mM EDTA and 0.01 % (w/v) CHAPS) at 25 °C for 2 h. Radioligand displacement experiments were performed using six concentrations of competing ligand in the presence of 10 nM [³H]8-ethyl-4-methyl-2-phenyl-(8*R*)-4,5,7,8-tetrahydro-1*H*-imidazo[2.1-*i*]purin-5-one ([³H]PSB11). At these concentrations, total radioligand binding did not exceed 10 % of that added to prevent ligand depletion. Nonspecific binding was determined in the presence of 100 µM NECA. Incubations were terminated by rapid vacuum filtration to separate the bound and free radioligand through prewetted 96-well GF/B filter plates using a PerkinElmer Filtermate-harvester (Perkin Elmer, Groningen, the Netherlands). Filters were subsequently washed 12 times with ice-cold 50 mM Tris-HCl supplemented with 10 mM MgCl₂, and 1 mM EDTA, pH 8.0 for CHO_{hA₃R}.

The plates of all four adenosine receptor assays were dried at 55 °C after which MicroscintTM-20-cocktail was added (Perkin Elmer, Groningen, The Netherlands). After 3 h the filter-bound radioactivity was determined by scintillation spectrometry using a 2450 MicroBeta Microplate Counter (Perkin Elmer, Groningen, The Netherlands).

Data analysis

All experimental data were analyzed using the non-linear regression curve fitting program GraphPad Prism 7.0 (GraphPad Software Inc., San Diego, CA). IC₅₀ values obtained from competition displacement binding data were converted into K_i values using the Cheng-Prusoff equation. The K_D value (1.6 nM) of [³H]DPCPX at CHO_{hA1R} membranes was taken from Kourounakis et al.¹⁸¹ The K_D value (1.0 nM) of [³H]ZM241385 at hA_{2A}R membranes, the K_D value (1.71 nM) of [³H]PSB603 at CH-spap-hA_{2B}R membranes, and the K_D value (17.3 nM) of [³H]PSB11 at CHO_{hA3R} membranes were taken from in-house determinations.

P2Y₁ receptor studies

Cell culture

Human astrocytoma cell line expressing human P2Y₁ receptor (1321N1-HA-P2Y₁, Kerfast) were maintained in high-glucose Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum and 1% Penicillin/Streptomycin (10,000 units penicillin and 10 mg streptomycin per mL in 0.9% NaCl, Sigma Aldrich) in tissue culture 75 cm² flasks and subcultured every 2-4 days (1:3, 1:10) once confluent.

Ca²⁺-flux assay

Fluo-4 Direct was prepared according to the manufacturer's instructions. Human Astrocytoma cell line stably expressing the P2Y₁ receptor (1321N1-HA-P2Y₁, Kerfast) was seeded into black clear-bottom Nunc 96 well plates (Thermo Fisher Scientific) at 3.0 – 4.0 × 10⁴ cells/well and incubated for 48 hours at 37°C and 5% CO₂ until cells reach confluence level of at least 85-90%. The medium was removed, and the cells were washed using 100 μL HBSS containing 20 mM HEPES. Loading cells with the fluorescent Ca²⁺ indicator Fluo-4 was performed at 37°C for 40 minutes and additional 20 minutes at room temperature, followed by 30 minutes of incubation in the presence (antagonist mode) of five different concentrations of antagonists (10⁻⁴ to 10⁻⁸ M) or absence of antagonists (agonist mode, mock solution 50 μL HBSS containing 20 mM HEPES and 2% DMSO). Followed by the application of ADP (concentration of determined EC₅₀-value, antagonist mode) or different concentrations of potential agonists (10⁻⁴ to 10⁻⁸ M, agonist mode) and the changes of intracellular Ca²⁺ concentrations were monitored over 200 seconds using a FlexStation® 3 Multi-Mode Microplate Reader (Molecular Devices, San Jose, CA, USA, SoftMax7 Pro, excitation: 494 nm, emission: 516 nm). The concentration-dependent increase or decrease of Ca²⁺-flux was plotted against the logarithmic concentrations of compounds.

Data analysis

The activation or inhibition curves of three independent measurements, each done in duplicates, were fitted to Hill-equation using GraphPad Prism software version 9.3.1 (GraphPad Software Inc. San Diego, CA, USA).

Synthetic procedures

(1*R*,2*R*,3*S*,4*S*,5*S*)-1-[[*tert*-Butyldiphenylsilyl]oxy]methyl-2,3-*O*-isopropylidenebicyclo[3.1.0]hexan-2,3,4-triol (**4**)

The procedure was modified according to reference [16]. (1*S*,2*S*,3*R*)-4-[[*tert*-Butyldiphenylsilyl]oxy]methyl-2,3-*O*-isopropylidene-4-cyclopenten-1,2,3-triol (1.01 g, 2.37 mmol) was dissolved in dry CH₂Cl₂ (13 mL) under a nitrogen atmosphere. The reaction was cooled down to -18 °C with an ice/salt bath. Diethylzinc (1 mol/L in hexane, 2.60 mL, 2.60 mmol, 1.1 eq.) was added dropwise, and the mixture was stirred for 15 min. Diiodomethane (0.22 mL, 2.73 mmol, 1.15 eq.) in dry CH₂Cl₂ (1.6 mL) was also added dropwise and the reaction was stirred for another 15 min. Both steps were repeated a second time. Then diethylzinc (1 mol/L in hexane, 2.60 mL, 2.60 mmol, 1.1 eq.) was added for the third time. After stirring for 15 min at -18 °C the reaction was allowed to warm to rt and stirred overnight. The reaction was quenched with saturated NH₄Cl-solution and was extracted five times with CH₂Cl₂. The organic phase was dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by fc (cyclohexane : ethyl acetate = 7:1, Ø = 5 cm, l = 22 cm, V = 30 mL) to afford the product **4** as a colorless oil (R_f = 0.20, cyclohexane : ethyl acetate = 5:1), yield 0.90 g (86 %). C₂₆H₃₄O₄Si (438.64 g/mol). Purity (HPLC:

method B): > 99 % (t_R = 18.94 min). Exact mass (APCI): m/z calculated for $C_{23}H_{27}O_2Si$ [$M-OH$, $-CO(CH_3)_2$] $^+$ 363.1775, found 363.1777. 1H -NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.66-7.60 (m, 4H, 2, 6- CH_{Ph}), 7.46-7.34 (m, 6H, 3, 4, 5- CH_{Ph}), 5.00 (dd, J = 6.9, 1.2 Hz, 1H, 2- CH), 4.54 (td, J = 6.9, 0.8 Hz, 1H, 3- CH), 4.45 (dt, J = 9.6, 6.1 Hz, 1H, 4- CH), 4.12 (q, J = 7.2 Hz, 0.2H, CH_2 , solvent: ethyl acetate), 4.07 (d, J = 11.0 Hz, 1H, $OCHH$), 3.29 (d, J = 11.0 Hz, 1H, $OCHH$), 2.33 (d, J = 9.7 Hz, 1H, OH), 2.04 (s, 0.3H, OCH_3 , solvent: ethyl acetate), 1.61 (dt, J = 9.3, 4.9 Hz, 1H, 5- CH), 1.54 (s, 3H, $C(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$), 1.26 (t, J = 7.1 Hz, 0.5H, CH_2CH_3 , solvent: ethyl acetate), 1.09 (t, J = 5.0 Hz, 1H, 6- CHH), 1.05 (s, 9H, $C(CH_3)_3$), 0.54 (ddt, J = 8.8, 5.3, 1.1 Hz, 1H, 6- CHH). ^{13}C -NMR (151 MHz, $CDCl_3$) δ (ppm) = 135.7 (4C, C-2, 6 $_{Ph}$), 133.8, 133.7 (2C, C-1 $_{Ph}$), 129.9 (2C, C-4 $_{Ph}$), 127.8 (4C, C-3, 5 $_{Ph}$), 113.0 (1C, $C(CH_3)_2$), 81.3 (1C, C-2), 79.9 (1C, C-3), 71.2 (1C, C-4), 65.4 (1C, OCH_2), 35.7 (1C, C-1), 33.0 (1C, C-5), 27.0 (3C, $C(CH_3)_3$), 26.3 (1C, $C(CH_3)_2$), 24.8 (1C, $C(CH_3)_2$), 19.4 (1C, $C(CH_3)_3$), 10.5 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm^{-1}) = 2932, 2859 (C- H_{aliph}), 1470 (C=C $_{aromat}$), 1107, 1080, 1042 (C-O), 741, 702 (C- H_{aromat} , out of plane).

7-Chloro-5-nitro-3H-imidazo[4,5-b]pyridine (7)

6-Chloro-1-deazapurine (1.01 g, 6.5 mmol) and di-*tert*-butyl dicarbonate (3.02 g, 16.6 mmol, 2.5 eq.) were suspended in CH_2Cl_2 (20 mL). DMAP (0.04 g, 0.3 mmol, 0.1 eq.) was added and the mixture was stirred for 1.5 h. The reaction was quenched with silica gel and filtered through a pad of Celite®. was redissolved in CH_2Cl_2 (20 mL). Tetrabutylammonium nitrate (3.07 g, 10.1 mmol, 1.5 eq.) was added and the mixture cooled to 0 °C with an ice bath. Trifluoroacetic anhydride (1.8 mL, 10.1 mmol, 1.5 eq.) was added dropwise and the reaction stirred for 2.5 h at rt. The solvent was evaporated, and the residue was dissolved in CH_3OH (40 mL). The solution was refluxed overnight. The mixture was concentrated until the product was precipitating but was still properly suspended. After cooling the suspension in the fridge for 1 h, the solid was filtered off, washed with ice cold CH_3OH and dried in vacuo to afford the product **77** as a beige solid (R_f = 0.43, CH_2Cl_2 : CH_3OH = 9:1), yield 1.02 g (78 %). $C_6H_4ClN_4O_2$ (198.57 g/mol). Melting point: 295.9 °C. Purity (HPLC: method B): > 99 % (t_R = 5.67 min). Exact mass (APCI): m/z calculated for $C_6H_4ClN_4O_2$ [$M+H$] $^+$ 199.0007, found 199.0017. 1H -NMR (600 MHz, $DMSO-d_6$) δ (ppm) = 8.90 (s, 1H, 2- CH), 8.36 (s, 1H, 6- CH). ^{13}C -NMR (151 MHz, $DMSO-d_6$) δ (ppm) = 151.5 (1C, C-5), 149.6 (1C, C-2), 112.8 (1C, C-6); C-3a, C-7 and C-7a were not visible. FT-IR (neat) $\tilde{\nu}$ (cm^{-1}) = 3098, 3013 (ν C- H_{aromat}), 2743, 2677, 2612, 2554 (N-H), 1543, 1501 (C=C $_{aromat}$), 833, 880 (C- H_{aromat} , out of plane).

(1R,2R,3S,4R,5S)-4-(5-Amino-7-chloro-3H-imidazo[4,5-b]pyridin-3-yl)-1-[(*tert*-butyldi-phenylsilyl)oxy]methyl}-2,3-O-isopropylidenebicyclo[3.1.0]hexane-2,3-diol (10)

The deazapurine **7** (0.29g, 1.48 mmol, 1.3 eq.) and triphenylphospane (0.61 g, 2.31 mmol, 2.1 eq.) were dissolved in THF (10 mL) under nitrogen atmosphere. DIAD (0.42 mL, 2.14 mmol, 1.9 eq.) was added dropwise at 0 °C. The mixture was stirred for 15 min at rt. A solution of the alcohol **4** (0.49 g, 1.11 mmol) in THF (13 mL) was added and the mixture was stirred at 70 °C for 1 h in the microwave at a power of 200 W. DIAD (0.42 mL, 2.14 mmol, 1.9 eq.) was added and the mixture was stirred again at 70 °C for 1 h in the microwave at a power of 200 W. DIAD (0.42 mL, 2.14 mmol, 1.9 eq.) was added and the mixture was stirred at 70 °C for 1 h in the microwave at a power of 200 W for the third time. The solvent was evaporated and the residue was purified by fc (cyclohexane : ethyl acetate = 5:1, \varnothing = 5 cm, l = 20 cm, V = 30 mL), but the intermediate was still heavily contaminated with DIAD and was directly dissolved in CH_3OH (40 mL). $Na_2S_2O_4$ (1.51 g, 8.64 mmol, 7.8 eq.) and 10 ml H_2O were added. The mixture was stirred for 3d at rt. The solvent was evaporated and the residue was purified by fc (cyclohexane : ethyl acetate = 5:1 \rightarrow 4:1 \rightarrow 2:1, \varnothing = 5 cm, l = 20 cm, V = 30 mL) to afford the product **10** as colorless solid (R_f = 0.42, cyclohexane : ethyl acetate = 1:1), yield 0.138 g (21 %). $C_{32}H_{37}ClN_4O_3Si$ (589.21 g/mol). Melting point: 88.9 °C. Purity (HPLC: method B): > 99 % (t_R = 21.36 min).

Exact mass (LC-MS-ESI): m/z calculated for $C_{32}H_{38}ClN_4O_3Si$ [$M+H$] $^+$ 589.2396, found 589.2401. 1H -NMR (600 MHz, $DMSO-d_6$) δ (ppm) = 8.15 (s, 1H, 2- $CH_{imidazopyridine}$), 7.63-7.58

(m, 4H, 2, 6-CH_{Ph}), 7.47-7.43 (m, 2H, 4-CH_{Ph}), 7.41-7.37 (m, 4H, 3, 5-CH_{Ph}), 6.52 (s, 1H, 6-CH_{imidazopyridine}), 6.26 (s, 2H, NH₂), 5.33 (dd, J = 7.1, 1.3 Hz, 1H, 2-CH), 4.89 (s, 1H, 4-CH), 4.65 (dd, J = 7.1, 1.5 Hz, 1H, 3-CH), 4.10 (d, J = 10.8 Hz, 1H, OCHH), 3.64 (d, J = 10.8 Hz, 1H, OCHH), 1.66 (ddd, J = 9.2, 4.4, 1.5 Hz, 1H, 5-CH), 1.44 (s, 3H, C(CH₃)₂), 1.19 (s, 3H, C(CH₃)₂), 1.02 (s, 9H, C(CH₃)₃), 0.97 (t, J = 4.7 Hz, 1H, 6-CHH), 0.88 (ddd, J = 9.1, 5.0, 1.5 Hz, 1H, 6-CHH); The ¹H-NMR spectrum displays small impurities in the range of about 5 %. ¹³C-NMR (151 MHz, DMSO-d₆) δ (ppm) = 157.4 (1C, C-5_{imidazopyridine}), 145.9 (1C, C-3_{imidazopyridine}), 138.3 (1C, C-2_{imidazopyridine}), 135.1 (4C, C-2, 6_{Ph}), 134.1 (1C, C-7_{imidazopyridine}), 132.7 (2C, C-1_{Ph}), 129.9 (2C, C-4_{Ph}), 127.9 (4C, C-3, 5_{Ph}), 124.5 (1C, C-7_{imidazopyridine}), 111.2 (1C, C(CH₃)₂), 104.1 (1C, C-6_{imidazopyridine}), 88.0 (1C, C-3), 80.7 (1C, C-2), 64.7 (1C, OCH₂), 57.8 (1C, C-4), 38.1 (1C, C-1), 29.9 (1C, C-5), 26.7 (3C, C(CH₃)₃), 25.9 (1C, C(CH₃)₂), 24.3 (1C, C(CH₃)₂), 18.8 (1C, C(CH₃)₃), 11.9 (1C, C-6); The ¹³C-NMR spectrum displays small impurities in the range of about 5 %. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3333 (N-H), 2932 (C-H_{aliphatic}), 1601, 1570 (C=C_{aromat.}), 1107, 1061, 1038 (C-O), 741, 702 (C-H_{aromat.}, out of plane).

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-(5-Amino-7-chloro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**11**)

Compound **10** (0.068 g, 0.12 mmol) was dissolved in CH₃OH (1.6 mL), trifluoroacetic acid (0.20 mL) and H₂O (0.20 mL) were added. The mixture was heated to 70 °C for 1 d. The solvent was evaporated and the residue was purified by semi-preparative HPLC (method B) to afford the alcohol **11** as a colorless solid (R_f = 0.2, CH₂Cl₂ : CH₃OH = 9:1), yield 0.012 g (34 %). C₁₃H₁₅ClN₄O₃ (310.74 g/mol). Purity (HPLC: method D): 99 % (t_R = 6.97 min). Exact mass (LC-MS-ESI): m/z calculated for C₁₃H₁₆ClN₄O₃ [M+H]⁺ 311.0905, found 311.0908. ¹H-NMR (600 MHz, DMSO-d₆) δ (ppm) = 8.32 (s, 1H, 2-CH_{imidazopyridine}), 6.49 (s, 1H, 6-CH_{imidazopyridine}), 6.23 (s, 2H, NH₂), 5.02 (s, 2H, CH₂OH, 3-OH), 4.71 (s, 1H, 4-CH), 4.57 (d, J = 6.3 Hz, 2H, 2-CH, 2-OH), 4.08 (d, J = 11.3 Hz, 1H, OCHH), 3.64 (d, J = 6.3 Hz, 1H, 3-CH), 3.12 (d, J = 11.3 Hz, 1H, OCHH), 1.41 (ddd, J = 8.7, 3.9, 1.4 Hz, 1H, 5-CH), 1.32 (t, J = 4.3 Hz, 1H, 6-CHH), 0.78 (ddd, J = 8.6, 4.7, 1.3 Hz, 1H, 6-CHH). ¹³C-NMR (151 MHz, DMSO-d₆) δ (ppm) = 157.2 (1C, C-5_{imidazopyridine}), 146.1 (1C, C-3_{imidazopyridine}), 138.5 (1C, C-2_{imidazopyridine}), 133.9 (1C, C-7_{imidazopyridine}), 124.4 (1C, C-7_{imidazopyridine}), 104.0 (1C, C-6_{imidazopyridine}), 76.1 (1C, C-3), 70.2 (1C, C-2), 62.2 (1C, OCH₂), 60.2 (1C, C-4), 36.3 (1C, C-1), 23.4 (1C, C-5), 11.1 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3321, 3206 (O-H), 2920 (C-H_{aliphatic}), 1601, 1574 (C=C_{aromat.}), 1061, 1003 (C-O).

(1*R*,2*R*,3*S*,4*R*,5*S*)-1-[(*tert*-Butyldiphenylsilyloxy)methyl]-4-(5,7-dichloro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-2,3-*O*-isopropylidenebicyclo[3.1.0]hexane-2,3-diol (**9**)

2,6-Dichloro-1-deazapurine (**6**, 0.16 g, 0.86 mmol, 1.2 eq.) and triphenylphosphane (0.36 g, 1.37 mmol, 1.9 eq.) were dissolved in THF (7 mL) under nitrogen atmosphere. DIAD (0.27 mL, 1.38 mmol, 1.9 eq.) was added dropwise at 0 °C. The mixture was stirred for 30 min at rt. A solution of the alcohol **4** (0.32 g, 0.73 mmol) in THF (7 mL) was added and the mixture was stirred at 70 °C for 1 h in the microwave at a power of 200 W. DIAD (0.27 mL, 1.38 mmol, 1.9 eq.) was added and the mixture was stirred at 70 °C for 1 h in the microwave at a power of 200 W again. DIAD (0.27 mL, 1.38 mmol, 1.9 eq.) was added and the mixture was stirred at 70 °C for 1 h in the microwave at a power of 200 W for the third time. The solvent was evaporated and the residue was purified by fc (cyclohexane : ethyl acetate = 7:1, Ø = 5 cm, l = 20 cm, V = 30 mL) to afford the product **87** as a colorless solid (R_f = 0.26, cyclohexane : ethyl acetate = 5:1), yield 0.40 g (89 %). C₃₂H₃₅Cl₂N₃O₃Si (608.64 g/mol). Melting point: 75.7 °C. Purity (HPLC: method C): 98 % (t_R = 17.28 min). Exact mass (LC-MS-ESI): m/z calculated for C₃₂H₃₆Cl₂N₃O₃Si [M+H]⁺ 608.1898, found 608.1899. ¹H-NMR (600 MHz, DMSO-d₆) δ (ppm) = 8.67 (s, 1H, 2-CH_{imidazopyridine}), 8.16 (s, 1H, 6-CH_{imidazopyridine}), 7.59 (ddt, J = 10.6, 6.8, 1.4 Hz, 4H, 2, 6-CH_{Ph}), 7.46-7.40 (m, 2H, 4-CH_{Ph}), 7.40-7.37 (m, 2H, 3, 5-CH_{Ph}), 7.36-7.32 (m, 2H, 3, 5-CH_{Ph}), 5.23 (dd, J = 7.1, 1.3 Hz, 1H, 2-CH), 5.04 (s, 1H, 4-CH), 4.77 (dd, J = 7.1, 1.6 Hz, 1H, 3-CH), 4.02 (d, J = 10.6 Hz, 1H, OCHH), 3.90 (d, J = 10.6 Hz, 1H, OCHH), 1.72 (ddd, J = 9.2, 4.5, 1.6 Hz, 1H, 5-CH), 1.46 (s, 3H, C(CH₃)₂), 1.18 (s, 3H, C(CH₃)₂), 1.01 (s, 10H, 6-CHH, C(CH₃)₃), 0.96 (ddd, J = 9.2, 5.1,

1.5 Hz, 1H, 6-CHH). ^{13}C -NMR (151 MHz, DMSO- d_6) δ (ppm) = 145.7 (1C, C-3aimidazopyridine), 144.9 (1C, C-2imidazopyridine), 144.2 (1C, C-5imidazopyridine), 135.2 (1C, C-7imidazopyridine), 135.1 (4C, C-2, 6Ph), 132.8 (2C, C-1Ph), 132.2 (1C, C-7aimidazopyridine), 129.8 (2C, C-4Ph), 127.8 (2C, C-3, 5Ph), 127.8 (2C, C-3, 5Ph), 118.1 (1C, C-6imidazopyridine), 111.4 (1C, C(CH₃)₂), 87.9 (1C, C-3), 81.6 (1C, C-2), 64.5 (1C, OCH₂), 59.3 (1C, C-4), 38.3 (1C, C-1), 29.4 (1C, C-5), 26.7 (3C, C(CH₃)₃), 25.9 (1C, C(CH₃)₂), 24.2 (1C, C(CH₃)₂), 18.8 (1C, C(CH₃)₃), 12.0 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 2978, 2932 (C-Haliphatic), 1589, 1562 (C=C_{aromat.}), 1065, 1042 (C-O), 741, 702 (C-H_{aromat.}, out of plane).

(1R,2R,3S,4R,5S)-4-(5,7-Dichloro-3H-imidazo[4,5-b]pyridin-3-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**12**)

Compound **9** (0.036 g, 0.06 mmol) was dissolved in CH₃OH (1.1 mL), trifluoroacetic acid (0.14 mL) and H₂O (0.14 mL) were added. The mixture was heated to 70 °C for 2 d. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the alcohol **12** as a colorless solid (*R*_f = 0.34, CH₂Cl₂ : CH₃OH = 9:1), yield 0.016 g (84 %). C₁₃H₁₃Cl₂N₃O₃ (330.17 g/mol). Purity (HPLC: method B): 98 % (*t*_R = 5.95 min). Exact mass (APCI): *m/z* calculated for C₁₃H₁₄Cl₂N₃O₃ [M+H]⁺ 330.0407, found 330.0406. ^1H -NMR (600 MHz, CD₃OD) δ (ppm) = 8.93 (s, 1H, 2-CHimidazopyridine), 7.47 (s, 1H, 6-CHimidazopyridin), 5.00 (s, 1H, 4-CH), 4.78 (dd, *J* = 6.6, 1.7 Hz, 1H, 2-CH), 4.28 (dd, *J* = 11.5, 0.9 Hz, 1H, OCHH), 3.91 (dt, *J* = 6.6, 1.3 Hz, 1H, 3-CH), 3.36 (d, *J* = 11.5 Hz, 1H, OCHH), 1.65 (ddd, *J* = 8.7, 3.9, 1.5 Hz, 1H, 5-CH), 1.58 (dd, *J* = 5.2, 3.9 Hz, 1H, 6-CHH), 0.78 (ddd, *J* = 8.7, 5.2, 1.8 Hz, 1H, 6-CHH). ^{13}C -NMR (151 MHz, CD₃OD) δ (ppm) = 147.2 (1C, C-3aimidazopyridine), 147.0 (1C, C-5imidazopyridine), 145.6 (1C, C-2imidazopyridine), 137.1 (1C, C-7imidazopyridine), 133.1 (1C, C-7aimidazopyridine), 119.9 (1C, C-6imidazopyridine), 77.5 (1C, C-3), 72.3 (1C, C-2), 64.3 (1C, OCH₂), 63.6 (1C, C-4), 37.9 (1C, C-1), 24.5 (1C, C-5), 12.2 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3244 (O-H), 2978 (C-Haliphatic), 1593, 1562 (C=C_{aromat.}), 1064, 1006 (C-O).

(1R,2R,3S,4R,5S)-4-[7-(Benzylamino)-5-chloro-3H-imidazo[4,5-b]pyridin-3-yl]-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**13**)

Compound **9** (0.26 g, 0.43 mmol) was dissolved in *N*-methyl-2-pyrrolidone (NMP, 5.5 mL). Benzylamine (0.78 mL, 7.14 mmol, 17 eq.) and *N,N*-diisopropylethylamine (DIPEA, 0.52 mL, 3.06 mmol, 7 eq.) were added. The mixture was stirred at 200 °C for 1 h in the microwave at a power of 200 W. The solution was directly purified by fc (CH₃CN : H₂O = 30:70 → 100:0, 50 mL/min, Biotage® SNAP C18, 120 g, V = 20 mL) to afford the protected product as a colorless solid (*R*_f = 0.44, cyclohexane : ethyl acetate = 1:1), yield 0.25 g (86 %). C₃₉H₄₃ClN₄O₃Si (679.33 g/mol). Melting point: 81.4 °C. Purity (HPLC: method C): 97 % (*t*_R = 17.58 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₃₉H₄₄ClN₄O₃Si [M+H]⁺ 678.2866, found 679.2898. ^1H -NMR (400 MHz, DMSO- d_6) δ (ppm) = 8.25 (s, 1H, 2-CHimidazopyridine), 7.92 (t, *J* = 6.5 Hz, 1H, NH), 7.64-7.57 (m, 4H, 2, 6-CHPh), 7.47-7.28 (m, 10H, 3, 4, 5-CHPh, 2, 3, 5, 6-CHbenzyl), 7.26-7.19 (m, 1H, 4-CHbenzyl), 6.29 (s, 1H, 6-CHimidazopyridine), 5.26 (dd, *J* = 7.1, 1.4 Hz, 1H, 2-CH), 4.92 (s, 1H, 4-CH), 4.65 (dd, *J* = 7.2, 1.5 Hz, 1H, 3-CH), 4.62 (s, 2H, CH₂ benzyl), 4.05 (d, *J* = 10.7 Hz, 1H, OCHH), 3.76 (d, *J* = 10.7 Hz, 1H, OCHH), 1.65 (ddd, *J* = 9.3, 4.4, 1.5 Hz, 1H, 5-CH), 1.44 (s, 3H, C(CH₃)₂), 1.18 (s, 3H, C(CH₃)₂), 1.01 (s, 10H, 6-CHH, C(CH₃)₃), 0.90 (ddd, *J* = 9.2, 5.1, 1.4 Hz, 1H, 6-CHH). ^{13}C -NMR (101 MHz, DMSO- d_6) δ (ppm) = 147.8 (1C, C-7imidazopyridine), 146.0 (1C, C-5imidazopyridine), 144.8 (1C, C-3aimidazopyridine), 139.2 (1C, C-1benzyl), 138.7 (1C, C-2imidazopyridine), 135.0 (4C, C-2, 6Ph), 132.8 (2C, C-1Ph), 129.8 (2C, C-4Ph), 128.4 (2C, C-3, 5benzyl), 127.8 (4C, C-3, 5Ph), 126.9 (2C, C-2, 6benzyl), 126.8 (1C, C-4benzyl), 122.2 (1C, C-7aimidazopyridine), 111.3 (1C, C(CH₃)₂), 98.0 (1C, C-6imidazopyridine), 88.2 (1C, C-3), 81.2 (1C, C-2), 64.7 (1C, OCH₂), 58.2 (1C, C-4), 45.3 (1C, CH₂ benzyl), 38.2 (1C, C-1), 29.8 (1C, C-5), 26.7 (3C, C(CH₃)₃), 25.9 (1C, C(CH₃)₂), 24.2 (1C, C(CH₃)₂), 18.8 (1C, C(CH₃)₃), 12.0 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 2978, 2932 (C-Haliphatic), 1608, 1582 (C=C_{aromat.}), 1111, 1069, 1038 (C-O), 737, 698 (C-H_{aromat.}, out of plane).

Next, the compound (0.080 g, 0.12 mmol) was dissolved in CH₃OH (2.5 mL), trifluoroacetic acid (0.32 mL) and H₂O (0.32 mL) were added. The mixture was heated to

70 °C for 2 d. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the alcohol **13** as a colorless solid (*R*_f = 0.20, CH₂Cl₂ : CH₃OH = 95:5), yield 0.034 g (72 %). C₂₀H₂₁ClN₄O₃ (400.86 g/mol). Purity (HPLC: method B): 99 % (*t*_R = 9.53 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₂₀H₂₂ClN₄O₃ [M+H]⁺ 401.1375, found 401.1367. ¹H-NMR (600 MHz, CD₃OD) δ (ppm) = 8.47 (s, 1H, 2-CH_{imidazopyridine}), 7.39-7.35 (m, 2H, 2, 6-CH_{benzyl}), 7.32 (dd, *J* = 8.5, 6.8 Hz, 2H, 3, 5-CH_{benzyl}), 7.28-7.23 (m, 1H, 4-CH_{benzyl}), 6.36 (s, 1H, 6-CH_{imidazopyridine}), 5.48 (s, 0.2H, CH₂Cl₂, solvent: dichloromethane), 4.83 (s, 1H, 4-CH), 4.76 (dd, *J* = 6.7, 1.7 Hz, 1H, 2-CH), 4.57 (s, 2H, CH₂ benzyl), 4.27 (dd, *J* = 11.6, 0.9 Hz, 1H, OCHH), 3.84 (dt, *J* = 6.7, 1.2 Hz, 1H, 3-CH), 3.32 (d, *J* = 11.5 Hz, 1H, OCHH), 1.62 (ddd, *J* = 8.8, 3.9, 1.5 Hz, 1H, 5-CH), 1.55 (dd, *J* = 5.2, 3.9 Hz, 1H, 6-CHH), 0.74 (ddd, *J* = 8.7, 5.2, 1.8 Hz, 1H, 6-CHH). ¹³C-NMR (151 MHz, CD₃OD) δ (ppm) = 149.2 (1C, C-7_{imidazopyridine}), 148.6 (1C, C-5_{imidazopyridine}), 146.1 (1C, C-3_{imidazopyridine}), 140.3 (1C, C-2_{imidazopyridine}), 139.4 (1C, C-1_{benzyl}), 129.7 (2C, C-3, 5_{benzyl}), 128.4 (2C, C-2, 6_{benzyl}), 128.3 (1C, C-4_{benzyl}), 123.4 (1C, C-7_{imidazopyridine}), 99.7 (1C, C-6_{imidazopyridine}), 77.6 (1C, C-3), 72.3 (1C, C-2), 64.4 (1C, OCH₂), 63.3 (1C, C-4), 47.5 (1C, CH₂ benzyl), 38.0 (1C, C-1), 24.4 (1C, C-5), 12.2 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3325 (O-H), 2978 (C-H_{aliphatic}), 1608, 1578 (C=C_{aromatic}), 1119, 1072 (C-O), 733, 694 (C-H_{aromatic}, out of plane).

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-[7-(Benzylamino)-5-methylthio-3*H*-imidazo[4,5-*b*]pyridin-3-yl]-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**14**)

Compound **13** (0.10 g, 0.15 mmol) was dissolved in DMF (5.5 mL). NaSCH₃ (0.21 g, 3.04 mmol, 20 eq.) was added. The mixture was stirred at 90 °C for 2 h in the microwave at a power of 200 W. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL). The purified intermediate was dissolved in CH₃OH (1 mL), trifluoroacetic acid (0.12 mL) and H₂O (0.12 mL) were added. The mixture was heated to 70 °C for 4 h. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the product **93** as a colorless solid alongside an impurity due to the incomplete conversion during formation of the methylthio ether. The mixture was dissolved in DMF (0.5 mL) and NaSCH₃ (0.041 g, 0.58 mmol, 4 eq.) was added. The mixture was stirred at 90 °C for 1 h in the microwave at a power of 200 W. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the product **93** as a beige solid with a small contamination with starting material. (*R*_f = 0.29, CH₂Cl₂ : CH₃OH = 9:1), yield 0.010 g (16 %). C₂₁H₂₄N₄O₃S (412.51 g/mol). Purity (HPLC: method B): 93 % (*t*_R = 9.78 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₂₁H₂₅N₄O₃S [M+H]⁺ 413.1642, found 413.1643. ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 8.28 (s, 1H, 2-CH_{imidazopyridine}), 7.41 (t, *J* = 6.4 Hz, 1H, NH), 7.38-7.27 (m, 4H, 2, 3, 5, 6-CH_{benzyl}), 7.25-7.19 (m, 1H, 4-CH_{benzyl}), 6.12 (s, 1H, 6-CH_{imidazopyridine}), 5.10 (s, 1H, 3-OH), 4.98 (s, 1H, CH₂OH), 4.79 (s, 1H, 4-CH), 4.58 (s, 3H, 2-CH, CH₂ benzyl), 4.46 (s, 1H, 2-OH), 4.06 (d, *J* = 11.3 Hz, 1H, OCHH), 4.03 (q, *J* = 7.1 Hz, 0.3H, CH₂, solvent: ethyl acetate), 3.68 (d, *J* = 6.5 Hz, 1H, 3-CH), 3.15 (d, *J* = 11.4 Hz, 1H, OCHH), 2.45 (s, 3H, SCH₃), 2.08 (s, 0.1H, CH₃CN, solvent: acetonitrile), 1.99 (s, 0.3H, OCH₃, solvent: ethyl acetate), 1.43 (ddd, *J* = 8.7, 4.6, 1.4 Hz, 1H, 5-CH), 1.33 (t, *J* = 4.3 Hz, 1H, 6-CHH), 1.17 (t, *J* = 7.1 Hz, 0.1H, CH₂CH₃, solvent: ethyl acetate), 0.59 (ddd, *J* = 8.6, 4.7, 1.6 Hz, 1H, 6-CHH); The ¹H-NMR spectrum displays small impurities in the range of about 5 % assigned to compound **13**. ¹³C-NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 153.9 (1C, C-5_{imidazopyridine}), 146.1 (1C, C-7_{imidazopyridine}), 146.0 (1C, C-3_{imidazopyridine}), 139.7 (1C, C-1_{benzyl}), 137.2 (1C, C-2_{imidazopyridine}), 128.3 (2C, C-3, 5_{benzyl}), 127.0 (2C, C-2, 6_{benzyl}), 126.7 (1C, C-4_{benzyl}), 120.9 (1C, C-7_{imidazopyridine}), 95.9 (1C, C-6_{imidazopyridine}), 76.2 (1C, C-3), 70.3 (1C, C-2), 62.3 (1C, OCH₂), 60.2 (1C, C-4), 45.4 (1C, CH₂ benzyl), 36.4 (1C, C-1), 23.3 (1C, C-5), 13.1 (1C, SCH₃), 11.1 (1C, C-6); The ¹³C-NMR spectrum displays small impurities in the range of about 5 % assigned to compound **13**. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3302 (O-H), 2978 (C-H_{aliphatic}), 1605, 1582 (C=C_{aromatic}), 1115, 1072, 1006 (C-O), 737, 698 (C-H_{aromatic}, out of plane).

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-[5-Chloro-7-[(4-methoxy)benzylamino]-3*H*-imidazo[4,5-*b*]pyridin-3-yl]-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**15**)

Compound **9** (0.41 g, 0.68 mmol) was dissolved in NMP (8 mL). 4-Methoxybenzylamine (1.3 mL, 9.95 mmol, 15 eq.) and DIPEA (0.56 mL, 3.29 mmol, 4.5 eq.) were added. The mixture was stirred at 200 °C for 5 min in the microwave at a power of 200 W and was directly purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 50 mL/min, Biotage® SNAP C18, 120 g, V = 20 mL) to afford the acetonide protected product (1*R*,2*R*,3*S*,4*R*,5*S*)-4-(7-Amino-5-chloro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-1-[(*tert*-butyldiphenylsilyloxy)methyl]-2,3-O-isopropylidenebicyclo[3.1.0]hexane-2,3-diol as a colorless solid (*R*_f = 0.35, cyclohexane : ethyl acetate = 1:1), yield 0.39 g (80 %). C₄₀H₄₅ClN₄O₄Si (708.29 g/mol). Melting point: 82.3 °C. Purity (HPLC: method C): 96 % (*t*_R = 17.51 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₄₀H₄₆ClN₄O₄Si [M+H]⁺ 709.2971, found 709.2958. ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 8.24 (s, 1H, 2-CH_{imidazopyridine}), 7.85 (t, *J* = 5.2 Hz, 1H, NH), 7.63-7.56 (m, 4H, 2, 6-CH_{Ph}), 7.46-7.32 (m, 6H, 3, 4, 5-CH_{Ph}), 7.32-7.27 (m, 2H, 2, 6-CH_{benzyl}), 6.91-6.86 (m, 2H, 3, 5-CH_{benzyl}), 6.29 (s, 1H, 6-CH_{imidazopyridine}), 5.25 (dd, *J* = 7.3, 1.2 Hz, 1H, 2-CH), 4.91 (s, 1H, 4-CH), 4.65 (dd, *J* = 7.1, 1.5 Hz, 1H, 3-CH), 4.53 (s, 2H, CH_{2 benzyl}), 4.04 (d, *J* = 10.7 Hz, 1.2H, OCHH, CH₂, solvent: ethyl acetate), 3.76 (d, *J* = 10.7 Hz, 1H, OCHH), 3.71 (s, 3H, OCH₃), 2.07 (s, 0.1H, CH₃CN, solvent: acetonitrile), 1.99 (s, 0.2H, OCH₃, solvent: ethyl acetate), 1.65 (ddd, *J* = 9.3, 4.5, 1.5 Hz, 1H, 5-CH), 1.45 (s, 3H, C(CH₃)₂), 1.18 (s, 3.2H, C(CH₃)₂, CH₂CH₃, solvent: ethyl acetate), 1.02 (s, 9H, C(CH₃)₃), 0.98 (t, *J* = 4.8 Hz, 1H, 6-CHH), 0.90 (ddd, *J* = 9.2, 5.2, 1.4 Hz, 1H, 6-CHH); The ¹H-NMR spectrum displays small impurities in the range of about 5 %. ¹³C-NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 158.2 (1C, C-4_{benzyl}), 147.8 (1C, C-7_{imidazopyridine}), 146.0 (1C, C-5_{imidazopyridine}), 144.7* (1C, C-3_{imidazopyridine}), 138.6 (1C, C-2_{imidazopyridine}), 135.0 (4C, C-2, 6_{Ph}), 132.8 (2C, C-1_{Ph}), 131.0* (1C, C-1_{benzyl}), 129.8 (2C, C-4_{Ph}), 128.3 (2C, C-2, 6_{benzyl}), 127.8 (4C, C-3, 5_{Ph}), 122.2 (1C, C-7_{imidazopyridine}), 113.8 (2C, C-3_{imidazopyridine}, 5_{benzyl}), 111.3 (1C, C(CH₃)₂), 98.0* (1C, C-6_{imidazopyridine}), 88.2 (1C, C-3), 81.2 (1C, C-2), 64.8 (1C, OCH₂, 58.2 (1C, C-4), 55.0 (1C, OCH₃), 44.7 (1C, CH_{2 benzyl}), 38.2 (1C, C-1), 29.8 (1C, C-5), 26.7 (3C, C(CH₃)₃), 25.9 (1C, C(CH₃)₂), 24.3 (1C, C(CH₃)₂), 18.8 (1C, C(CH₃)₃), 12.0 (1C, C-6); *: C-3_{imidazopyridine}, C-6_{imidazopyridine} and C-1_{benzyl} could only be seen in 2D NMR spectra. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3071 (ν C-H_{aromat.}), 2932 (C-H_{aliph.}), 1609, 1582 (C=C_{aromat.}), 1111, 1065, 1038 (C-O), 741, 702 (C-H_{aromat.}, out of plane).

Next, the acetonide-protected compound (0.050 g, 0.07 mmol) was dissolved in CH₃OH (1.6 mL), trifluoroacetic acid (0.20 mL) and H₂O (0.20 mL) were added. The mixture was heated to 70 °C for 1 d. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the alcohol **95** as a colorless solid (*R*_f = 0.19, CH₂Cl₂ : CH₃OH = 95:5), yield 0.027 g (89 %). C₂₁H₂₃ClN₄O₄ (430.89 g/mol). Purity (HPLC: method B): 98 % (*t*_R = 9.67 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₂₁H₂₄ClN₄O₄ [M+H]⁺ 431.1481, found 431.1486. ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 8.44 (s, 1H, 2-CH_{imidazopyridine}), 7.73 (t, *J* = 6.8 Hz, 1H, NH), 7.31-7.25 (m, 2H, 2, 6-CH_{benzyl}), 6.94-6.83 (m, 2H, 3, 5-CH_{benzyl}), 6.30 (s, 1H, 6-CH_{imidazopyridine}), 5.75 (s, 0.4H, CH₂Cl₂, solvent: dichloromethane), 4.72 (s, 1H, 4-CH), 4.58 (dd, *J* = 6.5, 1.5 Hz, 3H, 2-CH, CH_{2 benzyl}), 4.09 (d, *J* = 11.4 Hz, 1H, OCHH), 3.71 (s, 3H, OCH₃), 3.66 (dt, *J* = 6.4, 1.2 Hz, 1H, 3-CH), 3.15 (d, *J* = 11.4 Hz, 1H, OCHH), 1.44 (ddd, *J* = 8.8, 3.9, 1.4 Hz, 1H, 5-CH), 1.34 (t, *J* = 4.3 Hz, 1H, 6-CHH), 0.60 (ddd, *J* = 8.6, 4.7, 1.5 Hz, 1H, 6-CHH). ¹³C-NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 158.2 (1C, C-4_{benzyl}), 147.7 (1C, C-7_{imidazopyridine}), 145.9 (1C, C-5_{imidazopyridine}), 145.0 (1C, C-3_{imidazopyridine}), 138.5 (1C, C-2_{imidazopyridine}), 131.0 (1C, C-1_{benzyl}), 128.3 (2C, C-2, 6_{benzyl}), 121.8 (1C, C-7_{imidazopyridine}), 113.8 (2C, C-3, 5_{benzyl}), 98.0 (1C, C-6_{imidazopyridine}), 76.0 (1C, C-3), 70.3 (1C, C-2), 62.2 (1C, OCH₂), 60.5 (1C, C-4), 55.0 (1C, OCH₃), 54.9 (0.2C, CH₂Cl₂, solvent: dichloromethane), 44.9 (1C, CH_{2 benzyl}), 36.4 (1C, C-1), 23.2 (1C, C-5), 11.0 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3318 (O-H), 2920 (C-H_{aliph.}), 1609 (C=C_{aromat.}), 1119, 1080, 1030 (C-O), 737 (C-H_{aromat.}, out of plane).

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-(7-Amino-5-chloro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**16**)

The acetone-protected intermediate (1*R*,2*R*,3*S*,4*R*,5*S*)-4-(7-amino-5-chloro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-1-[(*tert*-butyldiphenylsilyloxy)methyl]-2,3-*O*-isopropylidenebicyclo[3.1.0]hexane-2,3-diol (0.26 g, 0.43 mmol) was dissolved in CH₂Cl₂ (2.7 mL), H₂O (0.3 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.038 g, 0.17 mmol, 1.5 eq.) were added. The mixture was stirred at rt overnight. H₂O was added and the mixture was extracted three times with CH₂Cl₂. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP C18, 12 g, V = 20 mL) to afford the amine as a beige solid. (*R*_f = 0.19, cyclohexane : ethyl acetate = 1:1), yield 0.049 g (74 %). C₃₂H₃₇ClN₄O₃Si (588.23 g/mol). Melting point: 101.0 °C. Purity (HPLC: method B): 98 % (*t*_R = 22.35 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₃₂H₃₈ClN₄O₃Si [M+H]⁺ 589.2396, found 589.2395. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.21 (s, 1H, 2-CH_{imidazopyridine}), 7.63-7.58 (m, 4H, 2, 6-CH_{Ph}), 7.47-7.42 (m, 2H, 4-CH_{Ph}), 7.41-7.37 (m, 4H, 3, 5-CH_{Ph}), 6.80 (s, 2H, NH₂), 6.38 (s, 1H, 6-CH_{imidazopyridine}), 5.75 (s, 0.1H, CH₂Cl₂, solvent: dichloromethane), 5.27 (dd, *J* = 7.0, 1.3 Hz, 1H, 2-CH), 4.90 (s, 1H, 4-CH), 4.64 (dd, *J* = 7.2, 1.5 Hz, 1H, 3-CH), 4.04 (d, *J* = 10.7 Hz, 1H, OCHH), 3.74 (d, *J* = 10.7 Hz, 1H, OCHH), 1.65 (ddd, *J* = 9.3, 4.4, 1.5 Hz, 1H, 5-CH), 1.45 (s, 3H, C(CH₃)₂), 1.19 (s, 3H, C(CH₃)₂), 1.02 (s, 9H, C(CH₃)₃), 0.98 (t, *J* = 4.8 Hz, 1H, 6-CHH), 0.89 (ddd, *J* = 9.2, 5.1, 1.5 Hz, 1H, 6-CHH). ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 148.9 (1C, C-7_{imidazopyridine}), 145.7 (1C, C-5_{imidazopyridine}), 145.3 (1C, C-3_{imidazopyridine}), 138.7 (1C, C-2_{imidazopyridine}), 135.1 (4C, C-2, 6_{Ph}), 132.8 (2C, C-1_{Ph}), 129.9 (2C, C-4_{Ph}), 127.9 (4C, C-3, 5_{Ph}), 122.1 (1C, C-7_{imidazopyridine}), 111.3 (1C, C(CH₃)₂), 100.5 (1C, C-6_{imidazopyridine}), 88.3 (1C, C-3), 81.2 (1C, C-2), 64.9 (1C, OCH₂), 58.1 (1C, C-4), 38.3 (1C, C-1), 29.9 (1C, C-5), 26.8 (3C, C(CH₃)₃), 25.9 (1C, C(CH₃)₂), 24.3 (1C, C(CH₃)₂), 18.9 (1C, C(CH₃)₃), 12.1 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3360 (N-H), 2978, 2932 (C-H_{aliph.}), 1624, 1601 (C=C_{aromat.}), 1111, 1065, 1038 (C-O), 741, 702 (C-H_{aromat.}, out of plane).

Next the acetone-protected intermediate (0.051 g, 0.09 mmol) was dissolved in CH₃OH (1.6 mL), trifluoroacetic acid (0.20 mL) and H₂O (0.20 mL) were added. The mixture was heated to 70 °C for 1 d. The solvent was evaporated and the residue was purified by semi-preparative HPLC (method B) to afford the alcohol **16** as a colorless solid (*R*_f = 0.24, CH₂Cl₂ : CH₃OH = 9:1), yield 0.016 g (60 %). C₁₃H₁₅ClN₄O₃ (310.74 g/mol). Purity (HPLC: method B): > 99 % (*t*_R = 4.11 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₁₃H₁₆ClN₄O₃ [M+H]⁺ 311.0905, found 311.0905. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.45 (s, 1H, 2-CH_{imidazopyridine}), 6.76 (s, 2H, NH₂), 6.39 (s, 1H, 6-CH_{imidazopyridine}), 4.72 (s, 1H, 4-CH), 4.57 (dd, *J* = 6.5, 1.6 Hz, 1H, 2-CH), 4.08 (d, *J* = 11.4 Hz, 1H, OCHH), 3.66 (d, *J* = 6.4 Hz, 1H, 3-CH), 3.14 (d, *J* = 11.4 Hz, 1H, OCHH), 1.44 (ddd, *J* = 8.8, 3.9, 1.4 Hz, 1H, 5-CH), 1.34 (t, *J* = 4.3 Hz, 1H, 6-CHH), 0.60 (ddd, *J* = 8.5, 4.7, 1.6 Hz, 1H, 6-CHH). ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 148.6 (1C, C-5_{imidazopyridine}), 145.6 (1C, C-7_{imidazopyridine}), 145.4 (1C, C-3_{imidazopyridine}), 138.7 (1C, C-2_{imidazopyridine}), 121.4 (1C, C-7_{imidazopyridine}), 100.5 (1C, C-6_{imidazopyridine}), 76.0 (1C, C-3), 70.3 (1C, C-2), 62.2 (1C, OCH₂), 60.6 (1C, C-4), 36.4 (1C, C-1), 23.2 (1C, C-5), 11.1 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3345, 3217 (O-H), 2924 (C-H_{aliph.}), 1632, 1601 (C=C_{aromat.}), 1115, 1069, 1007 (C-O).

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-(7-Amino-5-methylthio-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**17**)

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-(7-Amino-5-chloro-3*H*-imidazo[4,5-*b*]pyridin-3-yl)-1-[(*tert*-butyldiphenylsilyloxy)methyl]-2,3-*O*-isopropylidenebicyclo[3.1.0]hexane-2,3-diol (0.030 g, 0.05 mmol) was dissolved in DMF (1.5 mL). NaSCH₃ (0.078 g, 1.11 mmol, 22 eq.) was added. The mixture was stirred at 90 °C for 2 h in the microwave at a power of 200 W. H₂O was added and the reaction was extracted three times with ethyl acetate. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. Due to incomplete conversion, the residue was dissolved in DMF (1.5 mL), NaSCH₃ (0.054 g, 0.77 mmol, 15 eq.) was added. The mixture was stirred at 90 °C for 1 h in the microwave at a power of 200 W. H₂O was added and the reaction was extracted three times with ethyl acetate. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP C18, 12 g, V = 20 mL) to afford the methylthio ether as a colorless oil (*R*_f = 0.23,

CH₂Cl₂ : CH₃OH = 95:5), yield 0.011 g (58 %). C₁₇H₂₂N₄O₃S (362.45 g/mol). Melting point: 109.2 °C. Purity (HPLC: method B): 94 % (t_R = 9.14 min). Exact mass (LC-MS-ESI): m/z calculated for C₁₇H₂₃N₄O₃S [M+H]⁺ 363.1485, found 363.1493. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.15 (s, 1H, 2-CH_{imidazopyridine}), 6.39 (s, 2H, NH₂), 6.27 (s, 1H, 6-CH_{imidazopyridine}), 5.75 (s, 0.4H, CH₂Cl₂, solvent: dichloromethane), 5.22 (dd, *J* = 7.0, 1.4 Hz, 1H, 2-CH), 4.98 (t, *J* = 5.2 Hz, 1H, OH), 4.94 (s, 1H, 4-CH), 4.55 (dd, *J* = 7.1, 1.5 Hz, 1H, 3-CH), 3.86 (dd, *J* = 11.7, 3.2 Hz, 1H, OCHH), 3.36-3.31 (m, 1H, OCHH), 2.49 (s, 3H, SCH₃), 1.61 (ddd, *J* = 9.2, 4.4, 1.5 Hz, 1H, 5-CH), 1.44 (s, 3.3H, C(CH₃)₂), 1.17 (s, 3.3H, C(CH₃)₂), 0.98 (t, *J* = 4.8 Hz, 1H, 6-CHH), 0.88-0.84 (m, 1H, 6-CHH): ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 153.9 (1C, C-5_{imidazopyridine}), 147.1 (1C, C-7_{imidazopyridine}), 146.1 (1C, C-3_{imidazopyridine}), 137.5 (1C, C-2_{imidazopyridine}), 121.1 (1C, C-7_{imidazopyridine}), 111.2 (1C, C(CH₃)₂), 98.3 (1C, C-6_{imidazopyridine}), 88.5 (1C, C-3), 80.8 (1C, C-2), 62.6 (1C, OCH₂), 57.7 (1C, C-4), 54.9 (0.2C, CH₂Cl₂, solvent: dichloromethane), 38.7 (1C, C-1), 29.8 (1C, C-5), 25.9 (1C, C(CH₃)₂), 24.2 (1C, C(CH₃)₂), 13.2 (1C, SCH₃), 12.6 (1C, C-6): FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3352, 3202 (O-H), 2986, 2924 (C-H_{aliphatic}), 1624, 1582 (C=C_{aromatic}), 1057, 1026, 1015 (C-O).

Next the acetonide-protected methylthioether intermediate (0.025 g, 0.07 mmol) was dissolved in CH₃OH (1.6 mL), trifluoroacetic acid (0.20 mL) and H₂O (0.20 mL) were added. The mixture was heated to 50 °C overnight. The solvent was evaporated and the residue was purified by semi-preparative HPLC (method C) to afford the product **17** as a colorless solid (R_f = 0.22, CH₂Cl₂ : CH₃OH = 9:1), yield 0.012 g (55 %). C₁₄H₁₈N₄O₃S (322.38 g/mol). Purity (HPLC: method D): 99 % (t_R = 10.45 min). Exact mass (LC-MS-ESI): m/z calculated for C₁₄H₁₉N₄O₃S [M+H]⁺ 323.1172, found 323.1167. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.43 (s, 1H, 2-CH_{imidazopyridine}), 6.46 (s, 2H, NH₂), 6.31 (s, 1H, 6-CH_{imidazopyridine}), 4.81 (s, 1H, 4-CH), 4.57 (dd, *J* = 6.6, 1.5 Hz, 1H, 2-CH), 4.06 (d, *J* = 11.4 Hz, 1H, OCHH), 3.70 (d, *J* = 6.4 Hz, 1H, 3-CH), 3.15 (d, *J* = 11.4 Hz, 1H, OCHH), 2.54 (s, 0.4H, CH₃, solvent: DMSO), 2.50 (s, 3H, SCH₃), 2.07 (s, 0.1H, CH₃CN, solvent: acetonitrile), 1.45 (ddd, *J* = 8.7, 3.9, 1.3 Hz, 1H, 5-CH), 1.34 (t, *J* = 4.3 Hz, 1H, 6-CHH), 0.61 (ddd, *J* = 8.6, 4.6, 1.5 Hz, 1H, 6-CHH). ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 154.2 (1C, C-5_{imidazopyridine}), 146.5 (1C, C-7_{imidazopyridine}), 145.9 (1C, C-3_{imidazopyridine}), 137.2 (1C, C-2_{imidazopyridine}), 119.4 (1C, C-7_{imidazopyridine}), 98.7 (1C, C-6_{imidazopyridine}), 76.0 (1C, C-3), 70.2 (1C, C-2), 62.2 (1C, OCH₂), 60.4 (1C, C-4), 40.5 (0.1C, CH₃, solvent: DMSO), 36.4 (1C, C-1), 23.2 (1C, C-5), 13.1 (1C, SCH₃), 11.2 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3341, 3217 (O-H), 2920 (C-H_{aliphatic}), 1674, 1628, 1597 (C=C_{aromatic}), 1119, 1069, 1011 (C-O).

5-Chloro-6-nitro-3H-imidazo[4,5-*b*]pyridine (**19**)

2-Chloro-1-deazapurine (0.10 g, 0.66 mmol) and di-*tert*-butyl dicarbonate (0.20 g, 0.91 mmol, 1.4 eq.) were suspended in CH₂Cl₂ (1 mL). A catalytic amount DMAP (~1 mg) was added and the mixture was stirred for 2.5 h. The reaction was quenched with silica gel and filtered through a pad of Celite®. was redissolved in CH₂Cl₂ (2 mL). Tetrabutylammonium nitrate (0.30 g, 0.98 mmol, 1.5 eq.) was added and the mixture cooled to 0 °C with an ice bath. Trifluoroacetic anhydride (0.14 mL, 0.99 mmol, 1.5 eq.) was added dropwise and the reaction stirred for 5 h at rt and under reflux overnight. The solvent was evaporated, and the residue was purified by fc (CH₂Cl₂ : CH₃OH = 97.5:2.5 → 96.5:3.5 → 95.5, Ø = 3 cm, l = 24 cm, V = 10 mL) to afford the product **19** as light brown solid (76 %). C₆H₃ClN₄O₂ (198.57 g/mol). ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 8.87 (s, 1H, 7-CH), 8.80 (s, 1H, 2-CH), 3.17 (s, 0.4H, CH₃OH, solvent: methanol). ¹³C-NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 149.6 (1C, C-2), 139.9 (1C, C-5), 135.6 (1C, C-6), 48.6 (0.1H, CH₃OH, solvent: methanol); C-3a, C-7 and C-7a were not visible.

Crystal Data for C₆H₃ClN₄O₂ (M = 198.57 g/mol): orthorhombic, Pbc_a (No. 61), a = 11.3385(3) Å, b = 6.5407(2) Å, c = 20.0740(7) Å, V = 1488.72(8) Å³, Z = 8, 1.772 mg/m³, T = 173(2) K, μ(CuKα) = 0.479 mm⁻¹, Final R indices [*I* > 2σ(*I*)] R¹ = 0.0316, wR² = 0.0798, R indices (all data) R¹ = 0.0355, wR² = 0.0827

7-Chloro-5-nitro-3-tosyl-3H-imidazo[4,5-*b*]pyridine (**20**)

Compound **7** (0.50 g, 2.5 mmol) was suspended in CH₂Cl₂ (20 mL). Tosyl chloride (0.97 g, 5.1 mmol, 2 eq.) and DIPEA (0.88 mL, 5.1 mmol, 2 eq.) were added and the mixture stirred for 3 h at rt. The reaction was neutralized with saturated NH₄Cl-solution and was extracted with CH₂Cl₂. The organic phase was dried over anh. Na₂SO₄ and concentrated in vacuo. The residue was purified by fc (cyclohexane : ethyl acetate = 5:1 → 2:1, Ø = 6 cm, l = 22 cm, V = 65 mL). The mixed fractions were purified again using fc (cyclohexane : ethyl acetate = 5:1, Ø = 6 cm, l = 22 cm, V = 65 mL) to afford the product **20** as a colorless solid (R_f = 0.23, cyclohexane : ethyl acetate = 3:1), yield 0.81 g (91 %). C₁₃H₉ClN₄O₄S (352.75 g/mol). Melting point: 200.2 °C. Purity (HPLC: method B): > 99 % (t_R = 15.72 min). Exact mass (APCI): m/z calculated for C₁₃H₁₀ClN₄O₄S [M+H]⁺ 353.0106, found 353.0105. ¹H-NMR (400 MHz, CD₃CN) δ (ppm) = 8.88 (s, 1H, 2-CH), 8.39 (s, 1H, 6-CH), 8.22-8.18 (m, 2H, 2, 6-CH_{tosyl}), 7.48-7.43 (m, 2H, 3, 5-CH_{tosyl}), 2.40 (s, 3H, CH₃). ¹³C-NMR (101 MHz, CD₃CN) δ (ppm) = 153.6 (1C, C-5), 148.9 (1C, C-4_{tosyl}), 147.9 (1C, C-2), 144.0 (1C, C-3a), 139.1 (1C, C-7a), 138.5 (1C, C-7), 133.9 (1C, C-1_{tosyl}), 131.3 (2C, C-3, 5_{tosyl}), 130.0 (2C, C-2, 6_{tosyl}), 116.7 (1C, C-6), 21.8 (1C, CH₃). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3117, 3102 (ν C-H_{aromat.}), 2978 (C-H_{aliph.}), 1598, 1555 (C=C_{aromat.}), 1373, 1327 (NO₂), 1176 (S=O), 837, 814 (C-H_{aromat.}, out of plane).

N,N-Dibenzyl-*N'*-[4-chloro-2-(4-methylphenyl)sulfonamido-6-nitropyridin-3-yl]formimidamide (**21**)

Compound **20** (0.074 g, 0.21 mmol) was dissolved in CH₂Cl₂ (2 mL). Dibenzylamine (0.40 mL, 2.08 mmol, 10 eq.) was added and the mixture stirred overnight at rt. The reaction was washed with saturated NH₄Cl-solution and was extracted with CH₂Cl₂. The organic phase was dried over anh. Na₂SO₄ and concentrated in vacuo. The residue was purified by fc (cyclohexane : ethylacetate : CH₃OH = 25:3:2 + 1 % triethylamine, Ø = 2 cm, l = 25 cm, V = 10 mL) to afford the product **21** as a red solid. Red solid (R_f = 0.36, ethyl acetate = 100 %), yield 0.090 g (78 %). C₂₇H₂₄ClN₅O₄S (550.03 g/mol). Melting point: 171.2 °C. Purity (HPLC: method B): > 99 % (t_R = 21.02 min). Exact mass (LC-MS-ESI): m/z calculated for C₂₇H₂₅ClN₅O₄S [M+H]⁺ 550.1310, found 550.1285. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 10.30 (s, 1H, NH), 8.44 (s, 1H, N=CH), 8.09 (d, 2H, J = 8.1 Hz, 2, 6-CH_{tosyl}), 7.92 (s, 1H, 5-CH_{pyridine}), 7.43-7.26 (m, 12H, 3, 5-CH_{tosyl}, 2, 3, 4, 5, 6-CH_{benzyl}), 4.68 (s, 2H, CH₂ benzyl), 4.46 (s, 2H, CH₂ benzyl), 2.34 (s, 3H, CH₃); The ¹H-NMR spectrum displays small impurities in the range of about 5 %. ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 157.6 (1C, C-1), 147.1 (1C, C-6_{pyridine}), 142.9 (1C, C-4_{tosyl}), 139.8 (1C, C-4_{pyridine}), 136.5 (3C, C-1_{tosyl}, C-1_{benzyl}), 132.8 (1C, C-3_{pyridine}), 128.6 (2C, C-3, 5_{tosyl}), 128.5 (4C, C-3, 5_{benzyl}), 128.4 (2C, C-2, 6_{tosyl}), 128.2 (2C, C-2, 6_{benzyl}), 128.0 (2C, C-2, 6_{benzyl}), 127.8 (1C, C-4_{benzyl}), 127.2 (1C, C-4_{benzyl}), 112.8 (1C, C-5_{pyridine}), 53.6 (1C, CH₂ benzyl), 47.1 (1C, CH₂ benzyl), 21.0 (1C, CH₃); The signal for C-4_{pyridine} could not be seen in ¹³C-NMR spectrum. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3251 (N-H), 2978, 2924 (C-H_{aliph.}), 1616 (C=C_{aromat.}), 1327 (NO₂), 1161 (S=O), 829, 814, 748, 737 (C-H_{aromat.}, out of plane).

Crystal Data for C₂₇H₂₄ClN₅O₄S (M = 550.02 g/mol): monoclinic, P21/n (No. 14), a = 13.4033(2) Å, b = 9.4786(2) Å, β = 98.623(1)°, c = 20.9689(4) Å, V = 2633.87(8) Å³, Z = 4, 1.387 mg/m³, T = 173(2), μ(CuKα) = 0.268 mm⁻¹, Final R indices [I > 2σ(I)] R¹ = 0.0424, wR² = 0.0934, R indices (all data) R¹ = 0.0502, wR² = 0.0992

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-[6-(Dibenzylamino)-9H-purin-9-yl]-1-[(*tert*-butyldiphenylsilyl)oxy]methyl)-2,3-O-isopropylidenebicyclo[3.1.0]hexane-2,3-diol (**24**)

6-Chloropurine (**22**, 1.00 g, 6.47 mmol) was suspended in isopropanol (60 mL). Dibenzylamine (5.0 mL, 26.0 mmol, 4 eq.) was added. The mixture was stirred at 90 °C under reflux for 7 h. The solvent was evaporated and the residue was purified by fc (CH₂Cl₂ : CH₃OH = 59:1 → 29:1 + 0,5 % HCOOH, Ø = 6 cm, l = 20 cm, V = 65 mL) to afford the *N,N*-dibenzyladenine as a colorless solid (R_f = 0.36, ethyl acetate = 100 %), yield 1.91 g (94 %). C₁₉H₁₇N₅ (315.38 g/mol). Melting point: 186.4 °C. Purity (HPLC: method B): > 99 % (t_R = 15.31 min). Exact mass (APCI): m/z calculated for C₁₉H₁₈N₅ [M+H]⁺ 316.1557, found 316.1568. ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 13.14 (s, 1H, 9-NH), 8.28 (s, 1H, 2-CH), 8.14 (s, 1H, 8-CH), 7.46-7.34 (m, 10H, 2, 3, 4, 5, 6-CH_{benzyl}), 5.50 (s, 2H, CH₂ benzyl), 4.94 (s, 2H, CH₂ benzyl). ¹³C-NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 154.1 (1C, C-6), 151.9 (1C, C-2), 151.6

(1C, C-4), 138.5 (1C, C-8), 138.0 (1C, C-1_{benzyl}), 128.5 (4C, C-3, 5_{benzyl}), 127.4 (4C, C-2, 6_{benzyl}), 127.0 (2C, C-4_{benzyl}), 118.5 (1C, C-5), 50.6 (1C, CH₂ _{benzyl}), 48.5 (1C, CH₂ _{benzyl}). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3059 (v C-H_{aromat.}), 2978, (C-H_{aliph.}), 1574 (C=C_{aromat.}), 752, 737, 698 (C-H_{aromat.}, out of plane).

The *N,N*-dibenzyladenine (0.47 g, 1.48 mmol, 1.3 eq.) and triphenylphosphane (0.47 g, 1.78 mmol, 1.6 eq.) were dissolved in THF (10 mL) under nitrogen atmosphere. Diisopropyl azodicarboxylate (DIAD, 0.34 mL, 1.73 mmol, 1.5 eq.) was added dropwise at 0 °C. The mixture was stirred for 30 min at rt. A solution of the alcohol **4** (0.50 g, 1.15 mmol) in THF (10 mL) was added and the solution was stirred overnight. The solvent was evaporated and the residue was purified by fc (cyclohexane : ethyl acetate = 19:1 → 9:1, Ø = 6 cm, l = 20 cm, V = 65 mL) to afford the product **24** as a colorless solid (*R*_f = 0.29, cyclohexane : ethyl acetate = 9:1), yield 0.73 g (86 %). C₄₅H₄₉N₅O₃Si (736.00 g/mol). Melting point: 77.6 °C. Purity (HPLC: method C): > 99 % (*t*_R = 18.82 min). Exact mass (APCI): *m/z* calculated for C₄₅H₅₀N₅O₃Si [M+H]⁺ 736.3677, found 736.3707. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.30 (s, 1H, 8-CH_{purine}), 8.25 (s, 1H, 2-CH_{purine}), 7.60-7.55 (m, 4H, 2, 6-CH_{Ph}), 7.42-7.37 (m, 2H, 4-CH_{Ph}), 7.36-7.32 (m, 4H, 3, 5-CH_{Ph}), 7.31-7.24 (m, 10H, 2, 3, 4, 5, 6-CH_{benzyl}), 5.60 (s, 1H, CHH_{benzyl}), 5.47 (s, 1H, CHH_{benzyl}), 5.28 (dd, *J* = 7.0, 1.3 Hz, 1H, 2-CH), 4.98 (s, 1H, 4-CH), 4.96 (s, 1H, CHH_{benzyl}), 4.88 (s, 1H, CHH_{benzyl}), 4.76 (dd, *J* = 7.1, 1.4 Hz, 1H, 3-CH), 4.04 (d, *J* = 10.7 Hz, 1H, OCHH), 3.72 (d, *J* = 10.8 Hz, 1H, OCHH), 1.67 (ddd, *J* = 9.3, 4.5, 1.6 Hz, 1H, 5-CH), 1.46 (s, 3H, C(CH₃)₂), 1.39 (s, 1.6H, CH₂, solvent: cyclohexane), 1.20 (s, 3H, C(CH₃)₂), 1.01 (t, *J* = 4.8 Hz, 1H, 6-CHH), 0.98 (s, 9H, C(CH₃)₃), 0.90 (ddd, *J* = 9.1, 5.1, 1.5 Hz, 1H, 6-CHH). ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 154.1 (1C, C-6_{purine}), 152.0 (1C, C-2_{purine}), 150.0 (1C, C-4_{purine}), 138.5 (1C, C-8_{purine}), 137.9 (2C, C-1_{benzyl}), 135.1 (4C, C-2, 6_{Ph}), 132.8 (2C, C-1_{Ph}), 129.8 (2C, C-4_{Ph}), 128.5 (4C, C-3, 5_{benzyl}), 127.8 (4C, C-3, 5_{Ph}), 127.4 (4C, C-2, 6_{benzyl}), 127.1 (2C, C-4_{benzyl}), 119.0 (1C, C-5_{purine}), 111.3 (1C, C(CH₃)₂), 87.9 (1C, C-2), 81.1 (1C, C-3), 64.7 (1C, OCH₂), 58.4 (1C, C-4), 50.8 (1C, CH₂ _{benzyl}), 48.6 (1C, CH₂ _{benzyl}), 38.1 (1C, C-1), 29.9 (1C, C-5), 26.7 (3C, C(CH₃)₃), 26.3 (s, 0.8C, CH₂, solvent: cyclohexane), 25.9 (1C, C(CH₃)₂), 24.3 (1C, C(CH₃)₂), 18.8 (1C, C(CH₃)₃), 12.2 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 2978 (C-H_{aliph.}), 1574 (C=C_{aromat.}), 1107, 1064, 1037 (C-O), 737, 698 (C-H_{aromat.}, out of plane).

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-[6-(Dibenzylamino)-9*H*-purin-9-yl]-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**26**)

Compound **24** (0.125 g, 0.17 mmol) was dissolved in CH₃OH (3.6 mL), trifluoroacetic acid (0.40 mL) and H₂O (0.40 mL) were added. The mixture was heated to 70 °C for 2 d. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the alcohol **106** as a colorless solid (*R*_f = 0.24, ethyl acetate = 100 %), yield 0.051 g (65 %). C₂₆H₂₇N₅O₃ (457.53 g/mol). Purity (HPLC: method B): > 99 % (*t*_R = 11.99 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₂₆H₂₈N₅O₃ [M+H]⁺ 458.2187, found 458.2187. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.49 (s, 1H, 8-CH_{purine}), 8.31 (s, 1H, 2-CH_{purine}), 7.34-7.29 (m, 4H, 3, 5-CH_{benzyl}), 7.29-7.23 (m, 6H, 2, 4, 6-CH_{benzyl}), 5.63 (s, 1H, CHH_{benzyl}), 5.42 (s, 1H, CHH_{benzyl}), 5.25 (s, 1H, 3-OH), 5.03 (t, *J* = 5.0 Hz, 1H, CH₂OH), 4.97 (s, 1H, CHH_{benzyl}), 4.82 (s, 2H, CHH_{benzyl}, 4-CH), 4.58 (t, *J* = 5.2 Hz, 1H, 2-CH), 4.49 (t, *J* = 6.8 Hz, 1H, 2-OH), 4.07 (dd, *J* = 11.4, 4.9 Hz, 1H, OCHH), 3.72 (d, *J* = 6.4 Hz, 1H, 3-CH), 3.13 (dd, *J* = 11.4, 4.1 Hz, 1H, OCHH), 1.49 (ddd, *J* = 8.7, 3.9, 1.4 Hz, 1H, 5-CH), 1.37 (dd, *J* = 4.7, 3.9 Hz, 1H, 6-CHH), 0.61 (ddd, *J* = 8.5, 4.7, 1.6 Hz, 1H, 6-CHH). ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 154.1 (1C, C-6_{purine}), 151.9 (1C, C-2_{purine}), 150.1 (1C, C-4_{purine}), 138.3 (1C, C-8_{purine}), 137.9 (2C, C-1_{benzyl}), 128.5 (4C, C-3, 5_{benzyl}), 127.4 (4C, C-2, 6_{benzyl}), 127.1 (2C, C-4_{benzyl}), 118.9 (1C, C-5_{purine}), 75.9 (1C, C-3), 70.2 (1C, C-2), 62.3 (1C, OCH₂), 60.8 (1C, C-4), 50.7 (1C, CH₂ _{benzyl}), 48.6 (1C, CH₂ _{benzyl}), 36.4 (1C, C-1), 23.1 (1C, C-5), 11.2 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3310 (O-H), 3028 (v C-H_{aromat.}), 2978, 2920 (C-H_{aliph.}), 1578 (C=C_{aromat.}), 1068 (C-O), 698 (C-H_{aromat.}, out of plane).

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-[6-(Dibenzylamino)-2-chloro-9*H*-purin-9-yl]-1-[(*tert*-butyldiphenylsilyloxy)methyl]-2,3-*O*-isopropylidenebicyclo[3.1.0]hexane-2,3-diol (**25**)

2,6-Dichloropurine (2.02 g, 10.47 mmol) was dissolved in isopropanol (100 mL). Dibenzylamine (8.0 mL, 41.6 mmol, 3.9 eq.) was added. The mixture was stirred at 90 °C

under reflux for 1.5 h. The precipitated product was filtered off and purified by fc ($\text{CH}_2\text{Cl}_2 : \text{CH}_3\text{OH} = 59:1 \rightarrow 29:1 + 0,5 \% \text{HCOOH}$, $\varnothing = 8 \text{ cm}$, $l = 20 \text{ cm}$, $V = 100 \text{ mL}$) to afford the purine derivative as a colorless solid ($R_f = 0.37$, cyclohexane : ethyl acetate = 1:1), yield 3.27 g (88 %). $\text{C}_{19}\text{H}_{16}\text{ClN}_5$ (349.82 g/mol). Melting point: 260.0 °C. Purity (HPLC: method B): > 99 % ($t_R = 16.17 \text{ min}$). Exact mass (APCI): m/z calculated for $\text{C}_{19}\text{H}_{17}\text{ClN}_5 [\text{M}+\text{H}]^+$ 350.1167, found 350.1167. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ (ppm) = 13.29 (s, 1H, 9-NH), 8.16 (s, 1H, 8-CH), 7.36-7.30 (m, 4H, 3, 5- $\text{CH}_{\text{benzyl}}$), 7.30-7.24 (m, 6H, 2, 4, 6- $\text{CH}_{\text{benzyl}}$), 5.53 (s, 2H, $\text{CH}_2_{\text{benzyl}}$), 4.81 (s, 2H, $\text{CH}_2_{\text{benzyl}}$). $^{13}\text{C-NMR}$ (101 MHz, $\text{DMSO-}d_6$) δ (ppm) = 154.5 (1C, C-6), 152.8 (1C, C-4), 152.4 (1C, C-2), 139.2 (1C, C-8), 137.3 (1C, C-1 $_{\text{benzyl}}$), 128.5 (4C, C-3, 5 $_{\text{benzyl}}$), 127.5 (4C, C-2, 6 $_{\text{benzyl}}$), 127.2 (2C, C-4 $_{\text{benzyl}}$), 117.6 (1C, C-5), 50.8 (1C, $\text{CH}_2_{\text{benzyl}}$), 48.9 (1C, $\text{CH}_2_{\text{benzyl}}$). FT-IR (neat) $\tilde{\nu}$ (cm^{-1}) = 3066 (v C-H $_{\text{aromat}}$), 2978, (C-H $_{\text{aliph}}$), 1578 (C=C $_{\text{aromat}}$), 1076 (C-Cl), 741, 694 (C-H $_{\text{aromat}}$, out of plane).

Next, the purine derivative (1.04 g, 2.98 mmol, 1.3 eq.) and triphenylphosphane (0.90 g, 3.44 mmol, 1.5 eq.) were dissolved in THF (20 mL) under nitrogen atmosphere. DIAD (0.67 mL, 3.41 mmol, 1.5 eq.) was added dropwise at 0 °C. The mixture was stirred for 15 min at rt. A solution of the alcohol **4** (1.03 g, 2.35 mmol) in THF (20 mL) was added and the solution was stirred overnight. The solvent was evaporated and the residue was purified by fc (cyclohexane : ethyl acetate = 19:1 \rightarrow 9:1, $\varnothing = 6 \text{ cm}$, $l = 20 \text{ cm}$, $V = 65 \text{ mL}$) to afford the product **26** as a colorless solid ($R_f = 0.35$, cyclohexane : ethyl acetate = 1:1), yield 1.67 g (92 %). $\text{C}_{45}\text{H}_{48}\text{ClN}_5\text{O}_3\text{Si}$ (770.45 g/mol). Melting point: 84.7 °C. Purity (HPLC: method C): > 99 % ($t_R = 19.49 \text{ min}$). Exact mass (LC-MS-ESI): m/z calculated for $\text{C}_{45}\text{H}_{49}\text{ClN}_5\text{O}_3\text{Si} [\text{M}+\text{H}]^+$ 770.3288, found 770.3285. $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$) δ (ppm) = 8.29 (s, 1H, 8- $\text{CH}_{\text{purine}}$), 7.60-7.56 (m, 4H, 2, 6- CH_{Ph}), 7.42-7.25 (m, 16H, 2, 3, 4, 5, 6- $\text{CH}_{\text{benzyl}}$, 3, 4, 5- CH_{Ph}), 5.57 (d, $J = 15.7 \text{ Hz}$, 1H, $\text{CHH}_{\text{benzyl}}$), 5.47 (d, $J = 15.7 \text{ Hz}$, 1H, $\text{CHH}_{\text{benzyl}}$), 5.21 (dd, $J = 7.1, 1.3 \text{ Hz}$, 1H, 2-CH), 4.91 (s, 1H, 4-CH), 4.86 (d, $J = 15.4 \text{ Hz}$, 1H, $\text{CHH}_{\text{benzyl}}$), 4.79 (d, $J = 15.4 \text{ Hz}$, 1H, $\text{CHH}_{\text{benzyl}}$), 4.75 (dd, $J = 7.2, 1.5 \text{ Hz}$, 1H, 3-CH), 4.03 (d, $J = 10.7 \text{ Hz}$, 1H, OCHH), 3.87 (d, $J = 10.7 \text{ Hz}$, 1H, OCHH), 1.64 (ddd, $J = 9.2, 4.5, 1.6 \text{ Hz}$, 1H, 5-CH), 1.46 (s, 3H, $\text{C}(\text{CH}_3)_2$), 1.43 (s, 0.7H, CH_2 , solvent: cyclohexane), 1.19 (s, 3H, $\text{C}(\text{CH}_3)_2$), 0.98 (s, 10H, 6-CHH, $\text{C}(\text{CH}_3)_3$), 0.93 (ddd, $J = 9.1, 5.1, 1.4 \text{ Hz}$, 1H, 6-CHH). $^{13}\text{C-NMR}$ (151 MHz, $\text{DMSO-}d_6$) δ (ppm) = 154.5 (1C, C-6 $_{\text{purine}}$), 152.5 (1C, C-2 $_{\text{purine}}$), 151.1 (1C, C-4 $_{\text{purine}}$), 139.3 (1C, C-8 $_{\text{purine}}$), 137.4 (1C, C-1 $_{\text{benzyl}}$), 136.9 (1C, C-1 $_{\text{benzyl}}$), 135.0 (4C, C-2, 6 $_{\text{Ph}}$), 132.9 (2C, C-1 $_{\text{Ph}}$), 129.8 (2C, C-4 $_{\text{Ph}}$), 128.6 (4C, C-2, 6 $_{\text{benzyl}}$), 127.8 (4C, C-3, 5 $_{\text{Ph}}$), 127.7 (2C, C-2, 6 $_{\text{benzyl}}$), 127.5 (1C, C-2, 6 $_{\text{benzyl}}$), 127.3 (2C, C-4 $_{\text{benzyl}}$), 118.3 (1C, C-5 $_{\text{purine}}$), 111.3 (1C, $\text{C}(\text{CH}_3)_2$), 87.9 (1C, C-3), 81.6 (1C, C-2), 64.5 (1C, OCH $_2$), 58.9 (1C, C-4), 50.9 (1C, $\text{CH}_2_{\text{benzyl}}$), 49.2 (1C, $\text{CH}_2_{\text{benzyl}}$), 38.3 (1C, C-1), 29.6 (1C, C-5), 26.7 (3C, $\text{C}(\text{CH}_3)_3$), 26.3 (0.4C, CH_2 , solvent: cyclohexane), 25.9 (1C, $\text{C}(\text{CH}_3)_2$), 24.3 (1C, $\text{C}(\text{CH}_3)_2$), 18.8 (1C, $\text{C}(\text{CH}_3)_3$), 12.0 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm^{-1}) = 2978 (C-H $_{\text{aliph}}$), 1574 (C=C $_{\text{aromat}}$), 1111, 1069, 1042 (C-O), 740, 698 (C-H $_{\text{aromat}}$, out of plane).

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-[6-(Dibenzylamino)-2-chloro-9*H*-purin-9-yl]-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**27**)

Compound **25** (0.099 g, 0.13 mmol) was dissolved in CH_3OH (3.6 mL), trifluoroacetic acid (0.40 mL) and H_2O (0.40 mL) were added. The mixture was heated to 70 °C for 2 d. The solvent was evaporated and the residue was purified by fc ($\text{CH}_2\text{Cl}_2 : \text{CH}_3\text{OH} = 96:4$, $\varnothing = 2 \text{ cm}$, $l = 24 \text{ cm}$, $V = 10 \text{ mL}$) but still showed a small impurity by $^1\text{H-NMR}$. The impure product was purified again by fc ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 5:95 \rightarrow 100:0$, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, $V = 20 \text{ mL}$) to afford the pure alcohol **27** as a colorless solid ($R_f = 0.32$, ethyl acetate = 100 %), yield 0.052 g (82 %). $\text{C}_{26}\text{H}_{26}\text{ClN}_5\text{O}_3$ (491.98 g/mol). Purity (HPLC: method B): > 99 % ($t_R = 14.14 \text{ min}$). Exact mass (APCI): m/z calculated for $\text{C}_{26}\text{H}_{27}\text{ClN}_5\text{O}_3 [\text{M}+\text{H}]^+$ 492.1797, found 492.1784. $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$) δ (ppm) = 8.51 (s, 1H, 8- $\text{CH}_{\text{purine}}$), 7.36-7.31 (m, 4H, 3, 5- $\text{CH}_{\text{benzyl}}$), 7.30-7.25 (m, 6H, 2, 4, 6- $\text{CH}_{\text{benzyl}}$), 5.61 (d, $J = 15.7 \text{ Hz}$, 1H, $\text{CHH}_{\text{benzyl}}$), 5.41 (d, $J = 15.8 \text{ Hz}$, 1H, $\text{CHH}_{\text{benzyl}}$), 5.27 (s, 1H, 3-OH), 4.99 (t, $J = 5.0 \text{ Hz}$, 1H, CH_2OH), 4.88 (d, $J = 15.4 \text{ Hz}$, 1H, $\text{CHH}_{\text{benzyl}}$), 4.75 (s, 1H, $\text{CHH}_{\text{benzyl}}$), 4.72 (s, 1H, 4-CH), 4.56 (d, $J = 6.5 \text{ Hz}$, 1H, 2-CH), 4.50 (s, 1H, 2-OH), 4.07 (d, $J = 11.0 \text{ Hz}$, 1H, OCHH), 3.73 (d, $J = 6.2 \text{ Hz}$, 1H, 3-CH), 3.13 (d, $J = 11.3 \text{ Hz}$, 1H, OCHH), 1.47 (ddd, $J = 8.8, 3.8, 1.5 \text{ Hz}$, 1H, 5-CH), 1.36 (t, $J = 4.3 \text{ Hz}$, 1H, 6-CHH), 0.61 (ddd, $J = 8.6, 4.7, 1.5 \text{ Hz}$, 1H,

6-CHH). ^{13}C -NMR (151 MHz, DMSO- d_6) δ (ppm) = 154.5 (1C, C-6 $_{\text{purine}}$), 152.5 (1C, C-2 $_{\text{purine}}$), 151.4 (1C, C-4 $_{\text{purine}}$), 138.9 (1C, C-8 $_{\text{purine}}$), 137.4 (1C, C-1 $_{\text{benzyl}}$), 136.9 (1C, C-1 $_{\text{benzyl}}$), 128.6 (4C, C-3, 5 $_{\text{benzyl}}$), 127.7 (2C, C-2, 6 $_{\text{benzyl}}$), 127.4 (2C, C-2, 6 $_{\text{benzyl}}$), 127.3 (2C, C-4 $_{\text{benzyl}}$), 118.0 (1C, C-5 $_{\text{purine}}$), 75.8 (1C, C-3), 70.2 (1C, C-2), 62.2 (1C, OCH $_2$), 61.0 (1C, C-4), 50.8 (1C, CH $_2$ $_{\text{benzyl}}$), 49.1 (1C, CH $_2$ $_{\text{benzyl}}$), 36.4 (1C, C-1), 23.1 (1C, C-5), 11.1 (1C, C-6).

FT-IR (neat) $\tilde{\nu}$ (cm $^{-1}$) = 3341 (O-H), 2978 (C-H $_{\text{aliphatic}}$), 1574 (C=C $_{\text{aromatic}}$), 1069 (C-O), 698 (C-H $_{\text{aromatic}}$, out of plane).

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-[6-(Dibenzylamino)-2-methylthio-9*H*-purin-9-yl]-1-(hydroxymethyl)-2,3-*O*-isopropylidenebicyclo[3.1.0]hexane-2,3-diol (**28**)

Compound **25** (0.30 g, 0.39 mmol) was dissolved in DMF (15 mL). NaSCH $_3$ (0.41 g, 5.86 mmol, 15 eq.) was added. The mixture was stirred at 90 °C for 1 h in the microwave at a power of 200 W. The solvent was evaporated and the residue was purified by fc (cyclohexane : ethyl acetate = 6:4, \varnothing = 5 cm, l = 24 cm, V = 30 mL) to afford the product **28** as a colorless solid (R_f = 0.35, cyclohexane : ethyl acetate = 1:1), yield 0.227 g (89 %). C $_{30}$ H $_{33}$ N $_5$ O $_3$ S (543.69 g/mol). Melting point: 97.8 °C. Purity (HPLC: method B): 93 % (t_R = 18.60 min). Exact mass (LC-MS-ESI): m/z calculated for C $_{30}$ H $_{34}$ N $_5$ O $_3$ S [M+H] $^+$ 544.2377, found 544.2378. ^1H -NMR (400 MHz, DMSO- d_6) δ (ppm) = 8.24 (s, 1H, 8-CH $_{\text{purine}}$), 7.36-7.22 (m, 10H, 2, 3, 4, 5, 6-CH $_{\text{benzyl}}$), 5.11 (dd, J = 15.6, 15.1 Hz, 2H, CH $_2$ $_{\text{benzyl}}$), 5.20 (d, J = 7.1, 1.3 Hz, 1H, 2-CH), 4.94 (s, 1H, OH), 4.92 (s, 1H, 4-CH), 4.91-4.74 (m, 2H, CH $_2$ $_{\text{benzyl}}$), 4.61 (dd, J = 7.2, 1.5 Hz, 1H, 3-CH), 3.84 (dd, J = 11.6, 4.0 Hz, 1H, OCHH), 3.35 (d, J = 11.6, 3.9 Hz, 1H, OCHH), 2.41 (s, 3H, SCH $_3$), 1.65 (ddd, J = 9.2, 4.4, 1.5 Hz, 1H, 5-CH), 1.45 (s, 3H, C(CH $_3$) $_2$), 1.15 (s, 3H, C(CH $_3$) $_2$), 0.98 (t, J = 4.9 Hz, 1H, 6-CHH), 0.88 (ddd, J = 9.1, 5.1, 1.5 Hz, 1H, 6-CHH); The ^1H -NMR spectrum displays small impurities in the range of about 5 %. ^{13}C -NMR (101 MHz, DMSO- d_6) δ (ppm) = 163.6 (1C, C-2 $_{\text{purine}}$), 153.3 (1C, C-6 $_{\text{purine}}$), 150.9 (1C, C-4 $_{\text{purine}}$), 137.8 (1C, C-1 $_{\text{benzyl}}$), 137.6 (1C, C-8 $_{\text{purine}}$), 128.5 (4C, C-3, 5 $_{\text{benzyl}}$), 127.4 (4C, C-2, 6 $_{\text{benzyl}}$), 127.1 (2C, C-4 $_{\text{benzyl}}$), 116.6 (1C, C-5 $_{\text{purine}}$), 111.2 (1C, C(CH $_3$) $_2$), 88.3 (1C, C-3), 80.9 (1C, C-2), 62.6 (1C, OCH $_2$), 58.1 (1C, C-4), 50.9 (1C, CH $_2$ $_{\text{benzyl}}$), 48.9 (1C, CH $_2$ $_{\text{benzyl}}$), 38.7 (1C, C-1), 29.6 (1C, C-5), 25.8 (1C, C(CH $_3$) $_2$), 24.2 (1C, C(CH $_3$) $_2$), 13.8 (1C, SCH $_3$), 12.6 (1C, C-6); The ^{13}C -NMR spectrum displays small impurities in the range of about 5 %. FT-IR (neat) $\tilde{\nu}$ (cm $^{-1}$) = 3372 (O-H), 2982, 2924 (C-H $_{\text{aliphatic}}$), 1562 (C=C $_{\text{aromatic}}$), 1057, 1030 (C-O), 748, 733, 698 (C-H $_{\text{aromatic}}$, out of plane).

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-[6-(Dibenzylamino)-2-methylthio-9*H*-purin-9-yl]-1-(chloromethyl)-2,3-*O*-isopropylidenebicyclo[3.1.0]hexane-2,3-diol (**29**)

Cyanuric chloride (0.051 g, 0.28 mmol, 1.5 eq.) was stirred with DMF (0.08 mL, 1.04 mmol, 5.8 eq.) for 2 h at rt. Then CH $_2$ Cl $_2$ (1 mL) and the alcohol **28** (0.098 g, 0.18 mmol) were added and the mixture was stirred overnight. Water was added and the phases were separated. The organic phase was washed with K $_2$ CO $_3$ -solution, 0.05 M HCl and water. The organic phase was dried over anhydrous Na $_2$ SO $_4$; filtered and concentrated in vacuo. The residue was purified by fc (cyclohexane : ethyl acetate = 7:1, \varnothing = 2 cm, l = 20 cm, V = 10 mL) to afford the chloride **29** as a colorless solid (R_f = 0.35, cyclohexane : ethyl acetate = 5:1), yield 0.066 g (65 %). C $_{30}$ H $_{32}$ ClN $_5$ O $_2$ S (562.13 g/mol). Melting point: 182.4 °C. Purity (HPLC: method B): > 99 % (t_R = 21.54 min). Exact mass (LC-MS-ESI): m/z calculated for C $_{30}$ H $_{33}$ ClN $_5$ O $_2$ S [M+H] $^+$ 562.2038, found 562.2036. ^1H -NMR (600 MHz, CDCl $_3$) δ (ppm) = 7.86 (s, 1H, 8-CH $_{\text{purine}}$), 7.34-7.29 (m, 4H, 3, 5-CH $_{\text{benzyl}}$), 7.29-7.24 (m, 6H, 2, 4, 6-CH $_{\text{benzyl}}$), 5.50 (s, 2H, CH $_2$ $_{\text{benzyl}}$), 5.38 (dd, J = 7.2, 1.5 Hz, 1H, 2-CH), 5.01 (s, 1H, 4-CH), 4.95 (s, 2H, CH $_2$ $_{\text{benzyl}}$), 4.69 (dd, J = 7.2, 1.4 Hz, 1H, 3-CH), 3.94 (d, J = 11.6 Hz, 1H, ClCHH), 3.81 (d, J = 11.6 Hz, 1H, ClCHH), 2.50 (s, 3H, SCH $_3$), 1.75 (ddd, J = 9.4, 4.7, 1.5 Hz, 1H, 5-CH), 1.56 (s, 3H, C(CH $_3$) $_2$), 1.43 (s, 0.1H, CH $_2$, solvent: cyclohexane), 1.35 (dd, J = 5.9, 4.8 Hz, 1H, 6-CHH), 1.27 (s, 3H, C(CH $_3$) $_2$), 1.08 (ddd, J = 9.4, 5.9, 1.6 Hz, 1H, 6-CHH). ^{13}C -NMR (151 MHz, CDCl $_3$) δ (ppm) = 165.0 (1C, C-2 $_{\text{purine}}$), 154.2 (1C, C-6 $_{\text{purine}}$), 151.6 (1C, C-4 $_{\text{purine}}$), 137.9 (1C, C-1 $_{\text{benzyl}}$), 136.5 (1C, C-8 $_{\text{purine}}$), 128.7 (4C, C-3, 5 $_{\text{benzyl}}$), 128.0 (4C, C-2, 6 $_{\text{benzyl}}$), 127.5 (2C, C-4 $_{\text{benzyl}}$), 117.5 (1C, C-5 $_{\text{purine}}$), 112.6 (1C, C(CH $_3$) $_2$), 89.4 (1C, C-3), 82.4 (1C, C-2), 59.6 (1C, C-4), 51.2 (1C, CH $_2$ $_{\text{benzyl}}$), 49.2 (1C, ClCH $_2$), 49.0 (1C, CH $_2$ $_{\text{benzyl}}$), 39.0 (1C, C-1), 33.0 (1C, C-5),

26.2 (1C, C(CH₃)₂), 24.4 (1C, C(CH₃)₂), 16.4 (1C, C-6), 14.8 (1C, SCH₃). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 2978, 2928 (C-H_{aliphatic}), 1589, 1566 (C=C_{aromatic}), 1072, 1049 (C-O), 798 (C-Cl), 733, 694 (C-H_{aromatic}, out of plane).

(1R,2R,3S,4R,5S)-4-[6-(Dibenzylamino)-2-methylthio-9H-purin-9-yl]-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (**30**)

Compound **28** (0.080 g, 0.15 mmol) was dissolved in CH₃OH (2.5 mL), trifluoroacetic acid (0.32 mL) and H₂O (0.32 mL) were added. The mixture was heated to 70 °C for 2 h. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the alcohol **111** as a colorless solid (R_f = 0.32, ethyl acetate = 100 %), yield 0.036 g (48 %). C₂₇H₂₉N₅O₃S (503.62 g/mol). Purity (HPLC: method B): 98 % (tr = 14.50 min). Exact mass (APCI): m/z calculated for C₂₇H₃₀N₅O₃S [M+H]⁺ 492.2064, found 492.2066. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.35 (s, 1H, 8-CH_{purine}), 7.95 (s, 0.1H, CH, solvent: DMF), 7.31 (t, J = 7.5 Hz, 4H, 3, 5-CH_{benzyl}), 7.29-7.23 (m, 6H, 2, 4, 6-CH_{benzyl}), 5.61 (d, J = 15.8 Hz, 1H, CHH_{benzyl}), 5.41 (d, J = 15.8 Hz, 1H, CHH_{benzyl}), 5.19 (s, 1H, 3-OH), 4.97 (t, J = 5.1 Hz, 1H, CH₂OH), 4.92 (d, J = 14.7 Hz, 1H, CHH_{benzyl}), 4.78 (d, J = 14.7 Hz, 1H, CHH_{benzyl}), 4.75 (s, 1H, 4-CH), 4.57 (ddd, J = 8.1, 6.5, 1.6 Hz, 1H, 2-CH), 4.49 (d, 7.9 Hz, 1H, 2-OH), 4.05 (dd, J = 11.3, 5.3 Hz, 1H, OCHH), 3.72 (ddt, J = 6.4, 4.7, 1.3 Hz, 1H, 3-CH), 3.13 (dd, J = 11.4, 4.8 Hz, 1H, OCHH), 2.89 (s, 0.4H, CH₃, solvent: DMF), 2.73 (s, 0.3H, CH₃, solvent: DMF), 2.41 (s, 3H, SCH₃), 2.07 (s, 0.1H, CH₃CN, solvent: acetonitrile), 1.45 (ddd, J = 8.8, 3.9, 1.4 Hz, 1H, 5-CH), 1.34 (t, J = 4.3 Hz, 1H, 6-CHH), 0.60 (ddd, J = 8.6, 4.7, 1.7 Hz, 1H, 6-CHH); The ¹H-NMR spectrum displays small impurities in the range of about 5 %. ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 163.4 (1C, C-2_{purine}), 162.3 (0.1C, CH, solvent: DMF), 153.3 (1C, C-6_{purine}), 151.1 (1C, C-4_{purine}), 137.8 (2C, C-1_{benzyl}), 137.4 (1C, C-8_{purine}), 128.5 (4C, C-3, 5_{benzyl}), 127.4 (4C, C-2, 6_{benzyl}), 127.1 (2C, C-4_{benzyl}), 116.5 (1C, C-5_{purine}), 76.0 (1C, C-3), 70.2 (1C, C-2), 62.2 (1C, OCH₂), 60.6 (1C, C-4), 50.8 (1C, CH₂_{benzyl}), 48.9 (1C, CH₂_{benzyl}), 36.4 (1C, C-1), 35.8 (0.1C, CH₃, solvent: DMF), 30.8 (0.1C, CH₃, solvent: DMF), 23.2 (1C, C-5), 13.8 (1C, SCH₃), 11.1 (1C, C-6). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3368 (O-H), 2978, 2924 (C-H_{aliphatic}), 1562 (C=C_{aromatic}), 1069 (C-O), 733, 698 (C-H_{aromatic}, out of plane).

(1S,2R,3S,4R,5S)-4-[6-(Dibenzylamino)-2-methylthio-9H-purin-9-yl]-1-(chloromethyl)bicyclo[3.1.0]hexane-2,3-diol (**31**)

Compound **29** (0.055 g, 0.10 mmol) was dissolved in a mixture of CH₃OH (1.6 mL) and CH₂Cl₂ (1.5 mL). Trifluoroacetic acid (0.20 mL) and H₂O (0.20 mL) were added. The mixture was heated to 70 °C for 6 h. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the product **31** as a colorless solid (R_f = 0.31, cyclohexane : ethyl acetate = 1:1), yield 0.042 g (82 %). C₂₇H₂₈ClN₅O₂S (522.06 g/mol). Purity (HPLC: method B): 97 % (tr = 17.55 min). Exact mass (LC-MS-ESI): m/z calculated for C₂₇H₂₉ClN₅O₂S [M+H]⁺ 522.1725, found 522.1713. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.09 (s, 1H, 8-CH_{purine}), 7.32 (t, J = 7.5 Hz, 4H, 3, 5-CH_{benzyl}), 7.27 (d, J = 7.4 Hz, 6H, 2, 4, 6-CH_{benzyl}), 5.54 (d, J = 15.2 Hz, 1H, CHH_{benzyl}), 5.48 (d, J = 15.4 Hz, 1H, CHH_{benzyl}), 5.30 (s, 1H, 3-OH), 4.87 (d, J = 14.9 Hz, 1H, CHH_{benzyl}), 4.82 (d, J = 14.9 Hz, 1H, CHH_{benzyl}), 4.79 (t, J = 7.5 Hz, 1H, 2-OH), 4.70 (s, 1H, 4-CH), 4.62 (ddd, J = 7.8, 6.7, 1.6 Hz, 1H, 2-CH), 4.16 (d, J = 11.4 Hz, 1H, ClCHH), 4.03 (q, J = 7.1 Hz, 0.2H, CH₂, solvent: ethyl acetate), 3.94 (ddt, J = 6.4, 4.7, 1.5 Hz, 1H, 3-CH), 3.74 (d, J = 11.4 Hz, 1H, ClCHH), 2.41 (s, 3H, SCH₃), 1.99 (s, 0.3H, OCH₃, solvent: ethyl acetate), 1.69 (ddd, J = 9.2, 4.1, 1.2 Hz, 1H, 5-CH), 1.53 (t, J = 4.5 Hz, 1H, 6-CHH), 1.17 (t, J = 7.1 Hz, 0.1H, CH₂CH₃, solvent: ethyl acetate), 0.88 (ddd, J = 8.7, 4.8, 1.7 Hz, 1H, 6-CHH). ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 163.5 (1C, C-2_{purine}), 153.4 (1C, C-6_{purine}), 151.2 (1C, C-4_{purine}), 137.9 (1C, C-1_{benzyl}), 137.6 (1C, C-1_{benzyl}), 137.0 (1C, C-8_{purine}), 128.5 (4C, C-3, 5_{benzyl}), 127.4 (4C, C-2, 6_{benzyl}), 127.1 (2C, C-4_{purine}), 116.5 (1C, C-5_{purine}), 76.1 (1C, C-3), 70.9 (1C, C-2), 61.0 (1C, C-4), 59.8 (0.1C, CH₂, solvent: ethyl acetate), 50.8 (1C, CH₂_{benzyl}), 49.4 (1C, ClCH₂), 48.8 (1C, CH₂_{benzyl}), 35.9 (1C, C-1), 25.5 (1C, C-5), 20.8 (0.1C, OCH₃, solvent: ethyl acetate), 14.8 (1C, C-6), 14.1 (0.1C, CH₂CH₃, solvent: ethyl acetate), 13.8 (1C, SCH₃).

FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3341 (O-H), 2978 (C-H_{aliph.}), 1562 (C=C_{aromat.}), 1072 (C-O), 783 (C-Cl), 733, 694 (C-H_{aromat.}, out of plane).

Di-(tert-butyl)-N-[9-((1R,2R,3S,4R,5S)-1-[[tert-butyl(diphenylsilyl)oxy]methyl]-2,3-dihydroxy-2,3-O-isopropylidenebicyclo[3.1.0]hex-4-yl)-2-chloro 9H-purin-6-yl]dicarbamate (35)

2-Chloroadenine (3.02 g, 17.8 mmol) was suspended in THF (88 mL), di-*tert*-butyl dicarbonate (15.9 g, 73.1 mmol, 4.1 eq.) and DMAP (0.22 g, 1.82 mmol, 0.1 eq.) were added. The mixture was stirred at rt overnight. The solvent was evaporated and the residue redissolved in ethyl acetate. The organic phase was washed with 1 M HCl and brine. After drying over anhydrous Na₂SO₄, the solvent was evaporated. The residue was dissolved in CH₃OH (177 mL) and saturated NaHCO₃-solution (80 mL) was added. The mixture was stirred for 2.5 h at 50 °C. CH₃OH was evaporated and the aqueous residue diluted with H₂O. The aqueous phase was extracted four times with CH₂Cl₂. After drying over anhydrous Na₂SO₄, the solvent was evaporated. The residue was purified by fc (cyclohexane : ethyl acetate = 1:4, Ø = 6 cm, l = 10 cm, V = 65 mL), but only a mixture of product and byproducts were obtained. It was purified again by fc (cyclohexane : ethyl acetate = 1:1, Ø = 6 cm, l = 10 cm, V = 65 mL) to afford the pure product as a colorless solid (R_f = 0.17, cyclohexane : ethyl acetate = 1:1), yield 4.85 g (74 %). C₁₅H₂₀ClN₅O₄ (369.81 g/mol). Melting point: 85.9 °C. Purity (HPLC: method B): 99 % (tr = 13.25 min). Exact mass (APCI): m/z calculated for C₁₅H₂₁ClN₅O₄ [M+H]⁺ 370.1277, found 370.1277. ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 13.60 (s, 1H, NH), 8.60 (s, 1H, 8-CH_{purine}), 1.41 (s, 18H, C(CH₃)₃). ¹³C-NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 150.7 (1C, C-2_{purine}), 149.0 (2C, C=O), 146.5 (1C, C-8_{purine}), 83.5 (2C, C(CH₃)₃), 27.0 (6C, C(CH₃)₃); C-1, C-3 and C-5 were not visible. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3244 (N-H), 2978 (C-H_{aliph.}), 1778, 1736 (C=O), 1134, 1107 (C-O).

Next, the purine (1.14 g, 3.08 mmol, 1.1 eq.) and triphenylphosphane (1.05 g, 4.00 mmol, 1.5 eq.) were dissolved in THF (25 mL) under nitrogen atmosphere. DIAD (0.78 mL, 3.97 mmol, 1.5 eq.) was added dropwise at 0 °C. The mixture was stirred for 30 min at rt. A solution of the alcohol 4 (1.19 g, 2.70 mmol) in THF (22 mL) was added and the solution was stirred overnight. The solvent was evaporated and the residue was purified by fc (cyclohexane : ethyl acetate = 5:1 + 0.5 % triethylamine, Ø = 6 cm, l = 10 cm, V = 65 mL) to afford the product 35 as a colorless solid (R_f = 0.32, cyclohexane : ethyl acetate = 5:1), yield 1.80 g (84 %). C₄₁H₅₂ClN₅O₇Si (790.43 g/mol). Melting point: 88.6 °C. Purity (HPLC: method C): 98 % (tr = 18.48 min). Exact mass (APCI): m/z calculated for C₃₁H₃₇ClN₅O₃Si [M+H⁺, -2 COOC(CH₃)₃, +2H]⁺ 590.2349, found 590.2362. ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 8.74 (s, 1H, 8-CH_{purine}), 7.59 (ddd, J = 7.9, 6.4, 1.5 Hz, 4H, 2, 6-CH_{Ph}), 7.47-7.31 (m, 6H, 3, 4, 5-CH_{Ph}), 5.23 (dd, J = 7.1, 1.2 Hz, 1H, 2-CH_{bicyclohexane}), 5.04 (s, 1H, 4-CH_{bicyclohexane}), 4.83 (dd, J = 7.2, 1.6 Hz, 1H, 3-CH_{bicyclohexane}), 4.06 (d, J = 10.6 Hz, 1H, OCHH), 3.83 (d, J = 10.6 Hz, 1H, OCHH), 1.72 (ddd, J = 9.2, 4.5, 1.5 Hz, 1H, 5-CH_{bicyclohexane}), 1.46 (s, 3H, C(CH₃)₂), 1.41 (s, 18H, OC(CH₃)₃), 1.39 (s, 0.4H, CH₂, solvent: cyclohexane), 1.20 (s, 3H, C(CH₃)₂), 0.99 (s, 11H, 6-CH₂ bicyclohexane, SiC(CH₃)₃). ¹³C-NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 153.8 (1C, C-4_{purine}), 151.1 (1C, C-2_{purine}), 149.9 (1C, C-6_{purine}), 149.6 (2C, C=O), 144.8 (1C, C-8_{purine}), 135.0 (4C, C-2, 6_{Ph}), 132.7 (2C, C-1_{Ph}), 129.8 (2C, C-4_{Ph}), 127.8 (4C, C-3, 5_{Ph}), 126.9 (1C, C-5_{purine}), 111.5 (1C, C(CH₃)₂), 87.6 (1C, C-3_{bicyclohexane}), 84.1 (2C, OC(CH₃)₃), 81.4 (1C, C-2_{bicyclohexane}), 64.3 (1C, OCH₂), 59.4 (1C, C-4_{bicyclohexane}), 38.3 (1C, C-1_{bicyclohexane}), 29.4 (1C, C-5_{bicyclohexane}), 27.2 (6C, OC(CH₃)₃), 26.7 (3C, SiC(CH₃)₃), 26.3 (0.1C, CH₂, solvent: cyclohexane), 25.8 (1C, C(CH₃)₂), 24.3 (1C, C(CH₃)₂), 18.8 (1C, SiC(CH₃)₃), 11.9 (1C, C-6_{bicyclohexane}). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 2978, 2932 (C-H_{aliph.}), 1759 (C=O), 1593, 1574 (C=C_{aromat.}), 1107, 1069, 1038 (C-O), 741, 702 (C-H_{aromat.}, out of plane).

tert-Butyl-N-[9-[(1R,2R,3S,4R,5S)-2,3-dihydroxy-1-(hydroxymethyl)-2,3-O-isopropylidenebicyclo[3.1.0]hex-4-yl]-2-methylthio-9H-purin-6-yl]carbamate (37)

Compound 35 (1.00 g, 1.27 mmol) was dissolved in THF (20 mL). Tetrabutylammonium fluoride trihydrate (TBAF × 3H₂O, 0.60 g, 1.91 mmol, 1.5 eq.) was added and the mixture was stirred at rt for 1 h. The solvent was evaporated, and the residue was dissolved in DMF (20 mL). NaSCH₃ (1.35 g, 19.3 mmol, 15 eq.) was added, and the slurry was

stirred overnight. Next, H₂O (0.5 mL) was added, and the mixture was heated to 70 °C for 2 h. The reaction was concentrated in vacuo and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 50 mL/min, Biotage® SNAP C18, 120 g, V = 20 mL) to afford the alcohol **37** as a colorless solid (*R*_f = 0.24, ethyl acetate = 100 %), yield 0.37 g (63 %). C₂₁H₂₉N₅O₅S (463.55 g/mol). Melting point: 110.1 °C. Purity (HPLC: method B): 94 % (*t*_R = 12.27 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₂₁H₃₀N₅O₅S [M+H]⁺ 464.1962, found 464.1966. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 10.90 (s, 1H, NH), 8.42 (s, 1H, 8-CH_{purine}), 5.75 (s, 0.6H, CH₂Cl₂, solvent: dichloromethane), 5.23 (dd, *J* = 7.1, 1.3 Hz, 1H, 2-CH_{bicyclohexane}), 4.99 (s, 1H, OH), 4.95 (s, 1H, 4-CH_{bicyclohexane}), 4.65 (dd, *J* = 7.1, 1.5 Hz, 1H, 3-CH_{bicyclohexane}), 3.84 (dd, *J* = 11.5, 4.0 Hz, 1H, OCHH), 3.37 (dd, *J* = 11.5, 3.9 Hz, 1H, OCHH), 2.59 (s, 3H, SCH₃), 1.64 (ddd, *J* = 9.2, 4.4, 1.5 Hz, 1H, 5-CH_{bicyclohexane}), 1.48 (s, 9H, C(CH₃)₃), 1.45 (s, 3H, C(CH₃)₂), 1.18 (s, 3H, C(CH₃)₂), 0.98 (t, *J* = 4.8 Hz, 1H, 6-CHH_{bicyclohexane}), 0.89 (ddd, *J* = 9.1, 5.1, 1.5 Hz, 1H, 6-CHH_{bicyclohexane}); The ¹H-NMR spectrum displays small impurities in the range of about 5 %. ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 163.8 (1C, C-2_{purine}), 151.9 (1C, C-4_{purine}), 151.0 (1C, C=O), 149.7 (1C, C-6_{purine}), 140.9 (1C, C-8_{purine}), 120.6 (1C, C-5_{purine}), 111.3 (1C, C(CH₃)₂), 88.1 (1C, C-3_{bicyclohexane}), 80.9 (1C, C-2_{bicyclohexane}), 80.2 (1C, C(CH₃)₃), 62.5 (1C, OCH₂), 58.4 (1C, C-4_{bicyclohexane}), 54.9 (0.3C, CH₂Cl₂, solvent: dichloromethane), 38.8 (1C, C-1_{bicyclohexane}), 29.6 (1C, C-5_{bicyclohexane}), 27.9 (3C, C(CH₃)₃), 25.6 (1C, C(CH₃)₂), 24.2 (1C, C(CH₃)₂), 14.0 (1C, SCH₃), 12.6 (1C, C-6_{bicyclohexane}); The ¹³C-NMR spectrum displays small impurities in the range of about 5 %. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3341 (O-H), 2978 (C-H_{aliphatic}), 1759 (C=O), 1609, 1582 (C=C_{aromat}), 1134, 1061, 1015 (C-O).

tert-Butyl-*N*-(9-[(1*R*,2*R*,3*S*,4*R*,5*S*)-1-(azidomethyl)-2,3-dihydroxy-2,3-*O*-isopropylidenebicyclo[3.1.0]hex-4-yl]-2-methylthio-9*H*-purin-6-yl)carbamate (**38**)

The alcohol **37** (2.19 g, 4.72 mmol) was suspended in CH₂Cl₂ (110 mL), tosyl chloride (1.81 g, 9.49 mmol, 2 eq.), triethylamine (1.5 mL, 10.8 mmol, 2.3 eq.) and DMAP (0.066 g, 0.54 mmol, 0.1 eq.) were added. The mixture was stirred at rt overnight. Water was added and the mixture was extracted four times with CH₂Cl₂. The organic phase was dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was dissolved in DMF (60 mL) and NaN₃ (4.60 g, 70.8 mmol, 15 eq.) was added. The mixture was heated to 70 °C for 2 h. Water and brine were added and the reaction mixture was extracted four times with CH₂Cl₂. The organic phase was dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by fc (CH₃CN : H₂O = 5:95 → 80:20, 50 mL/min, Biotage® SNAP C18, 120 g, V = 20 mL) to afford the azide **38** as a colorless solid (*R*_f = 0.27, cyclohexane : ethyl acetate = 1:1), yield 1.26 g (55 %). C₃₁H₃₇ClN₅O₃Si (488.57 g/mol). Melting point: 83.8 °C. Purity (HPLC: method B): 98 % (*t*_R = 16.55 min). Exact mass (APCI): *m/z* calculated for C₃₁H₃₇ClN₅O₃Si [M+H]⁺ 489.2027, found 489.2027. ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 10.08 (s, 1H, NH), 8.31 (s, 1H, 8-CH_{purine}), 5.75 (s, 0.2H, CH₂Cl₂, solvent: dichloromethane), 5.25 (dd, *J* = 7.1, 1.3 Hz, 1H, 2-CH_{bicyclohexane}), 4.97 (s, 1H, 4-CH_{bicyclohexane}), 4.81 (dd, *J* = 7.1, 1.3 Hz, 1H, 3-CH_{bicyclohexane}), 3.74 (d, *J* = 13.0 Hz, 1H, NCHH), 3.47 (d, *J* = 13.0 Hz, 1H, NCHH), 2.60 (s, 3H, SCH₃), 2.08 (s, 0.1H, CH₃CN, solvent: acetonitrile), 1.71 (ddd, *J* = 9.3, 4.6, 1.5 Hz, 1H, 5-CH_{bicyclohexane}), 1.48 (s, 9H, C(CH₃)₃), 1.47 (s, 3H, C(CH₃)₂), 1.20 (s, 3H, C(CH₃)₂), 1.09 (t, *J* = 5.0 Hz, 1H, 6-CHH_{bicyclohexane}), 1.04 (ddd, *J* = 9.2, 5.3, 1.5 Hz, 1H, 6-CHH_{bicyclohexane}). ¹³C-NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 163.7 (1C, C-2_{purine}), 152.0 (1C, C-4_{purine}), 150.8 (1C, C=O), 149.6 (1C, C-6_{purine}), 141.5 (1C, C-8_{purine}), 120.8 (1C, C-5_{purine}), 111.5 (1C, C(CH₃)₂), 88.1 (1C, C-3_{bicyclohexane}), 82.8 (1C, C-2_{bicyclohexane}), 80.2 (1C, C(CH₃)₃), 59.0 (1C, C-4_{bicyclohexane}), 54.1 (1C, NCH₂), 36.3 (1C, C-1_{bicyclohexane}), 30.0 (1C, C-5_{bicyclohexane}), 27.8 (3C, C(CH₃)₃), 25.8 (1C, C(CH₃)₂), 24.1 (1C, C(CH₃)₂), 14.0 (1C, SCH₃), 13.9 (1C, C-6_{bicyclohexane}). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 2982, 2924 (C-H_{aliphatic}), 2099 (N=N=N), 1751, 1712 (C=O), 1605, 1578 (C=C_{aromat}), 1138, 1053 (C-O).

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-(6-Amino-2-methylthio-9*H*-purin-9-yl)-1-[[4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]methyl]bicyclo[3.1.0]hexane-2,3-diol (**39**)

The azide **38** (0.030 g, 0.06 mmol) was dissolved in *tert*-butanol (0.5 mL). Propargyl alcohol (0.015 mL, 0.26 mmol, 4.2 eq.), copper(II) acetylacetonate (0.001 g, 0.004 mmol,

0.06 eq.), sodium ascorbate (0.007 g, 0.04 mmol, 0.6 eq.) and H₂O (0.5 mL) were added. The mixture was stirred for 5 h at rt. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the Boc-protected triazole as a colorless solid (*R*_f = 0.30, CH₂Cl₂ : CH₃OH = 95:5), yield 0.020 g (59 %). C₂₄H₃₂N₈O₅S (544.63 g/mol). Purity (HPLC: method B): 97 % (*t*_R = 11.30 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₂₄H₃₂DN₈O₅S [M+H]⁺ 546.2352, found 546.2337. Exact mass (APCI): *m/z* calculated for C₁₉H₂₅N₈O₅S [M+2H⁺, -COOC(CH₃)₃]⁺ 445.1765, found 445.1765. ¹H-NMR (400 MHz, CD₃OD) δ (ppm) = 7.97 (s, 1H, 5-CH_{triazole}), 5.34 (dd, *J* = 7.1, 1.4 Hz, 1H, 2-CH_{bicyclohexane}), 5.00 (s, 1H, 4-CH_{bicyclohexane}), 4.95 (d, *J* = 14.6 Hz, 1H, NCHH), 4.87 (dd, *J* = 7.3, 1.5 Hz, 1H, 3-CH_{bicyclohexane}), 4.69 (dd, *J* = 13.2, 2.1 Hz, 2H, OCH₂), 4.52 (d, *J* = 14.6 Hz, 1H, NCHH), 3.35 (s, 0.8H, CH₃OH, solvent: methanol), 2.63 (s, 3H, SCH₃), 1.89 (ddd, *J* = 9.4, 4.7, 1.6 Hz, 1H, 5-CH_{bicyclohexane}), 1.58 (s, 9H, C(CH₃)₃), 1.47 (s, 3H, C(CH₃)₂), 1.26 (t, *J* = 5.2 Hz, 1H, 6-CHH_{bicyclohexane}), 1.22 (s, 3H, C(CH₃)₂), 1.15 (ddd, *J* = 9.4, 5.7, 1.5 Hz, 1H, 6-CHH_{bicyclohexane}); 8-CH_{purine} was not visible due to occurrence of deuterium exchange at this position. ¹³C-NMR (101 MHz, CD₃OD) δ (ppm) = 167.3 (1C, C-2_{purine}), 153.3 (1C, C-4_{purine}), 152.5 (1C, C=O), 150.9 (1C, C-6_{purine}), 149.2 (1C, C-4_{triazole}), 124.4 (1C, C-5_{triazole}), 120.8 (1C, C-5_{purine}), 113.6 (1C, C(CH₃)₂), 90.2 (1C, C-3_{bicyclohexane}), 84.6 (1C, C-2_{bicyclohexane}), 82.7 (1C, C(CH₃)₃), 61.7 (1C, C-4_{bicyclohexane}), 56.6 (1C, OCH₂), 54.8 (1C, NCH₂), 38.2 (1C, C-1_{bicyclohexane}), 33.4 (1C, C-5_{bicyclohexane}), 28.5 (3C, C(CH₃)₃), 26.2 (1C, C(CH₃)₂), 24.4 (1C, C(CH₃)₂), 15.2 (1C, C-6_{bicyclohexane}), 14.8 (1C, SCH₃); C-8_{purine} was not visible. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3341 (O-H), 3148 (N-H), 2978 (C-H_{aliph.}), 1751, 1717 (C=O), 1605, 1578 (C=C_{aromat.}), 1142, 1053 (C-O).

The triazole (0.015 g, 0.03 mmol) was dissolved in CH₃OH (0.8 mL), trifluoroacetic acid (0.10 mL) and H₂O (0.10 mL) were added. The mixture was heated to 70 °C for 6 h. The solvent was evaporated and the residue was purified by semi-preparative HPLC (method B) to afford the product **39** as a colorless solid (*R*_f = 0.30, CH₂Cl₂ : CH₃OH = 8:2), yield 0.006 g (54 %). C₁₆H₂₀N₈O₃S (404.14 g/mol). Purity (HPLC: method B): 97 % (*t*_R = 3.55 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₁₆H₂₀DN₈O₃S [M+H]⁺ 406.1515, found 406.1515 and for C₁₆H₂₁N₈O₃S [M+H]⁺ 405.1452, found 405.1454. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.00 (s, 1H, 5-CH_{triazole}), 7.42 (s, 0.3H, 8-CH_{purine}), 7.32 (s, 1H, NH₂), 4.73 (d, *J* = 14.5 Hz, 1H, NCHH), 4.61 (d, *J* = 1.8 Hz, 1H, 4-CH), 4.55-4.49 (m, 3H, NCHH, OCH₂), 4.52 (dd, *J* = 6.6, 1.4 Hz, 1H, 2-CH), 4.03 (q, *J* = 7.1 Hz, 0.1H, CH₂, solvent: ethyl acetate), 3.81 (dt, *J* = 6.5, 1.6 Hz, 1H, 3-CH), 2.47 (s, 3H, SCH₃), 1.99 (s, 0.1H, OCH₃, solvent: ethyl acetate), 1.67 (dd, *J* = 8.5, 4.0 Hz, 1H, 5-CH), 1.42 (t, *J* = 4.5 Hz, 1H, 6-CHH), 1.17 (t, *J* = 7.1 Hz, 0.1H, CH₂CH₃, solvent: ethyl acetate), 0.83 (ddd, *J* = 8.7, 4.9, 1.6 Hz, 1H, 6-CHH); 8-CH_{purine} showed a reduced intensity due to occurrence of deuterium exchange at this position. ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 163.8 (1C, C-2_{purine}), 155.4 (1C, C-6_{purine}), 149.7 (1C, C-4_{purine}), 148.0 (1C, C-4_{triazole}), 137.4 (1C, C-8_{purine}), 123.4 (1C, C-5_{triazole}), 116.4 (1C, C-5_{purine}), 76.5 (1C, C-3), 71.8 (1C, C-2), 61.1 (1C, C-4), 55.1 (1C, OCH₂) 52.2 (1C, NCH₂), 34.7 (1C, C-1), 24.3 (1C, C-5), 13.7 (1C, SCH₃), 12.8 (1C, C-6).

Methyl 1-([(1R,2R,3S,4R,5S)-4-(6-amino-2-methylthio-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hex-1-yl)methyl]-1H-1,2,3-triazole-4-carboxylate (40)

The azide **38** (0.054 g, 0.11 mmol) was dissolved in *tert*-butanol (0.8 mL), methyl propiolate (0.045 mL, 0.51 mmol, 4.6 eq.), copper(II) acetylacetonate (0.004 g, 0.02 mmol, 0.1 eq.), sodium ascorbate (0.010 g, 0.05 mmol, 0.5 eq.) and H₂O (0.8 mL) were added. The mixture was stirred at 80 °C for 1.5 h. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the triazole **125** as a colorless solid (*R*_f = 0.34, ethyl acetate = 100 %), yield 0.042 g (66 %). C₂₅H₃₂N₈O₆S (572.64 g/mol). Purity (HPLC: method B): 91 % (*t*_R = 14.38 min). Exact mass (APCI): *m/z* calculated for C₂₀H₂₅N₈O₄S [M+2H, -COOC(CH₃)₃]⁺ 473.1714, found 473.1709. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 10.11 (s, 1H, NH), 8.77 (s, 1H, 5-CH), 8.18 (s, 1H, 8-CH_{purine}), 5.75 (s, 0.2H, CH₂Cl₂, solvent: dichloromethane), 5.24 (dd, *J* = 7.1, 1.4 Hz, 1H, 2-CH_{bicyclohexane}), 4.98 (s, 1H, 4-CH_{bicyclohexane}), 4.97 (d, *J* = 14.5 Hz, 1H, NCHH), 4.83 (dd, *J* = 7.3, 1.5 Hz, 1H, 3-CH_{bicyclohexane}), 4.49 (d, *J* = 14.5 Hz, 1H,

NCHH), 3.84 (s, 3H, OCH₃), 2.57 (s, 3H, SCH₃), 2.01 (ddd, *J* = 9.4, 4.7, 1.6 Hz, 1H, 5-CH_{bicyclohexane}), 1.48 (s, 9H, C(CH₃)₃), 1.39 (s, 3H, C(CH₃)₂), 1.25 (ddd, *J* = 9.2, 5.4, 1.6 Hz, 1H, 6-CHH_{bicyclohexane}), 1.14 (s, 3H, C(CH₃)₂), 1.08 (t, *J* = 5.0 Hz, 1H, 6-CHH_{bicyclohexane}); The ¹H-NMR spectrum displays small impurities in the range of about 5 %. ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 163.8 (1C, C-2_{purine}), 160.7 (1C, C-4_{carbonyl}), 152.0 (1C, C-4_{purine}), 150.8 (1C, C-N_{carbonyl}), 149.6 (1C, C-6_{purine}), 141.4 (1C, C-8_{purine}), 138.7 (1C, C-4), 129.1 (1C, C-5), 120.7 (1C, C-5_{purine}), 111.5 (1C, C(CH₃)₂), 88.2 (1C, C-3_{bicyclohexane}), 82.4 (1C, C-2_{bicyclohexane}), 80.2 (1C, C(CH₃)₃), 59.1 (1C, C-4_{bicyclohexane}), 54.9 (0.1C, CH₂Cl₂, solvent: dichloromethane), 53.3 (1C, NCH₂), 51.8 (1C, OCH₃), 36.7 (1C, C-1_{bicyclohexane}), 31.8 (1C, C-5_{bicyclohexane}), 27.9 (3C, C(CH₃)₃), 25.8 (1C, C(CH₃)₂), 24.1 (1C, C(CH₃)₂), 14.1 (1C, C-6_{bicyclohexane}), 14.0 (1C, SCH₃); The ¹³C-NMR spectrum displays small impurities in the range of about 5 %. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 2978 (C-H_{aliphatic}), 1732 (C=O), 1605, 1578 (C=C_{aromat.}), 1142, 1069, 1053 (C-O).

The triazole (0.038 g, 0.07 mmol) was dissolved in CH₃OH (1.6 mL), trifluoroacetic acid (0.20 mL) and H₂O (0.20 mL) were added. The mixture was heated to 70 °C overnight. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP C18, 12 g, V = 20 mL) to afford the product **40** as a colorless solid (*R*_f = 0.32, CH₂Cl₂ : CH₃OH = 9:1), yield 0.013 g (44 %). C₁₇H₂₀N₈O₄S (432.46 g/mol). Purity (HPLC: method B): 96 % (*t*_R = 4.86 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₁₇H₂₁N₈O₄S [M+H]⁺ 433.1401, found 433.1402. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.76 (s, 1H, 5-CH), 7.55 (s, 1H, 8-CH_{purine}), 7.31 (s, 2H, NH₂), 5.26 (d, *J* = 4.8 Hz, 1H, 3-OH_{bicyclohexane}), 4.76-4.72 (m, 2H, 2-OH_{bicyclohexane}, NCHH), 4.69 (d, *J* = 14.5 Hz, 1H, NCHH), 4.63 (s, 1H, 4-CH_{bicyclohexane}), 4.52 (td, *J* = 7.3, 1.5 Hz, 1H, 2-CH_{bicyclohexane}), 4.09 (q, *J* = 5.3 Hz, 0.4H, CH₃OH, solvent: methanol), 3.90 (ddt, *J* = 6.5, 4.8, 1.6 Hz, 1H, 3-CH_{bicyclohexane}), 3.83 (s, 3H, OCH₃), 3.17 (d, *J* = 5.2 Hz, 0.8H, CH₃OH, solvent: methanol), 2.45 (s, 3H, SCH₃), 1.77 (dd, *J* = 8.5, 4.0 Hz, 1H, 5-CH_{bicyclohexane}), 1.43 (t, *J* = 4.5 Hz, 1H, 6-CHH_{bicyclohexane}), 0.91 (ddd, *J* = 8.7, 4.9, 1.6 Hz, 1H, 6-CHH_{bicyclohexane}). ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 163.9 (1C, C-2_{purine}), 160.7 (1C, C=O), 155.4 (1C, C-6_{purine}), 149.7 (1C, C-4_{purine}), 138.5 (1C, C-4), 137.6 (1C, C-8_{purine}), 129.4 (1C, C-5), 116.6 (1C, C-5_{purine}), 76.3 (1C, C-3_{bicyclohexane}), 72.2 (1C, C-2_{bicyclohexane}), 61.4 (1C, C-4_{bicyclohexane}), 53.2 (1C, NCH₂), 51.7 (1C, OCH₃), 48.6 (0.2C, CH₃OH, solvent: methanol), 34.4 (1C, C-1_{bicyclohexane}), 24.8 (1C, C-5_{bicyclohexane}), 13.7 (1C, SCH₃), 12.9 (1C, C-6_{bicyclohexane}). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3341 (O-H), 3148 (N-H), 2978 (C-H_{aliphatic}), 1678 (C=O), 1589 (C=C_{aromat.}), 1130, 1080, 1053 (C-O).

Methyl 2-(1-[(1R,2R,3S,4R,5S)-4-(6-amino-2-methylthio-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hex-1-yl]methyl)-1H-1,2,3-triazol-4-yl)acetate (41)

The azide **38** (0.045 g, 0.09 mmol) was dissolved in *tert*-butanol (0.75 mL), 3-butyonic acid (0.031 g, 0.37 mmol, 4 eq.), copper(II) acetylacetonate (0.001 g, 0.004 mmol, 0.04 eq.), sodium ascorbate (0.007 g, 0.04 mmol, 0.4 eq.) and H₂O (0.75 mL) were added. The mixture was stirred at rt for 6 h. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the triazole as a colorless solid (*R*_f = 0.18, CH₂Cl₂ : CH₃OH = 9:1), yield 0.017 g (33 %). C₂₅H₃₂N₈O₆S (572.64 g/mol). Purity (HPLC: method B): 84 % (*t*_R = 12.93 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₂₅H₃₃N₈O₆S [M+H]⁺ 573.2238, found 573.2223. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 10.11 (s, 1H, NH), 8.14 (s, 1H, 8-CH_{purine}), 8.00 (s, 1H, 5-CH_{triazole}), 5.19 (s, 1H, 2-CH_{bicyclohexane}), 4.97 (s, 1H, 4-CH_{bicyclohexane}), 4.83 (d, *J* = 13.7 Hz, 1H, NCHH), 4.79 (d, *J* = 7.0 Hz, 1H, 3-CH_{bicyclohexane}), 4.50 (d, *J* = 14.5 Hz, 1H, NCHH), 3.66 (s, 2H, 2-CH₂), 3.17 (s, 0.1H, CH₃OH, solvent: methanol), 2.58 (s, 3H, SCH₃), 1.90 (s, 1H, 5-CH_{bicyclohexane}), 1.49 (s, 9H, C(CH₃)₃), 1.42 (s, 3H, C(CH₃)₂), 1.15 (s, 4H, C(CH₃)₂, 6-CHH_{bicyclohexane}), 1.09 (s, 1H, 6-CHH_{bicyclohexane}). ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 171.5 (1C, C-1), 163.8 (1C, C-2_{purine}), 152.0 (1C, C-4_{purine}), 150.8 (1C, C-N_{carbonyl}), 149.6 (1C, C-6_{purine}), 141.3 (1C, C-8_{purine}), 140.5 (1C, C-4_{triazole}), 123.7 (1C, C-5_{triazole}), 120.5 (1C, C-5_{purine}), 111.5 (1C, C(CH₃)₂), 88.3 (1C, C-3_{bicyclohexane}), 82.3 (1C, C-2_{bicyclohexane}), 80.3 (1C, C(CH₃)₃), 58.9 (1C, C-4_{bicyclohexane}), 52.5 (1C, NCH₂), 36.6 (1C, C-1_{bicyclohexane}), 31.7 (1C, C-5_{bicyclohexane}), 31.6 (1C, C-2), 27.9 (3C, C(CH₃)₃), 25.8 (1C, C(CH₃)₂), 24.1 (1C, C(CH₃)₂), 14.0 (2C, C-6_{bicyclohexane}, SCH₃). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 2986 (C-H_{aliphatic}), 1721 (C=O), 1605, 1578 (C=C_{aromat.}), 1142, 1053 (C-O).

The triazole (0.065 g, 0.11 mmol) was dissolved in CH₃OH (1.7 mL), trifluoroacetic acid (0.20 mL) and H₂O (0.10 mL) were added. The mixture was heated to 60 °C for 1 d and then at rt overnight. The solvent was evaporated and the residue was purified by semi-preparative HPLC (method F) to afford the ester **41** as a colorless solid (*R*_f = 0.24, CH₂Cl₂ : CH₃OH = 9:1), yield 0.024 g (48 %). C₁₈H₂₂N₈O₄S (446.15 g/mol). Melting point: 214.6 °C. Purity (HPLC: method B): 98 % (*t*_R = 5.15 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₁₈H₂₃N₈O₄S [M+H]⁺ 447.1557, found 447.1558. The compound **41** shows two different rotamers a and b in the NMR spectra in a ratio of approximately 10:1. ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 8.58 (s, 0.1H, 5-CH_{triazole}, rotam. b), 8.04 (s, 1H, 5-CH_{triazole}, rotam. a), 7.72 (s, 0.1H, 8-CH_{purine}, rotam. b), 7.42 (s, 1H, 8-CH_{purine}, rotam. a), 7.30 (s, 2.1H, NH₂, rotam. a, b), 5.25 (d, *J* = 4.3 Hz, 1H, 3a-OH_{bicyclohexane}), 4.90 (d, *J* = 14.4 Hz, 0.1H, NCHH_{rotam. b}), 4.82 (d, *J* = 7.3 Hz, 0.1H, 2-CH_{bicyclohexane}, rotam. b), 4.81-4.72 (m, 2H, 2-OH_{bicyclohexane}, rotam. a, NCHH_{rotam. a}), 4.68 (s, 0.1H, 4-CH_{bicyclohexane}, rotam. b), 4.61 (s, 1H, 4-CH_{bicyclohexane}, rotam. a), 4.52 (d, *J* = 14.5 Hz, 1H, NCHH_{rotam. a}), 4.42 (t, *J* = 5.7 Hz, 1.1H, 2-CH_{bicyclohexane}, rotam. a, NCHH_{rotam. b}), 3.97 (dd, *J* = 7.0, 1.7 Hz, 0.1H, 3-CH_{bicyclohexane}, rotam. b), 3.86-3.72 (m, 3H, 3-CH_{bicyclohexane}, rotam. a, 2-CH₂, rotam. a), 3.63 (s, 3H, OCH₃, rotam. a), 3.58 (s, 0.2H, OCH₃, rotam. b), 3.52 (d, *J* = 16.8 Hz, 0.1H, 2-CHH_{rotam. b}), 2.47 (s, 2.9H, SCH₃, rotam. a, b), 1.85 (t, *J* = 4.7 Hz, 0.1H, 6-CHH_{bicyclohexane}, rotam. b), 1.67 (dd, *J* = 8.7, 4.0 Hz, 1H, 5-CH_{bicyclohexane}, rotam. a), 1.60 (dd, *J* = 9.1, 4.6 Hz, 0.1H, 5-CH_{bicyclohexane}, rotam. b), 1.42 (t, *J* = 4.5 Hz, 1H, 6-CHH_{bicyclohexane}, rotam. a), 0.83 (ddd, *J* = 8.7, 4.9, 1.5 Hz, 1H, 6-CHH_{bicyclohexane}, rotam. a), 0.67-0.57 (m, 0.1H, 6-CHH_{bicyclohexane}, rotam. b); The signal for 2-CHH_{rotam. b} is located under the H₂O signal and therefore only visible in 2D spectra. ¹³C-NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 170.4 (1C, C=O), 163.8 (1C, C-2_{purine}), 155.4 (1C, C-6_{purine}), 149.8 (1C, C-4_{purine}), 139.8 (1C, C-4_{triazole}), 137.4 (1C, C-8_{purine}), 124.2 (1C, C-5_{triazole}), 116.5 (1C, C-5_{purine}), 76.5 (1C, C-3_{bicyclohexane}), 71.8 (1C, C-2_{bicyclohexane}), 61.2 (1C, C-4_{bicyclohexane}), 52.2 (1C, NCH₂), 51.9 (1C, OCH₃), 34.7 (1C, C-1_{bicyclohexane}), 31.1 (1C, C-2), 24.4 (1C, C-5_{bicyclohexane}), 13.7 (1C, SCH₃), 12.9 (1C, C-6_{bicyclohexane}). The resolution was too low to identify the ¹³C-signals for rotamer b, therefore only rotamer a is described here. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3352 (O-H), 3244 (N-H), 1751 (C=O), 1624, 1585 (C=C_{aromat.}), 1142, 1119, 1084, 1057 (C-O).

Methyl 3-(1-((1R,2R,3S,4R,5S)-4-(6-amino-2-methylthio-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hex-1-yl)methyl)-1H-1,2,3-triazol-4-yl)propanoate (42)

The azide **38** (0.028 g, 0.06 mmol) was dissolved in *tert*-butanol (0.5 mL), 4-pentynoic acid (0.024 g, 0.24 mmol, 4.3 eq.), copper(II) acetylacetonate (0.001 g, 0.004 mmol, 0.07 eq.), sodium ascorbate (0.006 g, 0.03 mmol, 0.5 eq.) and H₂O (0.5 mL) were added. The mixture was stirred at rt for 5 h. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the triazole as a colorless solid (*R*_f = 0.27, CH₂Cl₂ : CH₃OH = 9:1), yield 0.018 g (54 %). C₂₆H₃₄N₈O₆S (586.67 g/mol). Purity (HPLC: method B): 96 % (*t*_R = 12.64 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₂₆H₃₄N₈O₆S [M+H]⁺ 588.2458, found 588.2452. ¹H-NMR (400 MHz, CD₃OD) δ (ppm) = 7.99 (s, 0.1H, 8-CH_{purine}), 7.82 (s, 1H, 5-CH_{triazole}), 5.23 (dd, *J* = 7.1, 1.4 Hz, 1H, 2-CH_{bicyclohexane}), 5.00 (s, 1H, 4-CH_{bicyclohexane}), 4.88-4.82 (m, 1H, 3-CH_{bicyclohexane}, NCHH), 4.52 (d, *J* = 14.6 Hz, 1H, NCHH), 3.35 (s, 0.2H, CH₃OH, solvent: methanol), 2.99 (t, *J* = 7.4 Hz, 2H, 3-CH₂), 2.67 (t, *J* = 7.4 Hz, 2H, 2-CH₂), 2.63 (s, 3H, SCH₃), 1.89 (ddd, *J* = 9.4, 4.6, 1.6 Hz, 1H, 5-CH_{bicyclohexane}), 1.58 (s, 9H, C(CH₃)₃), 1.48 (s, 3H, C(CH₃)₂), 1.26 (dd, *J* = 5.7, 4.7 Hz, 1H, 6-CHH_{bicyclohexane}), 1.22 (s, 3H, C(CH₃)₂), 1.13 (ddd, *J* = 9.4, 5.7, 1.5 Hz, 1H, 6-CHH_{bicyclohexane}); 8-CH_{purine} showed a reduced intensity and no coupling interaction due to occurrence of deuterium exchange at this position. ¹³C-NMR (101 MHz, CD₃OD) δ (ppm) = 176.3 (1C, C-1), 167.4 (1C, C-2_{purine}), 153.3 (1C, C-4_{purine}), 152.5 (1C, C-N_{carbonyl}), 150.9 (1C, C-6_{purine}), 147.9 (1C, C-4_{triazole}), 142.6 (1C, C-8_{purine}), 123.9 (1C, C-5_{triazole}), 120.7 (1C, C-5_{purine}), 113.6 (1C, C(CH₃)₂), 90.0 (1C, C-3_{bicyclohexane}), 84.4 (1C, C-2_{bicyclohexane}), 82.7 (1C, C(CH₃)₃), 61.6 (1C, C-4_{bicyclohexane}), 54.7 (1C, NCH₂), 38.2 (1C, C-1_{bicyclohexane}), 34.5 (1C, C-2), 33.2 (1C, C-5_{bicyclohexane}), 28.5 (3C, C(CH₃)₃), 26.2 (1C, C(CH₃)₂), 24.4 (1C, C(CH₃)₂), 22.0 (1C, C-3), 15.3 (1C, C-6_{bicyclohexane}), 14.8 (1C, SCH₃). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 2978 (C-H_{aliphatic}), 1717 (C=O), 1605, 1578 (C=C_{aromat.}), 1142, 1053 (C-O).

The triazole acid (0.015 g, 0.03 mmol) was dissolved in CH₃OH (0.4 mL), trifluoroacetic acid (0.05 mL) and H₂O (0.05 mL) were added. The mixture was stirred at rt for 3 d. The solvent was evaporated and the residue was purified by semi-preparative HPLC (method D) to afford the ester **42** as a colorless solid (*R*_f = 0.24, CH₂Cl₂ : CH₃OH = 9:1), yield 0.004 g (34 %). C₁₉H₂₄N₈O₄S (460.16 g/mol). Purity (HPLC: method B): 98 % (*t*_R = 5.67 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₁₉H₂₄N₈O₄S [M+H]⁺ 462.1777, found 462.1775 and for C₁₉H₂₅N₈O₄S [M+H]⁺ 461.1714, found 461.1709. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 7.88 (s, 1H, 5-CH_{triazole}), 7.30 (s, 0.4H, 8-CH_{purine}), 7.29 (s, 2H, NH₂), 5.24 (d, *J* = 4.7 Hz, 1H, 3-OH_{bicyclohexane}), 4.76 (d, *J* = 7.3 Hz, 1H, 2-OH_{bicyclohexane}), 4.73 (d, *J* = 14.5 Hz, 1H, NCHH), 4.61 (d, *J* = 1.7 Hz, 1H, 4-CH_{bicyclohexane}), 4.44 (d, *J* = 14.5 Hz, 1H, NCHH), 4.40 (td, *J* = 7.0, 1.7 Hz, 1H, 2-CH_{bicyclohexane}), 4.03 (q, *J* = 7.1 Hz, 0.1H, CH₂, solvent: ethyl acetate), 3.81 (tt, *J* = 6.3, 1.6 Hz, 1H, 3-CH_{bicyclohexane}), 3.58 (s, 3H, OCH₃), 2.88 (t, *J* = 7.5 Hz, 2H, 3-CH₂), 2.67 (t, *J* = 7.5 Hz, 2H, 2-CH₂), 2.46 (s, 3H, SCH₃), 1.99 (s, 0.1H, OCH₃, solvent: ethyl acetate), 1.65 (dd, *J* = 8.3, 4.1 Hz, 1H, 5-CH_{bicyclohexane}), 1.42 (t, *J* = 4.5 Hz, 1H, 6-CHH_{bicyclohexane}), 1.17 (t, *J* = 7.1 Hz, 0.1H, CH₂CH₃, solvent: ethyl acetate), 0.81 (ddd, *J* = 8.7, 4.9, 1.6 Hz, 1H, 6-CHH_{bicyclohexane}); 8-CH_{purine} showed a reduced intensity due to occurrence of deuterium exchange at this position. ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 172.6 (1C, C-1), 163.8 (1C, C-2_{purine}), 155.4 (1C, C-6_{purine}), 149.7 (1C, C-4_{purine}), 145.4 (1C, C-4_{triazole}), 137.3 (1C, C-8_{purine}), 122.7 (1C, C-5_{triazole}), 116.4 (1C, C-5_{purine}), 76.3 (1C, C-3_{bicyclohexane}), 71.7 (1C, C-2_{bicyclohexane}), 61.1 (1C, C-4_{bicyclohexane}), 52.0 (1C, NCH₂), 51.4 (1C, OCH₃), 34.8 (1C, C-1_{bicyclohexane}), 32.8 (1C, C-2), 24.2 (1C, C-5_{bicyclohexane}), 20.7 (1C, C-3), 13.6 (1C, SCH₃), 12.9 (1C, C-6_{bicyclohexane}).

(1*R*,2*R*,3*S*,4*R*,5*S*)-4-(6-Amino-2-methylthio-9*H*-purin-9-yl)-1-[[4-(aminomethyl)-1*H*-1,2,3-triazol-1-yl]methyl]bicyclo[3.1.0]hexane-2,3-diol (**43**)

The azide **38** (0.029 g, 0.06 mmol) was dissolved in *tert*-butanol (0.5 mL), propargylamine (0.016 mL, 0.25 mmol, 4.2 eq.), copper(II) acetylacetonate (0.001 g, 0.004 mmol, 0.06 eq.), sodium ascorbate (0.007 g, 0.04 mmol, 0.6 eq.) and H₂O (0.5 mL) were added. The mixture was stirred for 5 h at rt. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0 + 0.1 % trifluoroacetic acid, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL). The intermediate already partly decomposed (deprotection) during this purification and was therefore dissolved in CH₃OH (0.5 mL). Next, trifluoroacetic acid (0.05 mL) and H₂O (0.10 mL) were added and the mixture was heated to 70 °C for 1 d. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0 + 0.1 % trifluoroacetic acid, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL), but the product remained impure. The impure product was purified by semi-preparative HPLC (method D) to afford the pure product **43** as a colorless solid (*R*_f = 0.15, CH₃OH = 100 % + 1 % triethylamine), yield 0.002 g (8 %). C₁₆H₂₁N₉O₂S (403.47 g/mol). Purity (HPLC: method D): 95 % (*t*_R = 8.88 min). Exact mass (LC-MS-ESI): *m/z* calculated for C₁₆H₂₂N₉O₂S [M+H]⁺ 404.1612, found 404.1624. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 7.94 (s, 1H, 5-CH_{triazole}), 7.30 (s, 2H, NH₂), 7.29 (s, 1H, 8-CH_{purine}), 4.76 (d, *J* = 14.5 Hz, 1H, NCHH), 4.62 (s, 1H, 4-CH), 4.46 (d, *J* = 14.4 Hz, 1H, NCHH), 4.41 (dd, *J* = 6.6, 1.5 Hz, 1H, 2-CH), 3.81 (dt, *J* = 6.6, 1.6 Hz, 1H, 3-CH), 3.77 (s, 2H, NH₂CH₂), 2.46 (s, 3H, SCH₃), 1.66 (dd, *J* = 8.7, 4.0 Hz, 1H, 5-CH), 1.43 (t, *J* = 4.5 Hz, 1H, 6-CHH), 0.83 (ddd, *J* = 8.7, 4.9, 1.6 Hz, 1H, 6-CHH). ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 163.8 (1C, C-2_{purine}), 155.4 (1C, C-6_{purine}), 149.7 (1C, C-4_{purine}), 149.1 (1C, C-4_{triazole}), 137.3 (1C, C-8_{purine}), 122.7 (1C, C-5_{triazole}), 116.5 (1C, C-5_{purine}), 76.3 (1C, C-3), 71.7 (1C, C-2), 61.1 (1C, C-4), 52.0 (1C, NCH₂), 37.1 (1C, NH₂CH₂), 34.9 (1C, C-1), 24.3 (1C, C-5), 13.6 (1C, SCH₃), 12.9 (1C, C-6).

1-[(1*R*,2*R*,3*S*,4*R*,5*S*)-4-(6-Amino-2-methylthio-9*H*-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hex-1-yl]methyl]-1*H*-1,2,3-triazole-4-carboxylic acid (**44**)

The ester **40** (0.082 g, 0.19 mmol) was suspended in CH₃CN (0.7 mL) and H₂O (2 mL), NaOH-solution (2 M, 0.30 mL) was added. The mixture was heated to 60 °C overnight. The solvent was evaporated and the residue was purified by semi preparative HPLC (method A) to afford the carboxylic acid **44** as a colorless solid (*R*_f = 0.44, CH₂Cl₂ : CH₃OH = 1:1), yield 0.036 g (45 %). C₁₆H₁₈N₈O₄S (418.43 g/mol). Melting point:

139.3° C. Purity (HPLC: method B): > 99 % (t_R = 7.05 min). Exact mass (LC-MS-ESI): m/z calculated for $C_{16}H_{19}N_8O_4S$ $[M+H]^+$ 419.1244, found 419.1241. 1H -NMR (600 MHz, DMSO- d_6) δ (ppm) = 8.27 (s, 1H, 5-CH), 7.35 (s, 2H, NH₂), 7.24 (s, 1H, 8-CH_{purine}), 5.50 (s, 2H, 2-OH_{bicyclohexane}, 3-OH_{bicyclohexane}), 4.71 (d, J = 14.6 Hz, 1H, NCHH), 4.63 (d, J = 2.0 Hz, 1H, 4-CH_{bicyclohexane}), 4.53 (d, J = 14.5 Hz, 1H, NCHH), 4.44 (dd, J = 6.5, 1.5 Hz, 1H, 2-CH_{bicyclohexane}), 3.76 (dt, J = 6.6, 1.5 Hz, 1H, 3-CH_{bicyclohexane}), 2.47 (s, 3H, SCH₃), 2.07 (s, 0.1H, CH₃CN, solvent: acetonitrile), 1.67 (dd, J = 8.4, 3.7 Hz, 1H, 5-CH_{bicyclohexane}), 1.46 (t, J = 4.4 Hz, 1H, 6-CHH_{bicyclohexane}), 0.85 (ddd, J = 8.7, 4.8, 1.6 Hz, 1H, 6-CHH_{bicyclohexane}). ^{13}C -NMR (151 MHz, DMSO- d_6) δ (ppm) = 164.2 (1C, C=O), 163.9 (1C, C-2_{purine}), 155.4 (1C, C-6_{purine}), 149.7 (1C, C-4_{purine}), 148.3 (1C, C-4), 137.1 (1C, C-8_{purine}), 126.5 (1C, C-5), 116.4 (1C, C-5_{purine}), 76.8 (1C, C-3_{bicyclohexane}), 71.7 (1C, C-2_{bicyclohexane}), 60.8 (1C, C-4_{bicyclohexane}), 52.2 (1C, NCH₂), 34.7 (1C, C-1_{bicyclohexane}), 24.1 (1C, C-5_{bicyclohexane}), 13.7 (1C, SCH₃), 13.0 (1C, C-6_{bicyclohexane}). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3341 (O-H), 3198 (N-H), 1585 (C=O), 1539 (C=C_{aromat.}), 1057 (C-O).

2-(1-[(1R,2R,3S,4R,5S)-4-(6-Amino-2-methylthio-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hex-1-yl]methyl)-1H-1,2,3-triazol-4-yl)acetic acid (**45**)

The azide **38** (0.045 g, 0.09 mmol) was dissolved in *tert*-butanol (0.75 mL), 3-butynoic acid (0.031 g, 0.37 mmol, 4 eq.), copper(II) acetylacetonate (0.001 g, 0.004 mmol, 0.04 eq.), sodium ascorbate (0.007 g, 0.04 mmol, 0.4 eq.) and H₂O (0.75 mL) were added. The mixture was stirred at rt for 6 h. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the triazole as a colorless solid (R_f = 0.18, CH₂Cl₂ : CH₃OH = 9:1), yield 0.017 g (33 %). $C_{25}H_{32}N_8O_6S$ (572.64 g/mol). Purity (HPLC: method B): 84 % (t_R = 12.93 min). Exact mass (LC-MS-ESI): m/z calculated for $C_{25}H_{33}N_8O_6S$ $[M+H]^+$ 573.2238, found 573.2223. 1H -NMR (600 MHz, DMSO- d_6) δ (ppm) = 10.11 (s, 1H, NH), 8.14 (s, 1H, 8-CH_{purine}), 8.00 (s, 1H, 5-CH_{triazole}), 5.19 (s, 1H, 2-CH_{bicyclohexane}), 4.97 (s, 1H, 4-CH_{bicyclohexane}), 4.83 (d, J = 13.7 Hz, 1H, NCHH), 4.79 (d, J = 7.0 Hz, 1H, 3-CH_{bicyclohexane}), 4.50 (d, J = 14.5 Hz, 1H, NCHH), 3.66 (s, 2H, 2-CH₂), 3.17 (s, 0.1H, CH₃OH, solvent: methanol), 2.58 (s, 3H, SCH₃), 1.90 (s, 1H, 5-CH_{bicyclohexane}), 1.49 (s, 9H, C(CH₃)₃), 1.42 (s, 3H, C(CH₃)₂), 1.15 (s, 4H, C(CH₃)₂, 6-CHH_{bicyclohexane}), 1.09 (s, 1H, 6-CHH_{bicyclohexane}). ^{13}C -NMR (151 MHz, DMSO- d_6) δ (ppm) = 171.5 (1C, C-1), 163.8 (1C, C-2_{purine}), 152.0 (1C, C-4_{purine}), 150.8 (1C, C-N_{carbonyl}), 149.6 (1C, C-6_{purine}), 141.3 (1C, C-8_{purine}), 140.5 (1C, C-4_{triazole}), 123.7 (1C, C-5_{triazole}), 120.5 (1C, C-5_{purine}), 111.5 (1C, C(CH₃)₂), 88.3 (1C, C-3_{bicyclohexane}), 82.3 (1C, C-2_{bicyclohexane}), 80.3 (1C, C(CH₃)₃), 58.9 (1C, C-4_{bicyclohexane}), 52.5 (1C, NCH₂), 36.6 (1C, C-1_{bicyclohexane}), 31.7 (1C, C-5_{bicyclohexane}), 31.6 (1C, C-2), 27.9 (3C, C(CH₃)₃), 25.8 (1C, C(CH₃)₂), 24.1 (1C, C(CH₃)₂), 14.0 (2C, C-6_{bicyclohexane}, SCH₃). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 2986 (C-H_{aliphat.}), 1721 (C=O), 1605, 1578 (C=C_{aromat.}), 1142, 1053 (C-O).

The triazole (0.048 g, 0.08 mmol) was dissolved in CH₃CN (0.4 mL) and H₂O (1.4 mL), trifluoroacetic acid (0.20 mL) was added. The mixture was heated to 60 °C overnight. The solvent was evaporated and the was purified by semi-preparative HPLC (method E) to afford the product **45** as a colorless solid, yield 0.019 g (51 %). $C_{17}H_{20}N_8O_4S$ (432.46 g/mol). Melting point: 179.2 °C. Purity (HPLC: D): 99 % (t_R = 9.71 min). Exact mass (LC-MS-ESI): m/z calculated for $C_{17}H_{21}N_8O_4S$ $[M+H]^+$ 433.1401, found 433.1411. The compound **45** shows two different rotamers a and b in the NMR spectra in a ratio of approximately 7:1. 1H -NMR (400 MHz, DMSO- d_6) δ (ppm) = 8.54 (s, 0.2H, 5-CH_{triazole}, rotam. b), 8.02 (s, 1H, 5-CH_{triazole}, rotam. a), 7.70 (s, 0.1H, 8-CH_{purine}, rotam. b), 7.43 (s, 1H, 8-CH_{purine}, rotam. a), 7.30 (s, 2.4H, NH₂, rotam. a, b), 4.86 (d, J = 14.4 Hz, 0.2H, NCHH_{rotam. b}), 4.81 (d, J = 6.5 Hz, 0.2H, 2-CH_{bicyclohexane}, rotam. b), 4.75 (d, 1H, J = 14.5 Hz, NCHH_{rotam. a}), 4.68 (s, 0.2H, 4-CH_{bicyclohexane}, rotam. b), 4.61 (s, 1H, 4-CH_{bicyclohexane}, rotam. a), 4.52 (d, J = 14.5 Hz, 1H, NCHH_{rotam. a}), 4.47 (s, 0.2H, NCHH_{rotam. b}), 4.42 (d, J = 6.6 Hz, 1H, 2-CH_{bicyclohexane}, rotam. a), 3.95 (d, J = 6.7 Hz, 0.2H, 3-CH_{bicyclohexane}, rotam. b), 3.81 (d, 1H, J = 6.4 Hz, 3-CH_{bicyclohexane}, rotam. a), 3.66 (t, J = 19.2 Hz, 2H, 2-CH₂, rotam. a), 3.43 (d, J = 16.7 Hz, 0.1H, 2-CHH_{rotam. b}), 3.18 (d, J = 16.9 Hz, 0.1H, 2-CHH_{rotam. b}), 2.47 (s, 3.5H, SCH₃, rotam. a, b), 1.85 (s, 0.2H, 6-CHH_{bicyclohexane}, rotam. b), 1.66 (dd, J = 8.9, 3.9 Hz, 1H, 5-CH_{bicyclohexane}, rotam. a), 1.59 (s, 0.2H, 5-CH_{bicyclohexane}, rotam. b), 1.41 (t, J = 4.5 Hz, 1H, 6-CHH_{bicyclohexane}, rotam. a), 0.82 (dd, J = 9.0, 4.9 Hz, 1H, 6-CHH_{bicyclohexane}, rotam. a), 0.63 (s, 0.2H, 6-CHH_{bicyclohexane}, rotam. b). ^{13}C -NMR (101 MHz, DMSO- d_6) δ (ppm) = 171.6 (1C, C=O), 163.8 (1C, C-2_{purine}), 155.4 (1C, C-6_{purine}), 149.8 (1C, C-4_{purine}), 140.6

(1C, C-4triazole), 137.4 (1C, C-8purine), 124.1 (1C, C-5triazole), 116.5 (1C, C-5purine), 76.6 (1C, C-3bicyclohexane), 71.8 (1C, C-2bicyclohexane), 61.1 (1C, C-4bicyclohexane), 52.2 (1C, NCH₂), 34.7 (1C, C-1bicyclohexane), 31.7 (1C, C-2), 24.4 (1C, C-5bicyclohexane), 13.7 (1C, SCH₃), 12.9 (1C, C-6bicyclohexane); The resolution was too low to identify the ¹³C-signals for rotamer b, therefore only rotamer a is described here. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3518, 3329, 3198 (O-H), 2920 (C-H_{aliph.}), 1651 (C=O), 1586 (C=C_{aromat.}), 1123, 1092 (C-O).

3-[1-((1R,2R,3S,4R,5S)-4-[6-(tert-Butoxycarbonyl)amino-2-methylthio-9H-purin-9-yl]-2,3-dihydroxy-2,3-O-isopropylidenebicyclo[3.1.0]hex-1-yl)methyl]-1H-1,2,3-triazol-4-yl]propanoic acid (**46**)

The azide **38** (0.028 g, 0.06 mmol) was dissolved in *tert*-butanol (0.5 mL), 4-pentynoic acid (0.024 g, 0.24 mmol, 4.3 eq.), copper(II) acetylacetonate (0.001 g, 0.004 mmol, 0.07 eq.), sodium ascorbate (0.006 g, 0.03 mmol, 0.5 eq.) and H₂O (0.5 mL) were added. The mixture was stirred at rt for 5 h. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 100:0, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the triazole as a colorless solid (R_f = 0.27, CH₂Cl₂ : CH₃OH = 9:1), yield 0.018 g (54 %). C₂₆H₃₄N₈O₆S (586.67 g/mol). Purity (HPLC: method B): 96 % (t_R = 12.64 min). Exact mass (LC-MS-ESI): m/z calculated for C₂₆H₃₄N₈O₆S [M+H]⁺ 588.2458, found 588.2452. ¹H-NMR (400 MHz, CD₃OD) δ (ppm) = 7.99 (s, 0.1H, 8-CH_{purine}), 7.82 (s, 1H, 5-CH_{triazole}), 5.23 (dd, J = 7.1, 1.4 Hz, 1H, 2-CH_{bicyclohexane}), 5.00 (s, 1H, 4-CH_{bicyclohexane}), 4.88-4.82 (m, 1H, 3-CH_{bicyclohexane}, NCHH), 4.52 (d, J = 14.6 Hz, 1H, NCHH), 3.35 (s, 0.2H, CH₃OH, solvent: methanol), 2.99 (t, J = 7.4 Hz, 2H, 3-CH₂), 2.67 (t, J = 7.4 Hz, 2H, 2-CH₂), 2.63 (s, 3H, SCH₃), 1.89 (ddd, J = 9.4, 4.6, 1.6 Hz, 1H, 5-CH_{bicyclohexane}), 1.58 (s, 9H, C(CH₃)₃), 1.48 (s, 3H, C(CH₃)₂), 1.26 (dd, J = 5.7, 4.7 Hz, 1H, 6-CHH_{bicyclohexane}), 1.22 (s, 3H, C(CH₃)₂), 1.13 (ddd, J = 9.4, 5.7, 1.5 Hz, 1H, 6-CHH_{bicyclohexane}); 8-CH_{purine} showed a reduced intensity and no coupling interaction due to occurrence of deuterium exchange at this position. ¹³C-NMR (101 MHz, CD₃OD) δ (ppm) = 176.3 (1C, C-1), 167.4 (1C, C-2_{purine}), 153.3 (1C, C-4_{purine}), 152.5 (1C, C-N_{carbonyl}), 150.9 (1C, C-6_{purine}), 147.9 (1C, C-4_{triazole}), 142.6 (1C, C-8_{purine}), 123.9 (1C, C-5_{triazole}), 120.7 (1C, C-5_{purine}), 113.6 (1C, C(CH₃)₂), 90.0 (1C, C-3_{bicyclohexane}), 84.4 (1C, C-2_{bicyclohexane}), 82.7 (1C, C(CH₃)₃), 61.6 (1C, C-4_{bicyclohexane}), 54.7 (1C, NCH₂), 38.2 (1C, C-1_{bicyclohexane}), 34.5 (1C, C-2), 33.2 (1C, C-5_{bicyclohexane}), 28.5 (3C, C(CH₃)₃), 26.2 (1C, C(CH₃)₂), 24.4 (1C, C(CH₃)₂), 22.0 (1C, C-3), 15.3 (1C, C-6_{bicyclohexane}), 14.8 (1C, SCH₃). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 2978 (C-H_{aliph.}), 1717 (C=O), 1605, 1578 (C=C_{aromat.}), 1142, 1053 (C-O).

The triazole (0.070 g, 0.12 mmol) was dissolved in CH₃CN (0.7 mL) and H₂O (2 mL), trifluoroacetic acid (0.30 mL) was added. The mixture was stirred at rt for 1 d. The solvent was evaporated and the residue was purified by semi-preparative HPLC (method E) to afford the carboxylic acid **46** as a colorless solid, yield 0.010 g (19 %). C₁₈H₂₂N₈O₄S (446.49 g/mol). Melting point: 133.3 °C Purity (HPLC: D): 99 % (t_R = 10.32 min). Exact mass (LC-MS-ESI): m/z calculated for C₁₈H₂₃N₈O₄S [M+H]⁺ 447.1557, found 447.1557. The compound **46** shows three different rotamers a, b and c in the NMR spectra in a ratio of approximately 10:6:3. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.40 (s, 0.6H, 5-CH_{triazole}, rotam. b), 7.97 (s, 0.3H, 5-CH_{triazole}, rotam. c), 7.89 (s, 1H, 5-CH_{triazole}, rotam. a), 7.58 (s, 0.6H, 8-CH_{purine}, rotam. b), 7.36 (s, 0.3H, 8-CH_{purine}, rotam. c), 7.30 (s, 2.5H, 8-CH_{purine}, rotam. a, NH₂, rotam. b, c), 7.26 (s, 2H, NH₂, rotam. a), 5.24 (s, 0.6H, 3-OH_{bicyclohexane}), 4.80-4.75 (m, 1.3H, 2-CH_{bicyclohexane}, rotam. b, NCHH_{rotam. b}), 4.73 (d, J = 14.5 Hz, 1H, NCHH_{rotam. a}), 4.69 (s, 0.3H, 4-CH_{bicyclohexane}, rotam. c), 4.67 (s, 0.6H, 4-CH_{bicyclohexane}, rotam. b), 4.64 (d, J = 7.1 Hz, 0.3H, 2-CH_{bicyclohexane}, rotam. c), 4.62 (d, J = 1.7 Hz, 1H, 4-CH_{bicyclohexane}, rotam. a), 4.57 (d, J = 14.5 Hz, 0.3H, NCHH_{rotam. c}), 4.49-4.42 (m, 1.8H, NCHH_{rotam. a, b, c}), 4.41 (dd, J = 6.7, 1.5 Hz, 1H, 2-CH_{bicyclohexane}, rotam. a), 3.98 (d, J = 7.0 Hz, 0.2H, 3-CH_{bicyclohexane}, rotam. c), 3.92 (dd, J = 6.9, 1.7 Hz, 0.6H, 3-CH_{bicyclohexane}, rotam. b), 3.79 (dt, J = 6.6, 1.6 Hz, 1H, 3-CH_{bicyclohexane}, rotam. a), 2.85 (t, J = 7.6 Hz, 2H, 3-CH₂, rotam. a), 2.80 (t, J = 7.6 Hz, 0.6H, 3-CH₂, rotam. c), 2.66 (t, J = 7.6 Hz, 1.2H, 3-CH₂, rotam. b), 2.58 (dd, J = 8.3, 6.9 Hz, 2H, 2-CH₂, rotam. a), 2.53 (t, J = 7.0 Hz, 0.6H, 2-CH₂, rotam. c), 2.48 (s, 1.2H, 2-CH₂, rotam. b), 2.46 (s, 4.5H, SCH₃, rotam. a, b, c), 2.07 (s, 0.1H, CH₃CN, solvent: acetonitrile), 1.85 (t, J = 4.6 Hz, 0.6H, 6-CHH_{bicyclohexane}, rotam. b), 1.68-1.62 (m, 1.3H, 5-CH_{bicyclohexane}, rotam. a, 6-CHH_{bicyclohexane}, rotam. c), 1.58 (ddd, J = 9.1, 4.5, 1.7 Hz, 0.6H, 5-CH_{bicyclohexane}, rotam. b), 1.44 (dd, J = 4.6, 3.6 Hz, 0.3H, 5-CH_{bicyclohexane}, rotam. c), 1.42 (t, J = 4.5 Hz, 1H,

6- $\text{CHH}_{\text{bicyclohexane}}$, rotam. a), 0.81 (ddd, $J = 8.7, 4.9, 1.6$ Hz, 1H, 6- $\text{CHH}_{\text{bicyclohexane}}$, rotam. a), 0.68 (ddd, $J = 8.5, 3.0, 1.6$ Hz, 0.6H, 6- $\text{CHH}_{\text{bicyclohexane}}$, rotam. b), 0.60 (dd, $J = 9.4, 4.7$ Hz, 0.3H, 6- $\text{CHH}_{\text{bicyclohexane}}$, rotam. c); 3- $\text{OH}_{\text{bicyclohexane}}$ could not be clearly assigned to one of the three rotamers. ^{13}C -NMR (151 MHz, $\text{DMSO}-d_6$) δ (ppm) = 173.7 (0.6C, C-1rotam. a, c), 173.7 (0.3C, C-1rotam. b), 163.8 (1C, C-2purine, rotam. a), 163.7 (0.3C, C-2purine, rotam. b), 163.6 (0.2C, C-2purine, rotam. c), 155.4 (1C, C-6purine, rotam. a), 155.4 (0.5C, C-6purine, rotam. b, c), 149.7 (1C, C-4purine, rotam. a), 149.6 (0.5C, C-4purine, rotam. b, c), 145.8 (0.6C, C-4triazole, rotam. a), 145.4 (0.1C, C-4triazole, rotam. c), 145.1 (0.4C, C-4triazole, rotam. b), 137.8 (0.3C, C-8purine, rotam. b), 137.6 (0.1C, C-8purine, rotam. c), 137.3 (1C, C-8purine, rotam. a), 122.9 (0.4C, C-5triazole, rotam. b), 122.8 (0.2C, C-5triazole, rotam. c), 122.7 (1C, C-5triazole, rotam. a), 116.5 (1C, C-5purine, rotam. a), 116.4 (0.4C, C-5purine, rotam. b), 116.4 (0.1C, C-5purine, rotam. c), 86.4 (0.4C, C-3bicyclohexane, rotam. b), 86.1 (0.1C, C-3bicyclohexane, rotam. c), 79.7 (0.5C, C-2bicyclohexane, rotam. b), 78.6 (0.1C, C-2bicyclohexane, rotam. c), 76.3 (1C, C-3bicyclohexane, rotam. a), 71.7 (1C, C-2bicyclohexane, rotam. a), 61.1 (1C, C-4bicyclohexane, rotam. a), 61.0 (0.2C, C-4bicyclohexane, rotam. c), 60.7 (0.5C, C-4bicyclohexane, rotam. b), 54.4 (0.4C, NCH_2 , rotam. b), 53.2 (0.2C, NCH_2 , rotam. c), 52.0 (1C, NCH_2 , rotam. a), 37.4 (0.1C, C-1bicyclohexane, rotam. c), 36.4 (0.4C, C-1bicyclohexane, rotam. b), 34.8 (1C, C-1bicyclohexane, rotam. a), 33.4 (0.9C, C-2rotam. b, c), 33.3 (1C, C-2 rotam. a), 30.1 (0.5C, b-C-5bicyclohexane, rotam. b), 29.1 (0.2C, C-5bicyclohexane, rotam. c), 24.2 (1C, C-5bicyclohexane, rotam. a), 20.8 (0.3C, C-3rotam. c), 20.8 (1C, C-3rotam. a), 20.7 (0.6C, C-3rotam. b), 13.7 (1C, SCH_3 , rotam. a, c), 13.6 (0.4C, SCH_3 , rotam. b), 12.9 (1C, C-6bicyclohexane, rotam. a), 12.7 (0.2C, C-6bicyclohexane, rotam. c), 12.5 (1C, C-6bicyclohexane, rotam. b). FT-IR (neat) $\tilde{\nu}$ (cm^{-1}) = 3098 (N-H), 2943 (C-Haliphatic), 1713, 1670 (C=O), 1539 (C=C_{aromat.}), 1192, 1142 (C-O).

Triethylammonium 2-[(1R,2R,3S,4R,5S)-4-(6-Amino-2-methylthio-9H-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hex-1-yl]methyl]amino-3,4-dioxocyclobut-1-en-1-olate (47)

The azide **38** (0.032 g, 0.07 mmol) was dissolved in CH_3OH (2 mL), Pd/C (10 wt %, 0.003 g, 0.003 mmol, 0.004 eq.) was added and the mixture was flushed several times with H_2 -gas. The reaction was stirred overnight at 5 bar H_2 -atmosphere. The solvent was evaporated and the residue was purified by fc ($\text{CH}_2\text{Cl}_2 : \text{CH}_3\text{OH} = 95:5 + 1\%$ triethylamine, $\varnothing = 2$ cm, $l = 20$ cm, $V = 10$ mL) to afford the amine as a colorless solid ($R_f = 0.38$, $\text{CH}_2\text{Cl}_2 : \text{CH}_3\text{OH} = 95:5 + 1\%$ triethylamine), yield 0.018 g (60 %). $\text{C}_{21}\text{H}_{30}\text{N}_6\text{O}_4\text{S}$ (462.57 g/mol). Melting point: 111.4 °C. Purity (HPLC: method D): 90 % ($t_R = 15.74$ min). Exact mass (LC-MS-ESI): m/z calculated for $\text{C}_{21}\text{H}_{31}\text{N}_6\text{O}_4\text{S} [\text{M}+\text{H}]^+$ 463.2122, found 463.2125. ^1H -NMR (600 MHz, $\text{DMSO}-d_6$) δ (ppm) = 8.45 (s, 1H, 8- $\text{CH}_{\text{purine}}$), 5.26 (d, $J = 7.1$ Hz, 1H, 2- $\text{CH}_{\text{bicyclohexane}}$), 4.93 (s, 1H, 4- $\text{CH}_{\text{bicyclohexane}}$), 4.73 (dd, $J = 7.3, 1.5$ Hz, 1H, 3- $\text{CH}_{\text{bicyclohexane}}$), 3.17 (s, 0.3H, CH_3OH , solvent: methanol), 2.95 (d, $J = 13.3$ Hz, 1H, NCHH), 2.82 (d, $J = 13.3$ Hz, 1H, NCHH), 2.59 (s, 3H, SCH_3), 1.68 (ddd, $J = 8.3, 5.2, 1.5$ Hz, 1H, 5- $\text{CH}_{\text{bicyclohexane}}$), 1.48 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.45 (s, 3H, $\text{C}(\text{CH}_3)_2$), 1.18 (s, 3H, $\text{C}(\text{CH}_3)_2$), 0.94-0.90 (m, 2H, 6- $\text{CH}_2_{\text{bicyclohexane}}$). ^{13}C -NMR (151 MHz, $\text{DMSO}-d_6$) δ (ppm) = 163.7 (1C, C-2purine), 152.0 (1C, C-4purine), 150.9 (1C, C=O), 149.6 (1C, C-6purine), 141.5 (1C, C-8purine), 120.7 (1C, C-5purine), 111.3 (1C, $\text{C}(\text{CH}_3)_2$), 88.3 (1C, C-3bicyclohexane), 82.1 (1C, C-2bicyclohexane), 80.2 (1C, $\text{C}(\text{CH}_3)_3$), 59.2 (1C, C-4bicyclohexane), 43.6 (1C, NCH_2), 38.4 (1C, C-1bicyclohexane), 29.7 (1C, C-5bicyclohexane), 27.9 (3C, $\text{C}(\text{CH}_3)_3$), 25.9 (1C, $\text{C}(\text{CH}_3)_2$), 24.2 (1C, $\text{C}(\text{CH}_3)_2$), 14.0 (1C, SCH_3), 13.3 (1C, C-6bicyclohexane). FT-IR (neat) $\tilde{\nu}$ (cm^{-1}) = 2978, 2928 (C-Haliphatic), 1751, 1721 (C=O), 1605, 1574 (C=C_{aromat.}), 1142, 1053 (C-O).

The amine (0.105 g, 0.23 mmol) was dissolved in CH_2Cl_2 (2 mL). Dimethyl squarate (0.104 g, 0.73 mmol, 3.2 eq.) and triethylamine (0.20 mL, 1.44 mmol, 6.4 eq.) were added and the mixture was stirred at rt overnight. The solvent was evaporated and the residue was purified by fc ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 5:95 \rightarrow 100:0$, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, $V = 20$ mL) to afford the squaramide as a colorless solid ($R_f = 0.33$, ethyl acetate = 100 %), yield 0.087 g (67 %). $\text{C}_{26}\text{H}_{32}\text{N}_6\text{O}_7\text{S}$ (572.64 g/mol). Melting point: 148.4 °C. Purity (HPLC: method B): 90 % ($t_R = 13.02$ min). Exact mass (LC-MS-ESI): m/z calculated for $\text{C}_{26}\text{H}_{33}\text{N}_6\text{O}_7\text{S} [\text{M}+\text{H}]^+$ 573.2126, found 573.2130. The compound shows two different rotamers a and b in the NMR spectra in a ratio of approximately 5:4. ^1H -NMR (600 MHz, $\text{DMSO}-d_6$) δ (ppm) = 10.09 (s, 1H, $\text{NH}_{\text{purine}}$, rotam. a/b), 8.94 (s, 0.5H, $\text{NH}_{\text{squaramide}}$, rotam. a), 8.74 (s, 0.4H, $\text{NH}_{\text{squaramide}}$, rotam. b), 8.26 (s, 1H, 8- $\text{CH}_{\text{purine}}$, rotam. a/b), 5.25 (t, $J = 6.6$ Hz, 1H, 2- $\text{CH}_{\text{bicyclohexane}}$, rotam. a/b), 4.93 (s, 1H, 4- $\text{CH}_{\text{bicyclohexane}}$, rotam. a/b), 4.88 (d, $J = 7.1$ Hz, 0.4H, 3- $\text{CH}_{\text{bicyclohexane}}$, rotam. b), 4.83 (d, $J = 7.2$ Hz, 0.5H, 3- $\text{CH}_{\text{bicyclohexane}}$, rotam. a), 4.29 (s, 1.2H, OCH_3 , rotam. b), 4.24 (s, 1.5H, OCH_3 , rotam. a), 3.77 (q, $J = 14.2$ Hz, 0.9H, NCH_2 , rotam. b), 3.69 (d, $J = 13.2$ Hz, 1H, NCHH , rotam. a), 3.50 (d,

$J = 13.2$ Hz, 1H, NCHH_{rotam. a}), 3.17 (s, 0.2H, CH₃OH, solvent: methanol), 2.58 (d, $J = 4.0$ Hz, 3H, SCH₃, rotam. a/b), 1.77 (dt, $J = 13.0, 6.7$ Hz, 1H, 5-CH_{bicyclohexane}, rotam. a/b), 1.48 (s, 9H, C(CH₃)₃, rotam. a/b), 1.45 (s, 3H, C(CH₃)₂, rotam. a/b), 1.18 (s, 3H, C(CH₃)₂, rotam. a/b), 0.98 (d, $J = 7.0$ Hz, 1H, 6-CH₂ bicyclohexane, rotam. a/b). ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 189.3 (1C, C-1squaramide, rotam. a/b), 182.5 (0.3C, C-2squaramide, rotam. a), 182.1 (0.3C, C-2squaramide, rotam. b), 177.7 (0.3C, C-4squaramide, rotam. b), 176.7 (0.4C, C-4squaramide, rotam. a), 172.4 (0.4C, C-3squaramide, rotam. a), 171.9 (0.3C, C-3squaramide, rotam. a), 163.8 (1C, C-2purine, rotam. a/b), 152.0 (1C, C-4purine, rotam. a/b), 150.8 (1C, C-N_{carbonyl}, rotam. a/b), 149.6 (1C, C-6purine, rotam. a/b), 141.4 (1C, C-8purine, rotam. a/b), 120.8 (0.2C, C-5purine, rotam. b), 120.7 (0.3C, C-5purine, rotam. a), 111.4 (1C, C(CH₃)₂, rotam. a/b), 88.2 (0.6C, C-3bicyclohexane, rotam. a), 88.0 (0.5C, C-3bicyclohexane, rotam. b), 82.4 (0.8C, C-2bicyclohexane, rotam. a), 82.1 (0.6C, C-2bicyclohexane, rotam. b), 80.2 (1C, C(CH₃)₃, rotam. a/b), 60.1 (0.6C, OCH₃, rotam. a), 60.0 (0.5C, OCH₃, rotam. b), 59.3 (1C, C-4bicyclohexane, rotam. a/b), 46.7 (0.7C, NCH₂, rotam. a), 46.1 (0.5C, NCH₂, rotam. b), 37.5 (0.4C, C-1bicyclohexane, rotam. b), 37.2 (0.5C, C-1bicyclohexane, rotam. a), 30.3 (1C, C-5bicyclohexane, rotam. a/b), 27.9 (3C, C(CH₃)₃, rotam. a/b), 25.9 (1C, C(CH₃)₂, rotam. a/b), 24.1 (1C, C(CH₃)₂, rotam. a/b), 14.0 (1C, SCH₃, rotam. a/b), 13.2 (0.5C, C-6bicyclohexane, rotam. b), 13.0 (0.6C, C-6bicyclohexane, rotam. a). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3202 (N-H), 2986, 2936 (C-H_{aliphatic}), 1802, 1755, 1709 (C=O), 1601 (C=C_{aromat.}), 1138, 1049 (C-O).

The squaramide (0.085 g, 0.15 mmol) was dissolved in CH₃OH (3.2 mL), trifluoroacetic acid (0.40 mL) and H₂O (0.40 mL) were added. The mixture was stirred at rt for 5 d and was then heated to 70° C for 1 d. The solvent was evaporated and the residue was purified by semi-preparative HPLC (method G) to afford the product **47** as a colorless solid, yield 0.021 g (27 %). C₂₃H₃₃N₇O₅S (519.62 g/mol). Purity (HPLC: method D): 99 % (t_R = 6.26 min). Exact mass (LC-MS-ESI): m/z calculated for C₁₇H₁₇N₆O₅S [M-C₆H₁₆N]⁻ 417.0987, found 417.0984. The compound **47** shows three different rotamers a, b and c in the NMR spectra in a ratio of approximately 10:2:1. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 9.36 (s, 0.9H, NH_{triethylammonium}), 7.94 (s, 1H, 8-CH_{purine}, rotam. a), 7.90 (s, 0.2H, 8-CH_{purine}, rotam. b), 7.78 (s, 0.1H, 8-CH_{purine}, rotam. c), 7.40 (t, $J = 6.6$ Hz, 1H, NH_{squaramide}, rotam. a), 7.36 (s, 0.4H, NH_{squaramide}, rotam. b, c), 5.34 (d, $J = 7.7$ Hz, 1H, 2-CH_{bicyclohexane}, rotam. b), 5.16 (s, 0.4H, 3-OH_{bicyclohexane}, rotam. b, c), 5.02 (s, 1H, 3-OH_{bicyclohexane}, rotam. a), 4.85 (s, 0.2H, 4-CH_{bicyclohexane}, rotam. b), 4.72 (d, $J = 7.1$ Hz, 0.1H, 2-CH_{bicyclohexane}, rotam. c), 4.67 (s, 0.1H, 4-CH_{bicyclohexane}, rotam. c), 4.63 (d, $J = 8.1$ Hz, 0.2H, 3-CH_{bicyclohexane}, rotam. b), 4.61 (d, $J = 1.6$ Hz, 1H, 4-CH_{bicyclohexane}, rotam. a), 4.44 (d, $J = 6.3$ Hz, 1H, 2-CH_{bicyclohexane}, rotam. a), 3.99 (dd, $J = 14.2, 6.8$ Hz, 1H, NCHH_{rotam. a}), 3.89-3.80 (m, 0.3H, 3-CH_{bicyclohexane}, rotam. c, NCHH_{rotam. c}), 3.80-3.72 (m, 1.3H, NCHH_{rotam. b}, 3-CH_{bicyclohexane}, rotam. a), 3.69 (dd, $J = 14.1, 6.1$ Hz, 1H, NCHH_{rotam. b}), 3.51-3.47 (m, 0.2H, NCHH_{rotam. c}), 3.30 (dd, $J = 14.3, 6.2$ Hz, 1H, NCHH_{rotam. a}), 3.09 (q, $J = 7.3$ Hz, 6.6H, CH₂, triethylammonium), 2.49 (s, 0.6H, SCH₃, rotam. b), 2.48 (s, 0.2H, SCH₃, rotam. c), 2.47 (s, 3H, SCH₃, rotam. a), 1.84 (ddd, $J = 9.0, 4.2, 1.5$ Hz, 0.2H, 5-CH_{bicyclohexane}, rotam. b), 1.58 (dd, $J = 8.3, 3.8$ Hz, 1H, 5-CH_{bicyclohexane}, rotam. a), 1.52 (s, 0.1H, 6-CHH_{bicyclohexane}, rotam. c), 1.48 (dd, $J = 8.4, 4.3$ Hz, 0.1H, 5-CH_{bicyclohexane}, rotam. c), 1.34 (t, $J = 4.3$ Hz, 1H, 6-CHH_{bicyclohexane}, rotam. a), 1.16 (t, $J = 7.3$ Hz, 9.9H, 3-CH₃, triethylammonium), 1.09-1.06 (m, 0.3H, 6-CHH_{bicyclohexane}, rotam. c), 0.66 (ddd, $J = 8.5, 4.6, 1.5$ Hz, 1H, 6-CHH_{bicyclohexane}, rotam. a), 0.65-0.62 (m, 0.2H, 6-CHH_{bicyclohexane}, rotam. b), 0.57 (dd, $J = 9.0, 4.5$ Hz, 0.1H, 6-CHH_{bicyclohexane}, rotam. c). ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 198.1 (0.5C, C-4squaramide, rotam. a, b), 188.7 (2C, C-1squaramide, rotam. a, C-3squaramide, rotam. a), 188.4 (0.4C, C-1squaramide, rotam. b, C-3squaramide, rotam. b), 181.5 (1C, C-2squaramide, rotam. a), 181.4 (0.3C, C-2squaramide, rotam. b), 164.1 (0.1C, C-2purine, rotam. b), 163.7 (1C, C-2purine, rotam. a), 155.4 (1C, C-6purine, rotam. a), 155.4 (0.2C, C-6purine, rotam. b), 149.8 (1C, C-4purine, rotam. a), 149.5 (0.2C, C-4purine, rotam. b), 137.5 (0.1C, C-8purine, rotam. b), 137.3 (1C, C-8purine, rotam. a), 116.5 (0.1C, C-5purine, rotam. b), 116.5 (1C, C-5purine, rotam. a), 87.7 (0.2C, C-3bicyclohexane, rotam. b), 80.8 (0.2C, C-2bicyclohexane, rotam. b), 76.7 (1C, C-3bicyclohexane, rotam. a), 71.0 (1C, C-2bicyclohexane, rotam. a), 60.6 (1C, C-4bicyclohexane, rotam. a), 60.6 (0.3C, C-4bicyclohexane, rotam. b), 45.7 (5.0C, CH₂, triethylammonium), 44.7 (1C, NCH₂, rotam. a), 44.6 (0.2C, NCH₂, rotam. b), 35.8 (1C, C-1bicyclohexane, rotam. a), 27.5 (0.2C, C-5bicyclohexane, rotam. b), 22.5 (C, C-5bicyclohexane, rotam. a), 13.7 (0.2C, SCH₃, rotam. b), 13.6 (1C, SCH₃, rotam. a), 11.8 (0.2C, C-6bicyclohexane, rotam. b), 11.7 (1C, C-6bicyclohexane, rotam. a), 8.6 (4.6C, CH₃, triethylammonium); The signal for C-1bicyclohexane, rotam. b is located under the DMSO-*d*₆ signal and therefore only visible in 2D spectra. The resolution was too low to identify the ¹³C-signals for rotamer c, therefore only rotamer a and b are described here. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3321 (O-H), 3190 (N-H), 2924 (C-H_{aliphatic}), 1786 (C=O), 1528 (C=C_{aromat.}), 1065 (C-O).

Triethylammonium 2-(*N*-[(1*R*,2*R*,3*S*,4*R*,5*S*)-4-(6-amino-2-methylthio-9*H*-purin-9-yl)-2,3-dihydroxybicyclo[3.1.0]hex-1-yl]methyl)sulfamoyl)acetate (**48**)

The azide **38** (0.032 g, 0.07 mmol) was dissolved in CH₃OH (2 mL), Pd/C (10 wt %, 0.003 g, 0.003 mmol, 0.004 eq.) was added and the mixture was flushed several times with H₂-gas. The reaction was stirred overnight at 5 bar H₂-atmosphere. The solvent was evaporated and the residue was purified by fc (CH₂Cl₂ : CH₃OH = 95:5 + 1 % triethylamine, Ø = 2 cm, l = 20 cm, V = 10 mL) to afford the amine as a colorless solid (R_f = 0.38, CH₂Cl₂ : CH₃OH = 95:5 + 1 % triethylamine), yield 0.018 g (60 %).

The amine (0.16 g, 0.35 mmol) was dissolved in CH₂Cl₂ (8 mL), methyl-2-(chlorosulfonyl)acetate (0.068 g, 0.39 mmol, 1.1 eq.), triethylamine (0.10 mL, 0.72 mmol, 2 eq.) and a catalytical amount of DMAP (~5 mol %) were added. The mixture was stirred at rt overnight. The solvent was evaporated and the residue was purified by fc (CH₃CN : H₂O = 5:95 → 65:35, 12 mL/min, Biotage® SNAP Ultra C18, 12 g, V = 20 mL) to afford the sulfonamide as a colorless solid (R_f = 0.49, ethyl acetate = 100 %), yield 0.103 g (50 %). C₂₄H₃₄N₆O₈S₂ (598.69 g/mol). Purity (HPLC: method B): 90 % (t_R = 14.49 min). Exact mass (LC-MS-ESI): m/z calculated for C₂₄H₃₅N₆O₈S [M+H]⁺ 599.1952, found 599.1952. ¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 10.09 (s, 1H, NH_{purine}), 8.33 (s, 1H, 8-CH_{purine}), 7.76 (t, J = 6.4 Hz, 1H, NH_{sulfonamide}), 5.75 (s, 0.2H, CH₂Cl₂, solvent: dichloromethane), 5.20 (dd, J = 7.2, 1.2 Hz, 1H, 2-CH_{bicyclohexane}), 4.93 (s, 1H, 4-CH_{bicyclohexane}), 4.75 (dd, J = 7.3, 1.3 Hz, 1H, 3-CH_{bicyclohexane}), 4.23 (dd, J = 14.2, 1.6 Hz, 2H, 2-CH₂), 3.69 (s, 1H, OCH₃), 3.34-3.28 (m, 2H, NCH₂), 2.59 (s, 3H, SCH₃), 1.71 (ddd, J = 9.0, 4.7, 1.5 Hz, 1H, 5-CH_{bicyclohexane}), 1.48 (s, 9H, C(CH₃)₃), 1.46 (s, 3H, C(CH₃)₂), 1.21-1.15 (m, 3H, C(CH₃)₂), 1.03-0.95 (m, 2H, 6-CH₂ bicyclohexane). ¹³C-NMR (101 MHz, DMSO-*d*₆) δ (ppm) = 164.0 (1C, C-1), 163.8 (1C, C-2_{purine}), 152.0 (1C, C-4_{purine}), 150.8 (1C, C-N_{carbonyl}), 149.6 (1C, C-6_{purine}), 141.1 (1C, C-8_{purine}), 120.7 (1C, C-5_{purine}), 111.4 (1C, C(CH₃)₂), 88.2 (1C, C-3_{bicyclohexane}), 81.9 (1C, C-2_{bicyclohexane}), 80.2 (1C, C(CH₃)₃), 58.9 (1C, C-4_{bicyclohexane}), 56.1 (1C, C-2), 52.5 (1C, OCH₃), 45.5 (1C, NCH₂), 36.8 (1C, C-1_{bicyclohexane}), 29.9 (1C, C-5_{bicyclohexane}), 27.8 (3C, C(CH₃)₃), 25.8 (1C, C(CH₃)₂), 24.2 (1C, C(CH₃)₂), 14.0 (1C, SCH₃), 13.4 (1C, C-6_{bicyclohexane}). FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3283 (N-H), 2982, 2932 (C-H_{aliphatic}), 1744 (C=O), 1605, 1578 (C=C_{aromat.}), 1327, 1207 (S=O), 1138, 1053 (C-O).

The sulfonamide (0.090 g, 0.15 mmol) was dissolved in CH₃OH (3.2 mL), trifluoroacetic acid (0.40 mL) and H₂O (0.40 mL) were added. The mixture was stirred at 70° C overnight. The solvent was evaporated, and the residue was dissolved in CH₃CN (3.2 mL), 2 M NaOH-solution and H₂O (0.40 mL) were added. The mixture was stirred at 70° C overnight. The solvent was evaporated, and the residue was purified by semi-preparative HPLC (method E) to afford the product **48** as a colorless solid, yield 0.056 g (69 %). C₂₁H₃₅N₇O₆S₂ (545.21 g/mol). Purity (HPLC: method D): 99 % (t_R = 9.86 min). Exact mass (LC-MS-ESI): m/z calculated for C₁₅H₁₉N₆O₆S₂ [M-C₆H₁₆N] 443.0813, found 443.0826. The compound **48** shows two different rotamers a and b in the NMR spectra in a ratio of approximately 2:1. ¹H-NMR (600 MHz, DMSO-*d*₆) δ (ppm) = 8.10 (s, 1H, 8-CH_{purine}, rotam. a), 7.97 (s, 0.5H, 8-CH_{purine}, rotam. b), 7.29 (s, 3H, NH₂, rotam. a, NH_{rotam. a}), 7.25 (s, 1.5H, NH₂, rotam. b, NH_{rotam. b}), 5.12 (s, 1H, 3-OH_{bicyclohexane}, rotam. a), 4.78 (s, 0.3H, 2-CH_{bicyclohexane}, rotam. b), 4.70 (s, 0.5H, 4-CH_{bicyclohexane}, rotam. b), 4.61 (d, J = 1.9 Hz, 1H, 4-CH_{bicyclohexane}, rotam. a), 4.51 (dd, J = 6.5, 1.4 Hz, 1H, 2-CH_{bicyclohexane}, rotam. a), 4.01 (s, 0.3H, 3-CH_{bicyclohexane}, rotam. b), 3.91 (s, 0.5H, 2-CH_{rotam. b}), 3.84 (dt, J = 6.7, 1.6 Hz, 1H, 3-CH_{bicyclohexane}, rotam. a), 3.73 (dd, J = 14.6, 5.1 Hz, 2H, 2-CH₂ rotam. a, 2-CH_{rotam. b}), 3.39 (d, J = 13.5 Hz, 1H, NCH_{rotam. a}), 3.25 (s, 0.5H, NCH_{rotam. b}), 3.13 (s, 0.5H, NCH_{rotam. b}), 3.07 (d, J = 13.5 Hz, 1H, NCH_{rotam. a}), 2.93 (q, J = 7.5 Hz, 7.8 Hz, CH₂, triethylammonium), 2.48 (s, 3H, SCH₃, rotam. a), 1.54 (t, J = 4.6 Hz, 0.5H, 6-CH_{bicyclohexane}, rotam. b), 1.48 (dd, J = 8.5, 3.8 Hz, 1H, 5-CH_{bicyclohexane}, rotam. a), 1.33 (dd, J = 8.7, 4.8 Hz, 0.5H, 5-CH_{bicyclohexane}, rotam. b), 1.30 (t, J = 4.4 Hz, 1H, 6-CH_{bicyclohexane}, rotam. a), 1.11 (t, J = 7.3 Hz, 12.3 Hz, CH₃, triethylammonium), 0.72 (ddd, J = 8.6, 4.7, 1.5 Hz, 1H, 6-CH_{bicyclohexane}, rotam. a), 0.62 (dd, J = 9.6, 4.8 Hz, 0.5H, 6-CH_{bicyclohexane}, rotam. b); The signal for SCH₃, rotam. b is located under the DMSO-*d*₆ signal and therefore only visible in 2D spectra. ¹³C-NMR (151 MHz, DMSO-*d*₆) δ (ppm) = 165.0 (0.7C, C-1_{rotam. a, b}), 163.7 (1C, C-2_{purine}, rotam. a), 163.6 (0.4C, C-2_{purine}, rotam. b), 155.4 (1C, C-6_{purine}, rotam. a), 155.4 (0.4C, C-6_{purine}, rotam. b), 149.8 (1C, C-4_{purine}, rotam. a), 149.6 (0.4C, C-4_{purine}, rotam. b), 138.1 (0.2C, C-8_{purine}, rotam. b), 137.9 (1C, C-8_{purine}, rotam. a), 116.5 (0.8C, C-5_{purine}, rotam. a, b), 76.9 (1C, C-3_{bicyclohexane}, rotam. a), 71.6 (1C, C-2_{bicyclohexane},

rotam. a), 61.0 (1C, C-4bicyclohexane, rotam. a), 57.4 (1C, C-2rotam. a), 45.7 (1C, NCH₂, rotam. a), 45.3 (6.3C, CH₂, triethylammonium), 34.5 (1C, C-1bicyclohexane, rotam. a), 27.6 (0.4C, C-5bicyclohexane, rotam. b), 23.2 (1C, C-5bicyclohexane, rotam. a), 13.7 (1.3C, SCH₃, rotam. a, b), 12.6 (0.4C, C-6bicyclohexane, rotam. b), 12.5 (1C, C-6bicyclohexane, rotam. a), 9.0 (5.6C, CH₃, triethylammonium); The resolution was too low to identify the ¹³C-signals for rotamer b, therefore only those signals of rotamer b that are visible in the ¹³C-NMR spectrum are described here. FT-IR (neat) $\tilde{\nu}$ (cm⁻¹) = 3306 (O-H), 3132 (N-H), 2982, 2928 (C-H_{aliphatic}), 1612 (C=O), 1582 (C=C_{aromat.}), 1300 (S=O), 1150, 1119 (C-O), 1065 (S=O).

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Scheme S1: Synthesis of (N)-methanocarba alcohol 4. Synthetic procedures for the preparation of compound 4.

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