Supporting information

Structure-Based Design, Synthesis by Click Chemistry and *in Vivo* Activity of Highly Selective A_3 Adenosine Receptor Agonists

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Molecular Modeling Methods

A_3AR 3D Structure

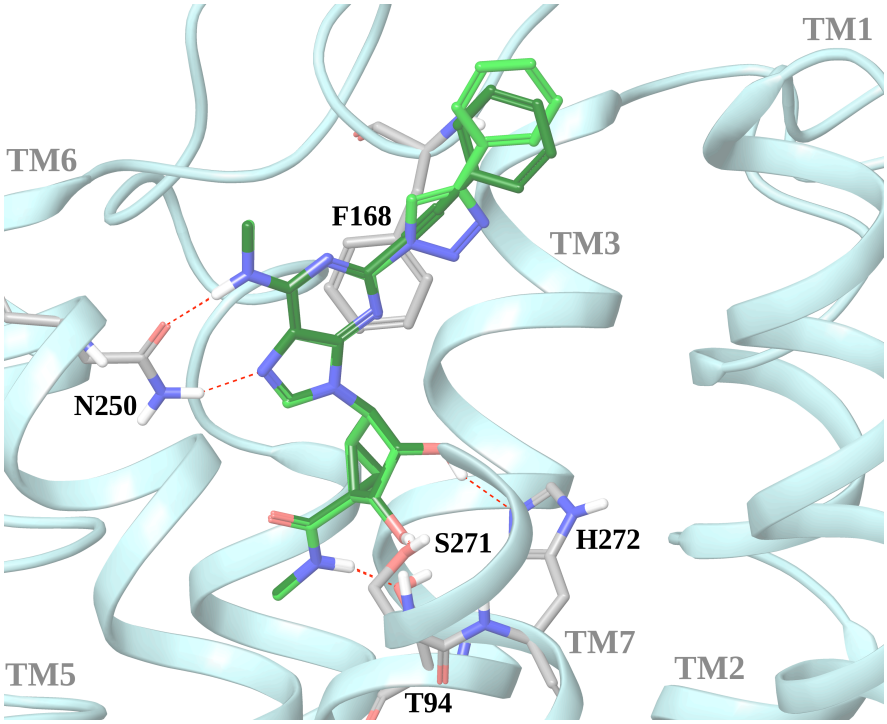
To perform docking studies, we used a previously reported[1,2] homology model of the hA_3AR built, based on a hybrid template, using the alignment and the homology modeling tools implemented in the MOE suite.[3] To build this model, an agonist-bound hA_{2A}AR crystal structure (PDB ID: 3QAK)[4] was used as a template for the entire A_3AR structure except for the extracellular terminus of TM2 and EL1. The X-ray structure of the β_2 adrenergic receptor in complex with the Gs protein (PDB ID: 3SN6),[5] after superimposition with the hA_{2A}AR crystal structure, was used as template to build the extracellular terminus of TM2. No structural template was used for the modeling of EL1. Methodological details have been previously reported.[1,2]

Molecular Docking

Structures of potential A_3AR ligands were built and prepared for docking using the Builder and the LigPrep tools implemented in the Schrödinger suite.[6] In particular, possible ionization states at pH 7±1 were generated using Epik, tautomers were generated and geometries were optimized using the OPLS_2005 force field.

Molecular docking of ligands at the hA_3AR model was performed by means of the Glide[7] package from the Schrödinger suite.[6] In particular, a Glide Grid was centered on the centroid of some key residues of the binding pocket of adenosine receptors, namely Phe (EL2), Asn (6.55), Trp (6.48) and His (7.43). The Glide Grid was built using an inner box (ligand diameter midpoint box) of 10 Å x 10 Å x 10 Å and an outer box (box within which all the ligand atoms must be contained) that extended 20 Å in each direction from the inner one. Docking of ligands was performed in the rigid binding site using the XP (extra precision) procedure. The top scoring docking conformations for each ligand were subjected to visual inspection and analysis of protein-ligand interactions to select the proposed binding conformations in agreement with the experimental data.

Figure S1. Comparison of the docking of the phenylethynyl structure **3a** (dark green) with the phenyl-triazolyl structure **3f** (light green) at the hybrid model of the hA_3AR. The positions of the terminal phenyl rings overlap to a large degree.



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[1] Tosh, D. K., Deflorian, F., Phan, K., Gao, Z. G., Wan, T. C., Gizewski, E., Auchampach, J. A., Jacobson, K. A. *J. Med. Chem.* 2012, **55**, 4847.

[2] Paoletta, S., Tosh, D. K., Finley, A., Gizewski, E., Moss, S. M., Gao, Z. G., Auchampach, J. A., Salvemini, D., Jacobson, K. A. *J. Med. Chem.* 2013, **56**, 5949.

[3] Molecular Operating Environment (MOE), version 2012.10, Chemical Computing Group Inc., 1255 University St., Suite 1600, Montreal, QC, H3B 3X3 (Canada).

[4] Xu, F., Wu, H., Katritch, V., Han, G. W., Jacobson, K. A., Gao, Z. G., Cherezov, V., Stevens, R. *Science* 2011, **332**, 322.

[5] Rasmussen, S. G. F., DeVree, B. T., Zou, Y., Kruse, A. C., Chung, K. Y., Kobilka, T. S., Thian, F. S., Chae, P. S., Pardon, E., Calinski, D., Mathiesen, J. M., Shah, S. T. A., Lyons, J. A., Caffrey, M., Gellman, S. H., Steyaert, J., Skiniotis, G., Weis, W. I., Sunahara, R. K., Kobilka, B. K. *Nature* 2011, **477**, 549.

[6] Schrödinger Suite 2014. Schrödinger, LLC, New York, NY.

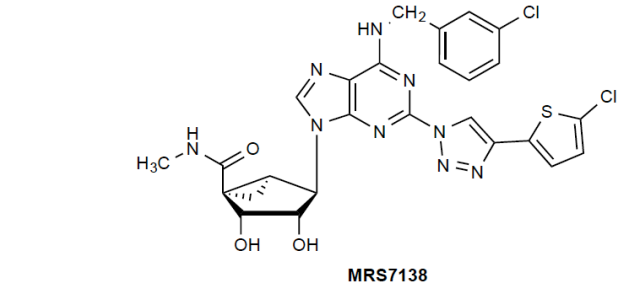
[7] Friesner, R. A., Banks, J. L., Murphy, R. B., Halgren, T. A., Klicic, J. J., Mainz, D. T., Repasky, M. P., Knoll, E. H., Shaw, D. E., Shelley, M., Perry, J. K., Francis, P., Shenkin, P. S. *J. Med. Chem.* 2004, **47**, 1739.

CCI calculations and results for Compound 17 at two doses.

All *in vivo* experiments were performed by methods described[1] and in accordance with the International Association for the Study of Pain and the National Institutes of Health guidelines on laboratory animal welfare and the recommendations by Saint Louis University Institutional Animal Care and Use Committee. All experiments were conducted with the experimenters blinded to treatment conditions.

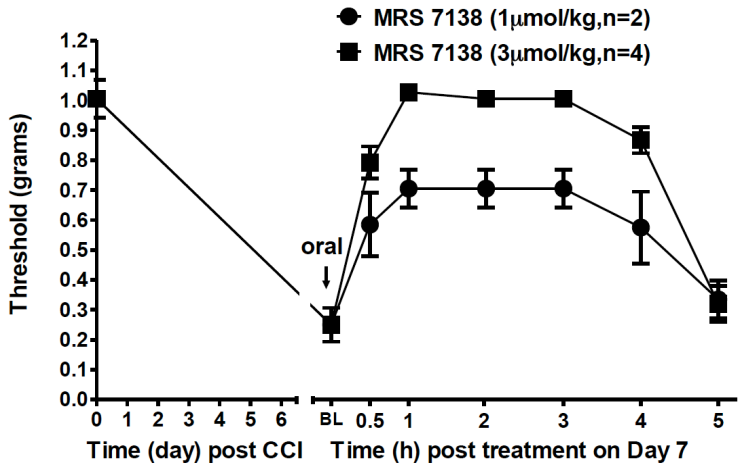
[1] Tosh, D. K., Finley, A., Paoletta, S., Moss, S. M., Gao, Z. G., Gizewski, E., Auchampach, J., Salvemini, D., Jacobson, K. A. *J. Med. Chem.* 2014, **57**, 9901.

Figure S2. Structure of MRS7138 **17** and *in vivo* activity at two doses.



MRS7138

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(6-((3-chlorobenzyl)amino)-2-(4-(5-chlorothiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide



%Analgesic effect was calculated by the following equation:

%Effect = [PWT (g) t_h − PWT (g) $t_{D7/BL}$] / [PWT (g) t_{D0} − PWT (g) $t_{D7/BL}$] × 100;

where, PWT (g) t_h = PWT (g) at 1 h (max) or 3 h post treatment; PWT (g) $t_{D7/BL}$= PWT (g) at D7/BL; and PWT (g) t_{D0} = PWT (g) at D0.

Statistical Analysis. Data are expressed as mean ± SEM for N animals. Differences in behavioral data from the full time course studies were analyzed by two-way ANOVA with Bonferroni comparisons using GraphPad Prism version 5.04 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com". Significant differences were defined at $P<0.05$.

Study of the decomposition of ferrocene compounds **4** and **20**.

Experimental procedures for timed decomposition of ethynyl ferrocene derivative 4.

A 25 nanomolar solution of ethynyl ferrocene derivative **4** was prepared in a water/HCl solution at pH = 1.6, and 10 μL of this solution was immediately direct injected into the ESI/TOF/MS instrument. The time = 0 spectrum is shown in Figure S1. After 30 min. the spectrum shown in Figure S2 was recorded. Note the complete disappearance of the ethynyl ferrocene derivative 4 after 30 min. The half-life of the ethynyl ferrocene derivative **4** was 5 min.

For triazole ferrocene derivative **20**, a 25 nanomolar solution was prepared in water/HCl at pH = 1.6, and 10 μL of this solution was immediately direct injected into the ESI/TOF/MS instrument. The time = 0 spectrum is shown in Figure S3. After 60 min. the spectrum shown in Figure S4 was recorded. There was no observable decomposition of the triazole ferrocene derivative **20** after 60 min.

The mass spectrometer was a Waters (Waltham, MA) ESI/TOF LCT Premiere operated at 10K resolution in the positive ion mode.

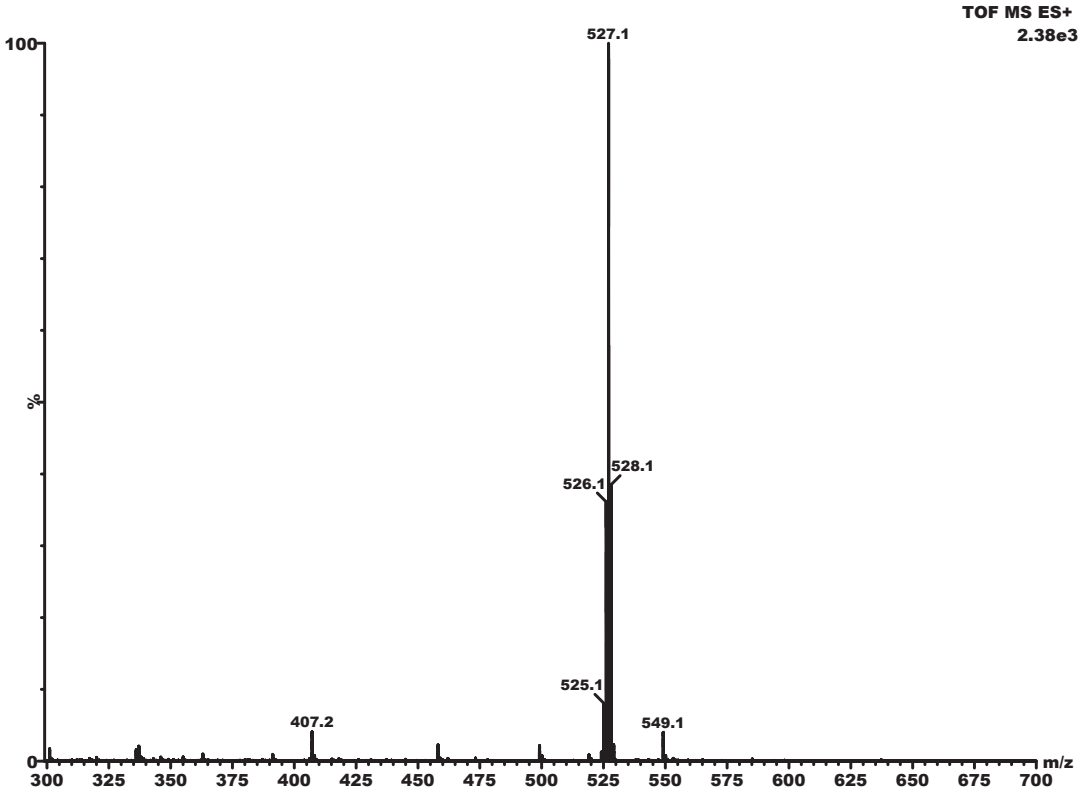


Figure S3. Positive ion ESI mass spectrum of ethynyl ferrocene derivative **4** immediately after preparation (time = 0) in a water solution at pH = 1.6.

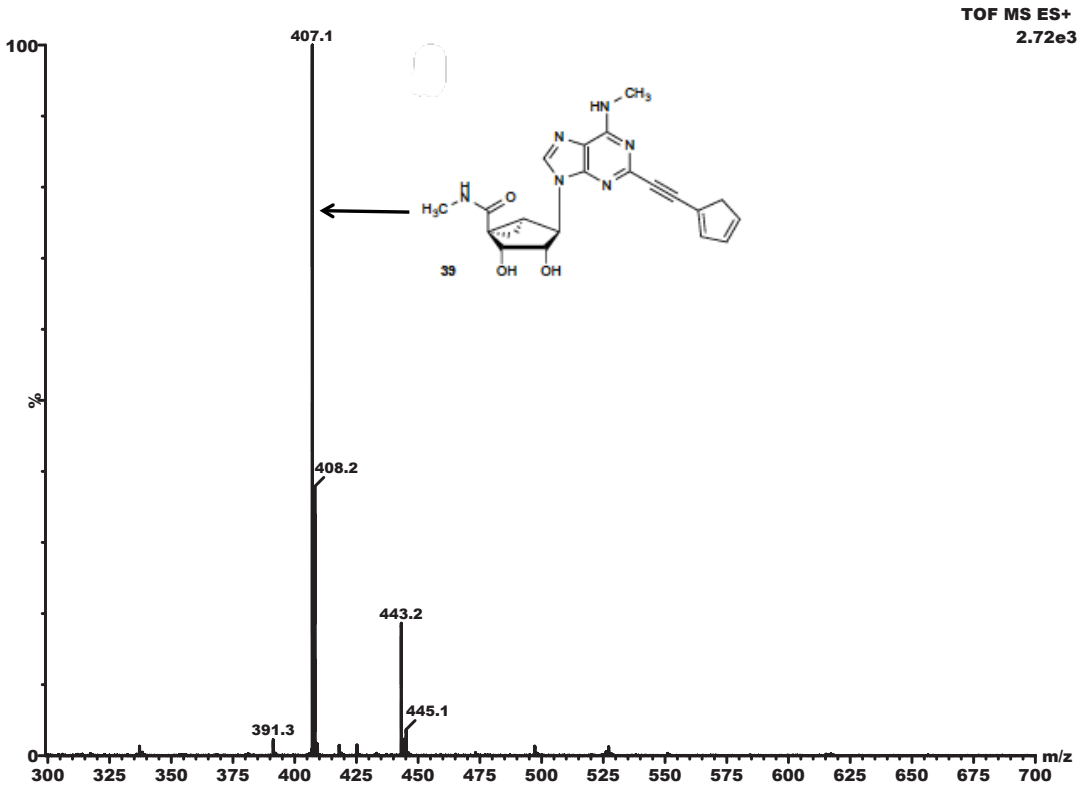


Figure S4. Positive ion ESI mass spectrum of ethynyl ferrocene derivative **4** after 30 minutes (time = 30) in a water solution at pH = 1.6.

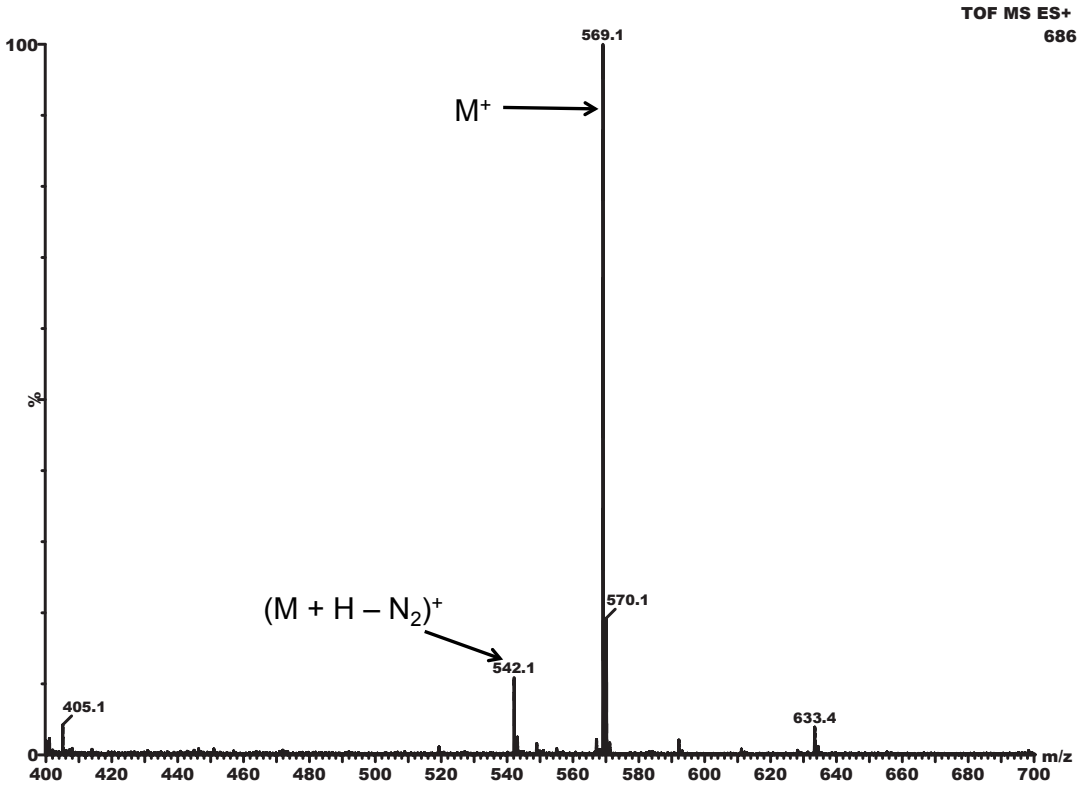


Figure S5. Positive ion ESI mass spectrum of triazole ferrocene derivative **20** at time = 0 in pH 1.6 water.

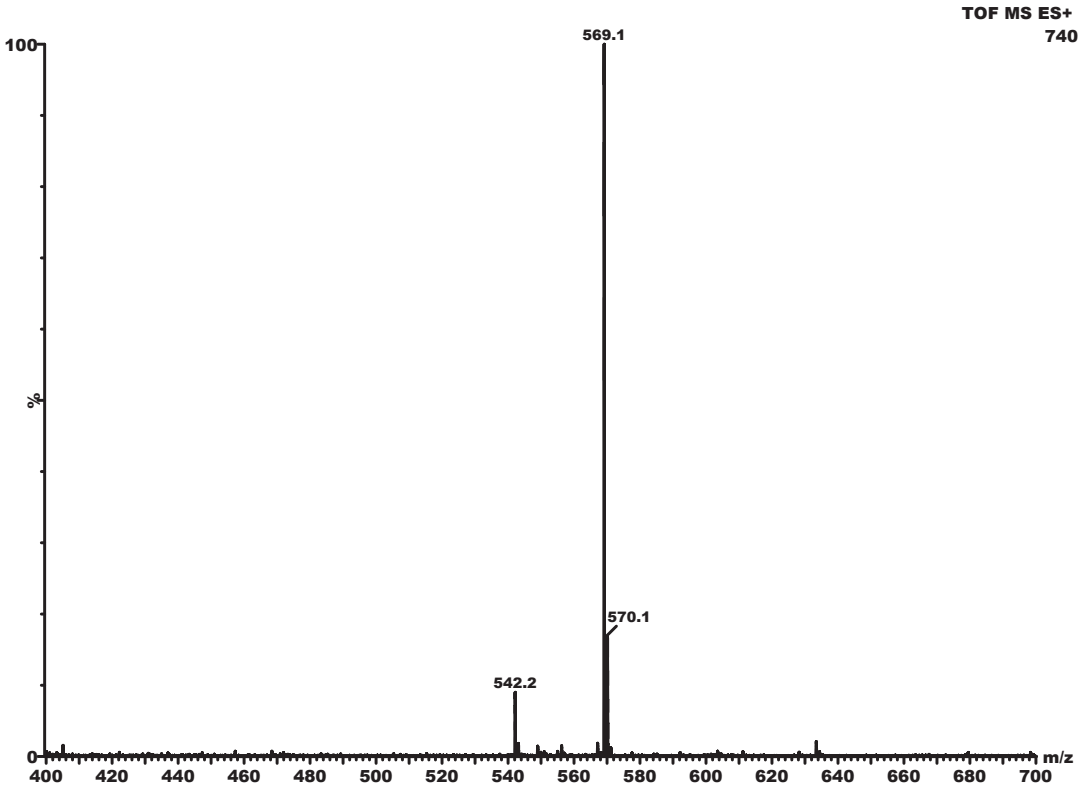


Figure S6. Positive ion ESI mass spectrum of triazole ferrocene derivative **20** at time = 60min. in pH 1.6 water.

Off-target interactions for compounds 12 and 14

Off-target interactions (from PDSP, protocols are available at https://pdspdb.unc.edu/html/tutorials/UNC-CH%20Protocol%20Book.pdf). Also, see Paoletta et al.[1] for a systematic modeling of off-target effects in this chemical series. Data for compounds **1**, **2** and **4** are reported there. Compound **4** has significant off-target interactions.

No significant interactions (<50% inhibition at 10 μM) for **12** and **14** were found at the following sites: $5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, $5HT_{1E}$, $5HT_{5A}$, α_{1A}, β_1, β_2, β_3, BZP rat brain site, D_1, D_3, D_4, D_5, delta opioid receptor (DOR), $GABA_A$, H_2, H_3, H_4, kappa opioid receptor (KOR), M_2, M_5, mu opioid receptor (MOR). Furthermore, there was no significant interaction at serotonin or norepinephrine transporters for any of the compounds listed below.

The only interactions noted for the present set of two newly synthesized compounds at IC_{50} <10 μM were with H_2 histamine (**12**, 50% inhibition at 10 μM) and sigma2 receptors (**12**, 50%; **14**, 62%) and the peripheral benzodiazepine receptor (TSPO, **14**, 54%). The interactions with neurotransmitter transport proteins will be reported elsewhere.

Key: K_i <1.0 μM +++; 1-10 μM ++; >10 μM +.
For comparison, off-target interactions of earlier reported compounds are listed here.[1,2]

1, MRS5698 (PDSP 26565)
α_{2A} ++ (4.8 μM)
α_{2B} ++ (2.9 μM)
α_{2C} ++ (2.0 μM)
β_3 ++ (1.5 μM)
$5HT_{1A}$ ++ (7.6 μM)
$5HT_{2B}$ ++ (2.6 μM)
$5HT_{2C}$ ++ (5.8 μM)
H_4 ++ (9.4 μM)
M_2 ++ (7.7 μM)
DOR ++ (2.4 μM)
σ_2 +++ (0.91 μM)
PBR +++ (0.34 μM)

2, MRS5980 (PDSP 30519)
No significant interactions (>50% at 10 μM) at all alpha, beta, histamine, 5HT, muscarinic, dopamine, BZP rat brain, GABA-A, KOR, DOR, MOR and BZP receptors.
However PBR (0.859 μM), Sigma-1 (Ki 1.41 μM), Sigma-2 (Ki 0.625 μM) receptors showed 60 – 70% inhibition at 10 μM.

4, MRS5979 (PDSP 32163)
Significant interactions (<10 μM, Ki values in μM in parentheses) at $5HT_{2A}$ (0.42), $5HT_{2B}$ (0.318), $5HT_{2C}$ (0.277), $5HT_3$ (2.62), $5HT_6$ (0.365), $5HT_7$ (0.898), α_{2B} (0.571), α_{2C} (0.858), M_1 (1.10), M_3 (1.70), M_4 (1.79) and H_1 (0.085) receptors. No significant interactions (>50% at 10 μM) at others.

12, MRS7112 (PDSP 33692)
Ki values were measured at H_2 histamine (Ki 2.21 μM) and Sigma-2 (Ki 2.35 μM) receptors.

14, MRS7111 (PDSP 33691)
Ki values were measured at PBR (>10 μM) and Sigma-2 (Ki 1.86 μM) receptors.

[1] Paoletta, S., Tosh, D. K., Salvemini, D., Jacobson, K. A. *PLoS ONE* 2014, **9**, e97858.
[2] Tosh, D. K., Finley, A., Paoletta, S., Moss, S. M., Gao, Z. G., Gizewski, E., Auchampach, J., Salvemini, D., Jacobson, K. A. *J. Med. Chem.* 2014, **57**, 9901.

Chemical synthesis

Materials and instrumentation

All reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO). ^{1}H NMR spectra were obtained with a Bruker 400 spectrometer using $CDCl_3$ and CD_3OD as solvents. Chemical shifts are expressed in δ values (ppm) with tetramethylsilane (δ 0.00) for $CDCl_3$ and water (δ 3.30) for CD_3OD. TLC analysis was carried out on glass sheets precoated with silica gel F254 (0.2 mm) from Aldrich. The purity of final nucleoside derivatives was checked using a Hewlett−Packard 1100 HPLC equipped with a Zorbax SB-Aq 5 μm analytical column (50 × 4.6 mm; Agilent Technologies Inc., Palo Alto, CA). Mobile phase: linear gradient solvent system, 5 mM TBAP (tetrabutylammonium dihydrogenphosphate)−CH_3CN from 80:20 to 0:100 in 13 min; the flow rate was 0.5 mL/min. Peaks were detected by UV absorption with a diode array detector at 230, 254, and 280 nm. All derivatives tested for biological activity showed >95% purity by HPLC analysis (detection at 254 nm). Low-resolution mass spectrometry was performed with a JEOL SX102 spectrometer with 6-kV Xe atoms following desorption from a glycerol matrix or on an Agilent LC/MS 1100 MSD, with a Waters (Milford, MA) Atlantis C18 column. High resolution mass spectroscopic (HRMS) measurements were performed on a proteomics optimized Q-TOF-2 (Micromass-Waters) using external calibration with polyalanine, unless noted. Observed mass accuracies are those expected based on known performance of the instrument as well as trends in masses of standard compounds observed at intervals during the series of measurements. Reported masses are observed masses uncorrected for this time-dependent drift in mass accuracy. All of the monosubsituted alkyne intermediates were purchased from Sigma-Aldrich (St. Louis, MO), Small Molecules, Inc. (Hoboken, NJ), Anichem (North Brunswick, NJ), PharmaBlock, Inc. (Sunnyvale, CA), Frontier Scientific (Logan, UT) and Tractus (Perrineville, NJ).

(1*S*,2*R*,3*S*,4*R*,5*S*)-2,3-dihydroxy-*N*-methyl-4-(6-(methylamino)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-9*H*-purin-9-yl)bicyclo[3.1.0]hexane-1-carboxamide (5)

Phenylacetylene (6.5 μL, 0.059 mmol) and tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl] amine (TBTA, 1 mg, 0.001 mmol) were added to a solution of compound **30** (15.2 mg, 0.042 mmol) in a mixture of *t*-butanol (0.5 mL) and water (0.5 mL). Subsequently freshly prepared 1M sodium ascorbate solution (42.2 μL, 0.042 mmol) followed by 7.5% solution of copper sulphate (70.4 μL, 0.021 mmol) was added into the reaction mixture and stirred at room temperature for overnight. Solvent was evaporated and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 20:1) to give the compound **5** (17 mg, 86%) as a colorless powder. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.11 (s, 1H), 8.11 (s, 1H), 7.99 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 2H), (t, *J* = 7.2 Hz, 1H), 5.26 (d, *J* = 6.4 Hz, 1H), 4.92 (s, 1H), 4.15 (d, *J* = 6.8 Hz, 1H), 3.24 (br s, 3H), 2.80 (s, 3H), 2.15-2.12 (m, 1H), 1.85 (t, *J* = 5.2 Hz, 1H), 1.47-1.45 (m, 1H). HRMS calculated for $C_{22}H_{24}N_9O_3$ $(M + H)^+$: 462.2002; found 462.2007.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(2-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)-6-(methylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (6)

Compound **6** (55%) was prepared from compound **30** following the same method for compound **5**. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.21 (s, 1H), 8.154 (s, 1H), 8.150 (s, 1H), 7.58 (d, *J* = 6.4 Hz, 1H), 7.51-7.41 (m, 2H), 5.31 (d, *J* = 6.8 Hz, 1H), 4.94 (s, 1H), 4.16 (d, *J* = 6.4 Hz, 1H), 3.22 (br s, 3H), 2.80 (s, 3H), 2.12-2.09 (m, 1H), 1.84 (t, *J* = 4.8 Hz, 1H), 1.46-1.44 (m, 1H). HRMS calculated for $C_{22}H_{23}N_9O_3Cl$ $(M + H)^+$: 496.1607; found 496.1610.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(3,4-difluorophenyl)-1*H*-1,2,3-triazol-1-yl)-6-(methylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (7)

Compound **7** (84%) was prepared from compound **30** following the same method for compound **5**. ^{1}H NMR (DMSO-d6, 400 MHz) δ 9.42 (s, 1H), 8.38 (d, *J* = 4.4 Hz, 1H), 8.19 (s, 1H), 8.18-8.13 (m, 1H), 7.97-7.96 (m, 1H), 7.63-7.55 (m, 2H), 5.39 (d, *J* = 4.4 Hz, 1H), 5.17 (t, *J* = 6.8 Hz, 1H), 4.92 (d, *J* = 7.6 Hz, 1H), 4.8 (s, 1H), 4.04 (s, 1H), 3.30 (s, 1H), 3.10 (d, *J* = 4.4 Hz, 3H), 2.60 (d, *J* = 4.4

Hz, 3H), 1.89-1.86 (m, 1H), 1.56 (t, *J* = 4.8 Hz, 1H), 1.38-1.35 (m, 1H). HRMS calculated for $C_{22}H_{22}N_9O_3F_2$ $(M + H)^+$: 498.1808; found 498.1811.

(1*S*,2*R*,3*S*,4*R*,5*S*)-2,3-dihydroxy-*N*-methyl-4-(6-(methylamino)-2-(4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)-9*H*-purin-9-yl)bicyclo[3.1.0]hexane-1-carboxamide (8)

Compound **8** (86%) was prepared from compound **30** following the same method for compound **5**. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.32 (s, 1H), 8.65 (d, *J* = 4.4 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.13 (s, 1H), 8.00 (t, *J* = 6.4 Hz, 1H), 7.46-7.43 (m, 1H), 5.32 (d, *J* = 6.8 Hz, 1H), 4.94 (s, 1H), 4.17 (d, *J* = 6.8 Hz, 1H), 3.24 (br s, 3H), 2.82 (s, 3H), 2.15-2.09 (m, 1H), 1.84 (t, *J* = 5.2 Hz, 1H), 1.47-1.45 (m, 1H). HRMS calculated for $C_{21}H_{23}N_{10}O_3$ $(M + H)^+$: 463.1949; found 463.1950.

(1*S*,2*R*,3*S*,4*R*,5*S*)-2,3-dihydroxy-*N*-methyl-4-(6-(methylamino)-2-(4-(pyrimidin-2-yl)-1*H*-1,2,3-triazol-1-yl)-9*H*-purin-9-yl)bicyclo[3.1.0]hexane-1-carboxamide (9)

Compound **9** (79%) was prepared from compound **30** following the same method for compound **5**. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.41 (s, 1H), 8.93-8.92 (m, 2H), 8.13 (s, 1H), 7.49 (t, *J* = 4.8 Hz, 1H), 5.31 (d, *J* = 7.2 Hz, 1H), 4.94 (s, 1H), 4.17 (d, *J* = 6.4 Hz, 1H), 3.24 (br s, 3H), 2.83 (s, 3H), 2.13-2.10 (m, 1H), 1.85 (t, *J* = 4.8 Hz, 1H), 1.47-1.45 (m, 1H). HRMS calculated for $C_{20}H_{22}N_{11}O_3$ $(M + H)^+$: 464.1902; found 464.1904.

(1*S*,2*R*,3*S*,4*R*,5*S*)-2,3-dihydroxy-*N*-methyl-4-(6-(methylamino)-2-(4-(pyrazin-2-yl)-1*H*-1,2,3-triazol-1-yl)-9*H*-purin-9-yl)bicyclo[3.1.0]hexane-1-carboxamide (10)

Compound **10** (81%) was prepared from compound **30** following the same method for compound **5**. ^{1}H NMR (DMSO-d6, 400 MHz) δ 9.38 (s, 1H), 9.35 (s, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 8.68 (d, *J* = 2.8 Hz, 1H), 8.43 (d, *J* = 4.8 Hz, 1H), 8.19 (s, 1H), 5.46 (s, 1H), 5.13 (s, 1H), 4.90 (d, *J* = 2.8 Hz, 1H), 4.81 (s, 1H), 4.03 (s, 1H), 3.08 (d, *J* = 4.8 Hz, 3H), 2.64 (d, *J* = 4.4 Hz, 1H), 1.90-1.87 (m, 1H), 1.59 (t, *J* = 4.8 Hz, 1H), 1.36-1.33 (m, 1H). HRMS calculated for $C_{20}H_{22}N_{11}O_3$ $(M + H)^+$: 464.1902; found 464.1904.

(1*S*,2*R*,3*S*,4*R*,5*S*)-2,3-dihydroxy-*N*-methyl-4-(2-(4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-1,2,3-triazol-1-yl)-6-(methylamino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexane-1-carboxamide (11)

Compound **11** (88%) was prepared from compound **30** following the same method for compound **5**. ^{1}H NMR (DMSO-d6, 400 MHz) δ 8.98 (s, 1H),), 8.34 (d, *J* = 4.8 Hz, 1H), 8.23 (s, 1H), 8.17 (s, 1H), 7.95 (s, 1H), 7.63 (d, *J* = 4.4 Hz, 1H), 5.40 (d, *J* = 4.0 Hz, 1H), 5.17 (t, *J* = 6.0 Hz, 1H), 4.89 (d, *J* = 7.6 Hz, 1H), 4.80 (s, 1H), 4.03 (s, 1H), 3.91 (s, 3H), 3.07 (d, *J* = 4.4 Hz, 3H), 2.60 (d, *J* = 4.4 Hz, 1H), 1.87-1.84 (m, 1H), 1.56 (t, *J* = 4.8 Hz, 1H), 1.37-1.34 (m, 1H). HRMS calculated for $C_{20}H_{23}N_{11}O_3$ $(M + Na)^+$: 488.1883; found 488.1878.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(furan-2-yl)-1*H*-1,2,3-triazol-1-yl)-6-(methylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (12)

Compound **12** (92%) was prepared from compound **30** following the same method for compound **5**. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.94 (s, 1H), 8.11 (s, 1H), 7.66 (s, 1H), 6.96 (d, *J* = 3.2 Hz, 1H), 6.62-6.60 (m, 1H), 5.25 (d, *J* = 6.4 Hz, 1H), 4.91 (s, 1H), 4.15 (d, *J* = 6.8 Hz, 1H), 3.22 (br s, 3H), 2.82 (s, 3H), 2.14-2.11 (m, 1H), 1.85 (t, *J* = 4.8 Hz, 1H), 1.46-1.43 (m, 1H). HRMS calculated for $C_{20}H_{23}N_{11}O_3$ $(M + H)^+$: 452.1789; found 452.1791.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(benzofuran-2-yl)-1*H*-1,2,3-triazol-1-yl)-6-(methylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (13)

Compound **13** (91%) was prepared from compound **30** following the same method for compound **5**. ^{1}H NMR (DMSO-d6, 400 MHz) δ 9.27 (s, 1H), 8.42 (d, *J* = 4.4 Hz, 1H), 8.19 (s, 1H), 7.74-7.63 (m, 3H), 7.49 (s, 1H), 7.40-7.29 (m, 2H), 5.46 (s, 1H), 5.13 (s, 1H), 4.93 (d, *J* = 6.4 Hz, 1H), 4.81 (s, 1H), 4.04 (d, *J* = 5.6 Hz, 1H), 3.10 (d, *J* = 4.4 Hz, 3H), 2.66 (d, *J* = 4.4 Hz, 3H), 1.92-1.88 (m, 1H), 1.59 (t, *J* = 4.8 Hz, 1H), 1.37-1.34 (m, 1H). HRMS calculated for $C_{24}H_{24}N_9O_4$ $(M + H)^+$: 502.1946;

found 502.1947.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(5-chlorothiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)-6-(methylamino)-9H-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (14)
Compound **14** (89%) was prepared from compound **30** following the same method for compound **5**. ^{1}H NMR (DMSO-d6, 400 MHz) δ 9.28 (s, 1H), 8.39 (d, *J* = 4.4 Hz, 1H), 8.19 (s, 1H), 7.60-7.59 (m, 2H), 7.23 (d, *J* = 4.0 Hz, 1H), 5.40 (s, 1H), 5.15 (s, 1H), 4.90 (d, *J* = 6.8 Hz, 1H), 4.80 (s, 1H), 4.03 (s, 1H), 3.08 (d, *J* = 4.4 Hz, 3H), 2.61 (d, *J* = 4.4 Hz, 3H), 1.88-1.85 (m, 1H), 1.57 (t, *J* = 4.8 Hz, 1H), 1.37-1.34 (m, 1H). HRMS calculated for $C_{20}H_{21}N_9O_3SCl$ (M + H) $^+$: 502.1171; found 502.1173.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(5-chlorothiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)-6-(ethylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (15)
Compound **15** (85%) was prepared from compound **31** following the same method for compound **5**. ^{1}H NMR (DMSO-d6, 400 MHz) δ 9.24 (s, 1H), 8.46 (t, *J* = 5.6 Hz, 1H), 8.19 (s, 1H), 7.60 (d, *J* = 4.0 Hz, 1H), 7.21 (d, *J* = 3.6 Hz, 1H), 5.38 (d, *J* = 4.8 Hz, 1H), 5.16 (t, *J* = 6.8 Hz, 1H), 4.89 (d, *J* = 8.0 Hz, 1H), 4.80 (s, 1H), 4.03 (s, 1H), 3.63 (t, *J* = 6.8 Hz, 1H), 2.61 (d, *J* = 4.8 Hz, 3H), 1.88-1.85 (m, 1H), 1.56 (d, *J* = 4.8 Hz, 1H), 1.37-1.35 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H). HRMS calculated for $C_{21}H_{23}N_9O_3SCl$ (M + H) $^+$: 516.1328; found 516.1331.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(5-chlorothiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)-6-(cyclobutylamino) -9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (16)
Compound 1**6** (93%) was prepared from compound **32** following the same method for compound **5**. ^{1}H NMR (DMSO-d6, 400 MHz) δ 9.24 (s, 1H), 8.75 (d, *J* = 4.0 Hz, 1H), 8.21 (s, 1H), 7.62-7.60 (m, 2H), 7.23 (d, *J* = 4.0 Hz, 1H), 5.41 (d, *J* = 4.4 Hz, 1H), 5.15 (t, *J* = 6.4 Hz, 1H), 4.91 (d, *J* = 7.8 Hz, 1H), 4.80 (s, 1H), 4.02 (d, *J* = 5.2 Hz, 1H), 2.60 (d, *J* = 4.8 Hz, 1H), 2.33-2.32 (m, 2H), 2.24-2.19 (m, 2H), 1.87-1.84 (m, 1H), 1.74-1.68 (m, 2H), 1.56 (t, *J* = 4.8 Hz, 1H), 1.36-1.33 (m, 1H). HRMS calculated for $C_{23}H_{24}N_9O_3SClNa$ (M + Na) $^+$: 564.1309; found 564.1300.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(6-((3-chlorobenzyl)amino)-2-(4-(5-chlorothiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (17)
Compound **17** (92%) was prepared from compound **33** following the same method for compound **5**. ^{1}H NMR (DMSO-d6, 400 MHz) δ 9.24 (s, 1H), 9.07 (t, *J* = 6.0 Hz, 1H), 8.23 (s, 1H), 7.60-7.57 (m, 3H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.30-7.28 (m, 1H), 7.23 (d, *J* = 4.0 Hz, 1H), 5.40 (d, *J* = 4.8 Hz, 1H), 5.16 (d, *J* = 6.8 Hz, 1H), 4.91 (d, *J* = 7.8 Hz, 1H), 4.81 (s, 1H), 4.05 (t, *J* = 5.2 Hz, 1H), 2.60 (d, *J* = 4.4 Hz, 3H), 1.89-1.86 (m, 1H), 1.56 (t, *J* = 4.8 Hz, 1H), 1.37-1.34 (m, 1H). HRMS calculated for $C_{26}H_{23}N_9O_3SCl_2Na$ (M + Na) $^+$: 634.0914; found 634.0917.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(5-chlorothiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)-6-(phenethylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (18)
Compound **18** (90%) was prepared from compound **34** following the same method for compound **5**. ^{1}H NMR (DMSO-d6, 400 MHz) δ 9.21 (s, 1H), 8.54 (t, *J* = 5.6 Hz, 1H), 8.19 (s, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.34-7.26 (m, 4H), 2.48 (d, *J* = 3.6 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 5.40 (d, *J* = 4.4 Hz, 1H), 5.15 (t, *J* = 6.8 Hz, 1H), 4.92 (d, *J* = 7.8 Hz, 1H), 4.80 (s, 1H), 4.03 (s,1H), 3.85-3.80 (m, 2H), 3.00 (t, *J* = 7.8 Hz, 2H), 2.61 (s, 3H), 1.89-1.86 (m, 1H), 1.58 (t, *J* = 4.8 Hz, 1H), 1.37-1.34 (m, 1H). HRMS calculated for $C_{27}H_{27}N_9O_3SCl$ (M + H) $^+$: 592.1646; found 592.1644.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(5-bromothiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)-6-(methylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (19)
Compound **19** (92%) was prepared from compound **30** following the same method for compound **5**. ^{1}H NMR (DMSO-d6, 400 MHz) δ 9.27 (s, 1H), 8.38 (d, *J* = 4.4 Hz, 1H), 8.19 (s, 1H), 7.61 (d, *J* = 4.4 Hz, 1H), 7.55 (d, *J* = 4.0 Hz, 1H), 7.33 (d, *J* = 4.0 Hz, 1H), 5.40 (d, *J* = 4.4 Hz, 1H), 5.15 (t, *J* =

6.8 Hz, 1H), 4.90 (d, *J* = 8.0 Hz, 1H), 4.80 (s, 1H), 4.02 (s, 1H), 3.07 (d, *J* = 4.4 Hz, 3H), 2.61 (d, *J* = 4.4 Hz, 3H), 1.88-1.85 (m, 1H), 1.57 (t, *J* = 4.8 Hz, 1H), 1.37-1.34 (m, 1H). HRMS calculated for $C_{20}H_{21}N_9O_3SBr$ $(M + H)^+$: 546.0666; found 546.0667.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-(4-(ferrocene-2-yl)-1*H*-1,2,3-triazol-1-yl)-6-(methylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (20)

Compound **20** (89%) was prepared from compound **30** following the same method for compound **5**. ^{1}H NMR (DMSO-d6, 400 MHz) δ 8.89 (s, 1H), 8.34 (d, *J* = 4.0 Hz, 1H), 8.18 (s, 1H), 7.64 (d, *J* = 4.0 Hz, 1H), 5.39 (d, *J* = 4.0 Hz, 1H), 5.21 (t, *J* = 6.8 Hz, 1H), 4.94-4.90 (m, 3H), 4.81 (s, 1H), 4.37 (s, 2H), 4.09 (s, 6H), 4.08-4.05 (m, 1H), 3.09 (d, *J* = 4.4 Hz, 3H), 2.63 (d, *J* = 4.4 Hz, 1H), 1.86-1.84 (m, 1H), 1.56 (d, *J* = 4.4 Hz, 1H), 1.39-1.35 (m, 1H). HRMS calculated for $C_{26}H_{27}N_9O_3Fe$ $(M)^+$: 569.1586; found 569.1589.

Ethyl (3a*R*,3b*S*,4a*S*,5*R*,5a*S*)-5-(2-iodo-6-(methylamino)-9*H*-purin-9-yl)-2,2-dimethyltetra hydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3a*H*)-carboxylate (23a)

Methylamine hydrochloride (0.353 g, 5.23 mmol) and triethylamine (1.4 mL, 16.6 mmol) were added to a solution of compound **22** (0.528 g, 1.04 mmol) in anhydrous methanol (15 mL) and stirred at room temperature for overnight. Solvent was evaporated under vacuum and residue was purified on flash silica gel column chromatography (hexane:ethyl acetate=1:1) to give the compound **23a** (0.470 g, 94%) as a foamy solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.94 (s, 1H), 5.83 (d, *J* = 7.2 Hz, 1H), 4.94 (s, 1H), 4.80 (d, *J* = 6.0 Hz, 1H), 4.33-4.27 (m, 2H), 3.05 (br s, 3H), 2.25-2.21 (m, 1H), 1.65-1.61 (m, 1H), 1.53-1.49 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 3H). HRMS calculated for $C_{18}H_{23}IN_5O_4$ $(M + H)^+$: 500.1072; found 500.1075.

Ethyl(3a*R*,3b*S*,4a*S*,5*R*,5a*S*)-5-(6-(ethylamino)-2-iodo-9*H*-purin-9-yl)-2,2-dimethyltetra hydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3a*H*)-carboxylate (23b)

Compound **23b** (89%) was prepared from compound **22** following the same method for compound **23a**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.94 (s, 1H), 5.83 (d, *J* = 6.0 Hz, 1H), 4.94 (s, 1H), 4.81 (d, *J* = 6.0 Hz, 1H), 4.33-4.24 (m, 2H), 3.56 (br s, 2H), 2.25-2.21 (m, 1H), 1.64-1.60 (m, 1H), 1.53-1.49 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.29-1.23 (m, 6H). HRMS calculated for $C_{19}H_{25}IN_5O_4$ $(M + H)^+$: 514.0946; found 514.0948.

Ethyl(3a*R*,3b*S*,4a*S*,5*R*,5a*S*)-5-(6-(cyclobutylamino)-2-iodo-9*H*-purin-9-yl)-2,2-dimethyl tetrahydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3a*H*)-carboxylate (23c)

Compound **23c** (85%) was prepared from compound **22** following the same method for compound **23a**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.95 (s, 1H), 5.82 (d, *J* = 6.0 Hz, 1H), 4.93 (s, 1H), 4.81 (d, J = 5.6 Hz, 1H), 4.33-4.28 (m, 2H), 4.68 (br s, 1H), 2.43-2.40 (m, 2H), 2.24-2.20 (m, 1H), 2.10-2.05 (m, 2H), 1.82-1.80 (m, 2H), 1.64-1.60 (m, 1H), 1.53 (s, 3H), 1.50 (t, *J* = 5.2 Hz, 1H), 1.34 (t, *J* = 6.0 Hz, 3H), 1.30 (s, 3H). HRMS calculated for $C_{21}H_{27}IN_5O_4$ $(M + H)^+$: 540.1102; found 540.1105.

(3a*R*,3b*S*,4a*S*,5*R*,5a*S*)-5-(2-iodo-6-(methylamino)-9*H*-purin-9-yl)-*N*,2,2-trimethyltetra hydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3a*H*)-carboxamide (24a)

40% Methylamine solution (aqueous, 10 mL) was added to a solution of compound **23a** (0.470, 0.94 mmol) in methanol (12 mL) and stirred at room temperature for 24 h. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH=40:1) to give the compound **24a** (0.360 g, 79%) as a white powder. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.95 (s, 1H), 5.72 (d, *J* = 7.2 Hz, 1H), 4.93 (s, 1H), 4.84 (d, *J* = 7.2 Hz, 1H), 3.05 (br s, 3H), 2.90 (s, 3H), 2.17-2.11 (m, 1H), 1.54-1.49 (m, 4H), 1.39 (t, *J* = 5.2 Hz, 1H), 1.30 (s, 3H). HRMS calculated for $C_{17}H_{22}IN_6O_3$ $(M + H)^+$: 485.0798; found 485.0803.

(3a*R*,3b*S*,4a*S*,5*R*,5a*S*)-5-(6-(ethylamino)-2-iodo-9*H*-purin-9-yl)-*N*,2,2-trimethyltetra hydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3a*H*)-carboxamide (24b)

Compound **24b** (75%) was prepared from compound **23b** following the same method for compound **24a**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.96 (s, 1H), 5.72 (d, *J* = 6.0 Hz, 1H), 4.92 (s, 1H), 4.84 (d, *J* = 6.0 Hz, 1H), 3.56 (br s, 2H), 2.90 (s, 3H), 2.15-2.11 (m,1H), 1.53-1.49 (m, 4H), 1.38 (t, *J* = 5.2 Hz, 1H), 1.30 (s, 3H), 1.27 (t, *J* = 6.8 Hz, 3H). HRMS calculated for $C_{18}H_{24}IN_6O_3$ (M + H) $^+$: 499.0949; found 499.0952.

(3a*R*,3b*S*,4a*S*,5*R*,5a*S*)-5-(6-(cyclobutylamino)-2-iodo-9*H*-purin-9-yl)-*N*,2,2-trimethyltetra hydrocyclopropa[3,4]cyclopenta[1,2-*d*][1,3]dioxole-3b(3a*H*)-carboxamide (24c)

Compound **24c** (78%) was prepared from compound **23c** following the same method for compound **24a**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.97 (s, 1H), 5.71 (d, *J* = 6.4 Hz, 1H), 4.92 (s, 1H), 4.83 (d, *J* = 6.0 Hz, 1H), 2.89 (s, 3H), 2.44-2.38 (m, 2H), 2.13-2.04 (m, 3H), 1.84-1.78 (m, 2H), 1.54 (s, 3H), 1.52-1.49 (m, 1H), 1.39 (t, *J* = 5.2 Hz, 1H), 1.30 (s, 3H). HRMS calculated for $C_{20}H_{26}IN_6O_3$ (M + H) $^+$: 525.1111; found 525.1100.

(1*S*,2*R*,3*S*,4*R*,5*S*)-2,3-dihydroxy-4-(2-iodo-6-(methylamino)-9*H*-purin-9-yl)-*N*-methyl bicycle[3.1.0]hexane-1-carboxamide (25)

A solution of compound **24a** (16 mg, 0.03 mmol) in methanol (2 mL) and 10% trifluoromethane sulfonic acid (2 mL) was heated at 70 ^{o}C for 5 h. Solvent was evaporated under vacuum, and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 25:1) to give the compound **25** (13 mg, 88%) as a white powder. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.94 (s, 1H), 5.12 (d, *J* = 5.2 Hz, 1H), 4.80 (s, 1H), 3.99 (d, *J* = 5.6 Hz, 1H), 3.05 (br s, 3H), 2.90 (s, 3H), 2.06-2.02 (m, 1H), 1.80 (t, *J* = 4.8 Hz, 1H), 1.38-1.34 (m, 1H). HRMS calculated for $C_{14}H_{18}IN_6O_3$ (M + H) $^+$: 445.0485; found 445.0489.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(6-(ethylamino)-2-iodo-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo [3.1.0]hexane-1-carboxamide (26)

Compound **26** (91%) was prepared from compound **24b** following the same method for compound **25**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.94 (s, 1H), 5.11 (d, *J* = 5.6 Hz, 1H), 4.79 (s, 1H), 3.99 (d, *J* = 6.4 Hz, 1H), 3.57 (br s, 2H), 2.90 (s, 3H), 2.05-2.02 (m, 1H), 1.80 (t, *J* = 5.2 Hz, 1H), 1.38-1.35 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H). HRMS calculated for $C_{15}H_{20}IN_6O_3$ (M + H) $^+$: 459.0642; found 459.0637.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(6-(cyclobutylamino)-2-iodo-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (27)

Compound **27** (85%) was prepared from compound **24c** following the same method for compound **25**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.96 (s, 1H), 5.11 (d, *J* = 5.2 Hz, 1H), 4.79 (s, 1H), 4.67 (br s, 1H), 3.98 (d, *J* = 5.2 Hz, 1H), 2.90 (s, 3H), 2.44-2.40 (m, 2H), 2.13-2.07 (m, 3H), 1.83-1.79 (m, 3H), 1.38-1.34 (m, 1H). HRMS calculated for $C_{17}H_{22}IN_6O_3$ (M + H) $^+$: 485.0798; found 485.0794.

(1*S*,2*R*,3*S*,4*R*,5*S*)-2,3-dihydroxy-4-(2-iodo-6-(phenethylamino)-9*H*-purin-9-yl)-*N*-methyl bicyclo[3.1.0]hexane-1-carboxamide (29)

Compound **29** (87%) was prepared from compound **24e** following the same method for compound **25**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.93 (s, 1H), 7.28 (d, *J* = 4.0 Hz, 4H), 7.20-7.17 (m, 1H), 5.11 (d, *J* = 6.4 Hz, 1H), 4.79 (s, 1H), 3.99 (d, *J* = 6.8 Hz, 1H), 3.77 (br s, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 2.90 (s, 3H), 2.05-2.02 (m, 1H), 1.80 (t, *J* = 5.2 Hz, 1H), 1.37-1.34 (m, 1H). HRMS calculated for $C_{21}H_{24}IN_6O_3$ (M + H) $^+$: 535.0955; found 535.0957.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-azido-6-(methylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-N-methyl bicyclo[3.1.0]hexane-1-carboxamide (30)

Sodium ascorbate (6.6 mg, 0.03 mmol) and $CuSO_4.5H_2O$ (4.15 mg, 0.016 mmol) were added to a mixture of compound **25** (74 mg, 0.16 mmol), NaN_3 (21.6 mg, 0.33 mmol), L-Proline (3.8 mg, 0.03 mmol), Na_2CO_3 (3.5 mg, 0.03 mmol) in ^{t}BuOH (1 mL)-H_2O (1 mL) and heated at 65 ^{o}C for

overnight. The reaction mixture was quenched by addition of dilute ammonium hydroxide solution and was extracted with ethyl acetate. The combined organic layer was washed with brine, dried, filtered and concentrated under vacuum. The crude mixture was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 15:1) to give the azido derivative **30** (55 mg, 91%) as a colorless powder. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.95 (s, 1H), 5.03 (d, *J* = 5.2 Hz, 1H), 4.76 (s, 1H), 4.00 (d, *J* = 5.2 Hz, 1H), 3.09 (br s, 3H), 2.86 (s, 3H), 2.08-2.04 (m, 1H), 1.81 (t, *J* = 4.8 Hz, 1H), 1.38-1.34 (m, 1H). HRMS calculated for $C_{14}H_{18}N_9O_3$ $(M + H)^+$: 360.1533; found 360.1538.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-azido-6-(ethylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (31)

Compound **31** (83%) was prepared from compound **26** following the same method for compound **30**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.98 (s, 1H), 5.02 (d, *J* = 5.6 Hz, 1H), 4.75 (s, 1H), 3.99 (d, *J* = 6.4 Hz, 1H), 3.60 (br s, 2H), 2.86 (s, 3H), 2.08-2.02 (m, 1H), 1.81 (t, *J* = 4.8 Hz, 1H), 1.38-1.34 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). HRMS calculated for $C_{15}H_{20}N_9O_3$ $(M + H)^+$: 374.1684; found 374.1682.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-azido-6-(cyclobutylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (32)

Compound **32** (87%) was prepared from compound **27** following the same method for compound **30**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.96 (s, 1H), 5.02 (d, *J* = 5.2 Hz, 1H), 4.75 (s, 1H), 4.66 (br s, 1H), 4.00 (d, *J* = 5.2 Hz, 1H), 2.86 (s, 3H), 2.46-2.41 (m, 2H), 2.13-2.03 (m, 3H), 1.85-1.79 (m, 3H), 1.38-1.35 (m, 1H). HRMS calculated for $C_{17}H_{22}N_9O_3$ $(M + H)^+$: 400.1846; found 400.1846.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-azido-6-((3-chlorobenzyl)amino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (33)

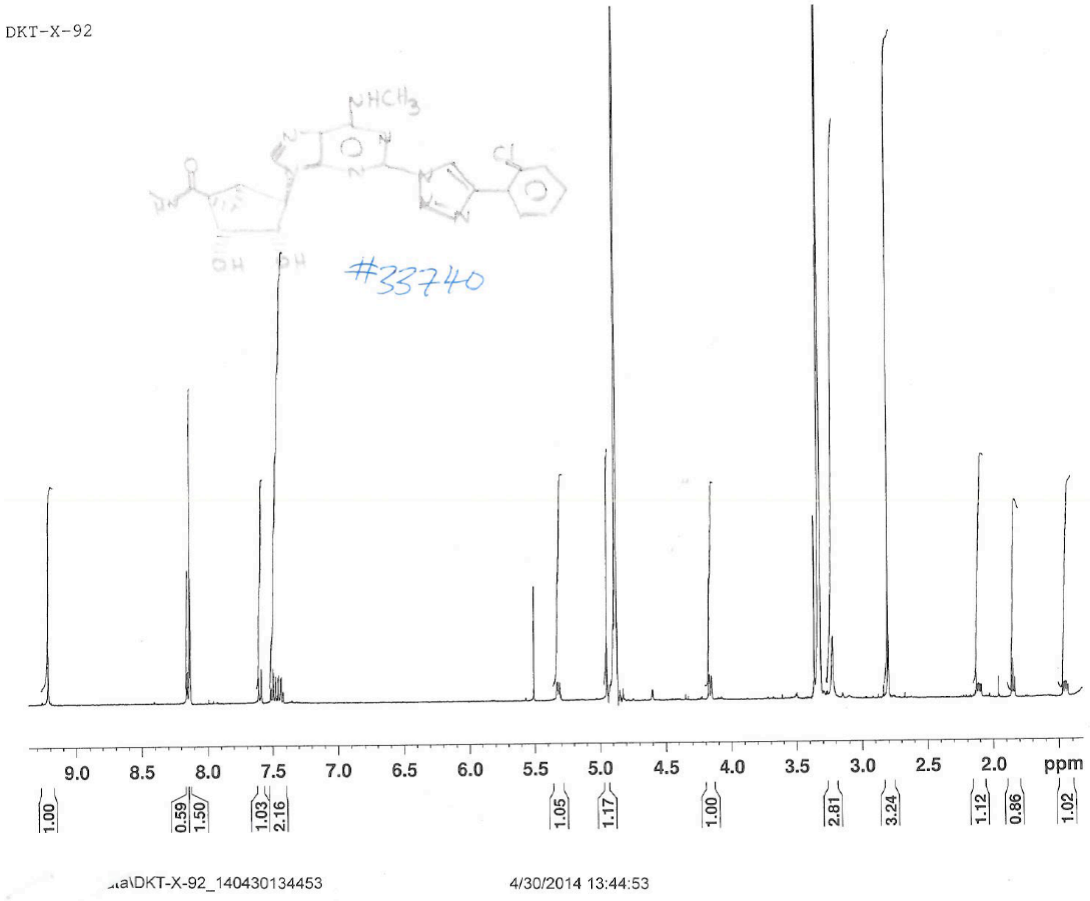
Compound **33** (82%) was prepared from compound **28** following the same method for compound **30**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.98 (s, 1H), 7.41 (s, 1H), 7.34-7.23 (m, 3H), 5.02 (d, *J* = 5.2 Hz, 1H), 4.75 (s, 1H), 4.73 (s, 2H), 3.99 (d, *J* = 5.2 Hz, 1H), 2.86 (s, 3H), 2.07-2.02 (m, 1H), 1.80 (t, *J* = 4.8 Hz, 1H), 1.38-1.35 (m, 1H). HRMS calculated for $C_{20}H_{21}N_9O_3Cl$ $(M + H)^+$: 470.1456; found 470.1461.

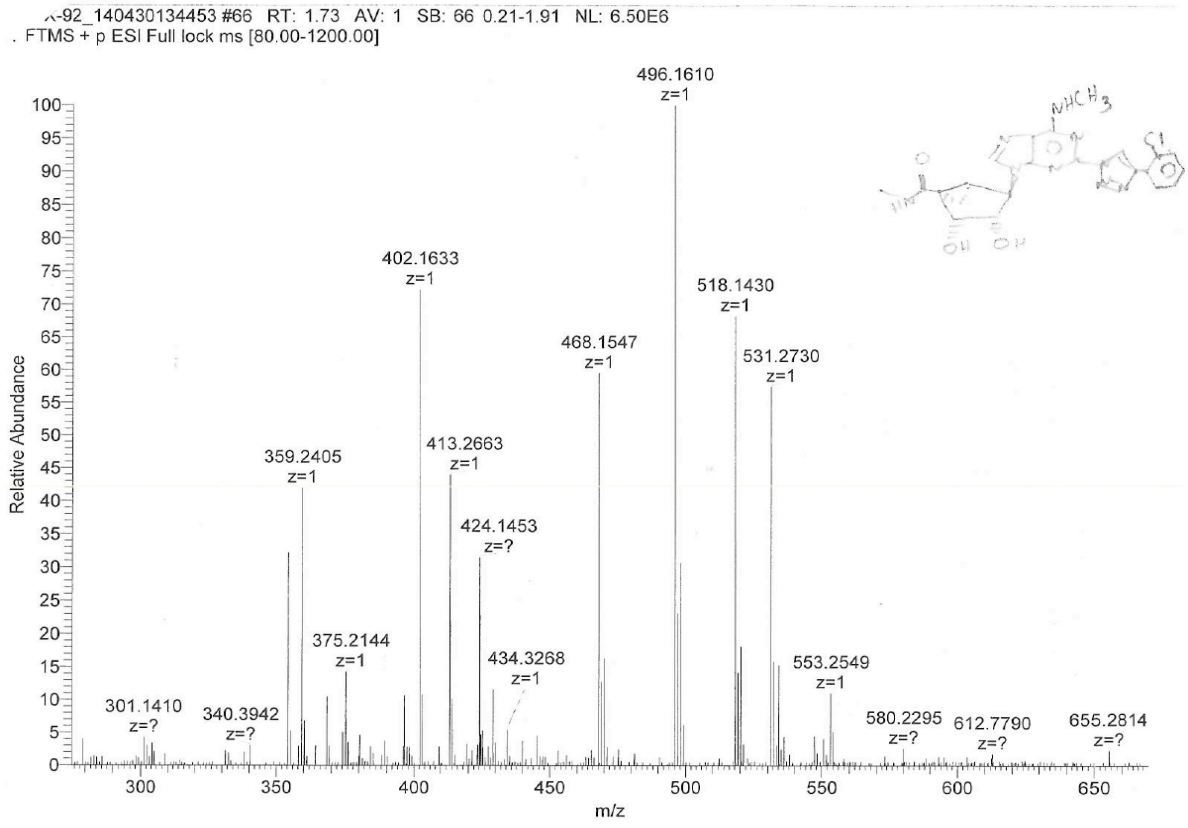
(1*S*,2*R*,3*S*,4*R*,5*S*)-4-(2-azido-6-(phenethylamino)-9*H*-purin-9-yl)-2,3-dihydroxy-*N*-methylbicyclo[3.1.0]hexane-1-carboxamide (34)

Compound **34** (90%) was prepared from compound **29** following the same method for compound **30**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.95 (s, 1H), 7.26 (d, *J* = 4.0 Hz, 4H), 7.20-7.17 (m, 1H), 5.02 (d, *J* = 6.8 Hz, 1H), 4.75 (s, 1H), 3.99 (d, *J* = 6.4 Hz, 1H), 3.80 (t, *J* = 6.8 Hz, 2H), 2.98 (t, *J* = 7.4 Hz, 2H), 2.85 (s, 3H), 2.06-2.03 (m, 1H), 1.81 (t, *J* = 4.8 Hz, 1H), 1.38-1.34 (m, 1H). HRMS calculated for $C_{21}H_{24}N_9O_3$ $(M + H)^+$: 450.2002; found 450.2009.

Representative ^{1}H-NMR and Mass Spectra

Compound 6

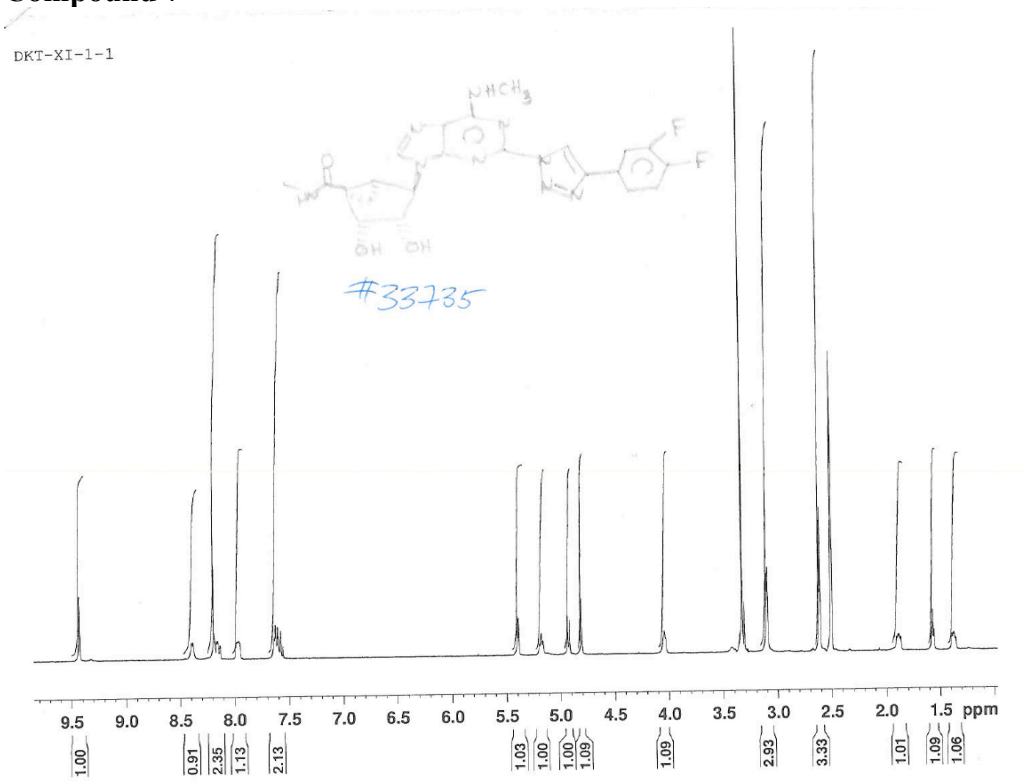


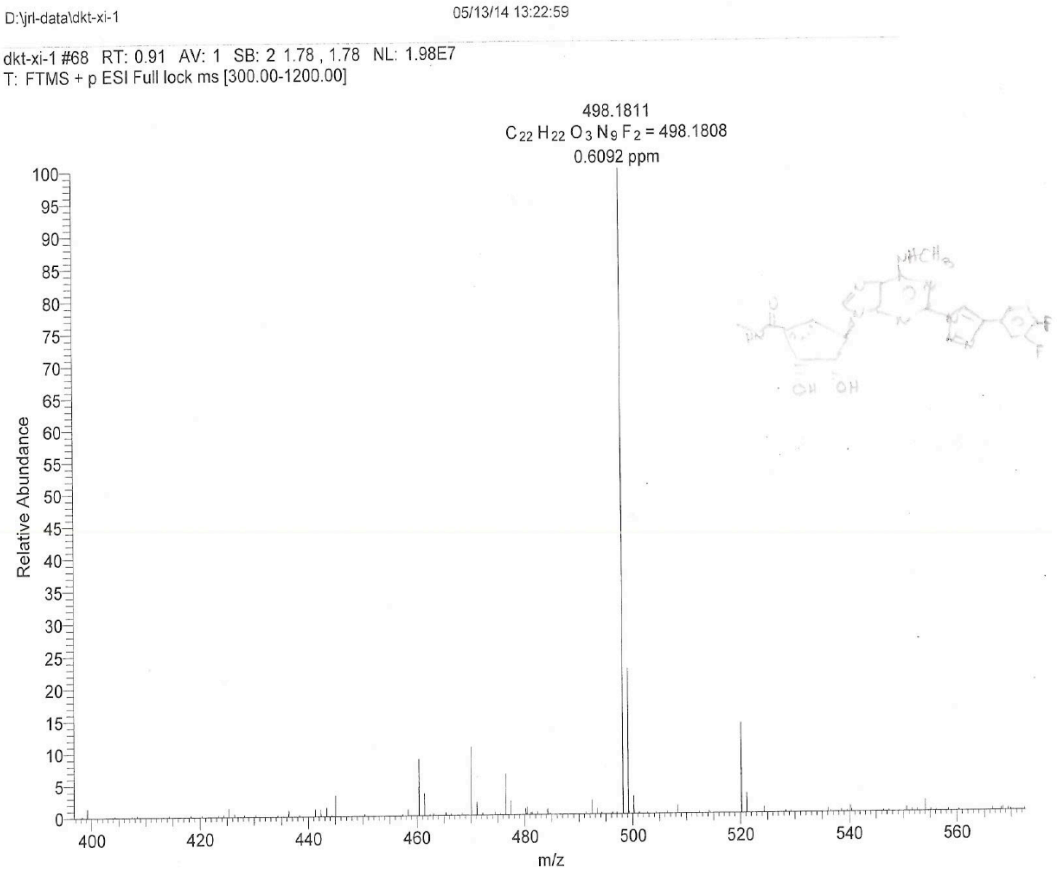


491.16-501.16

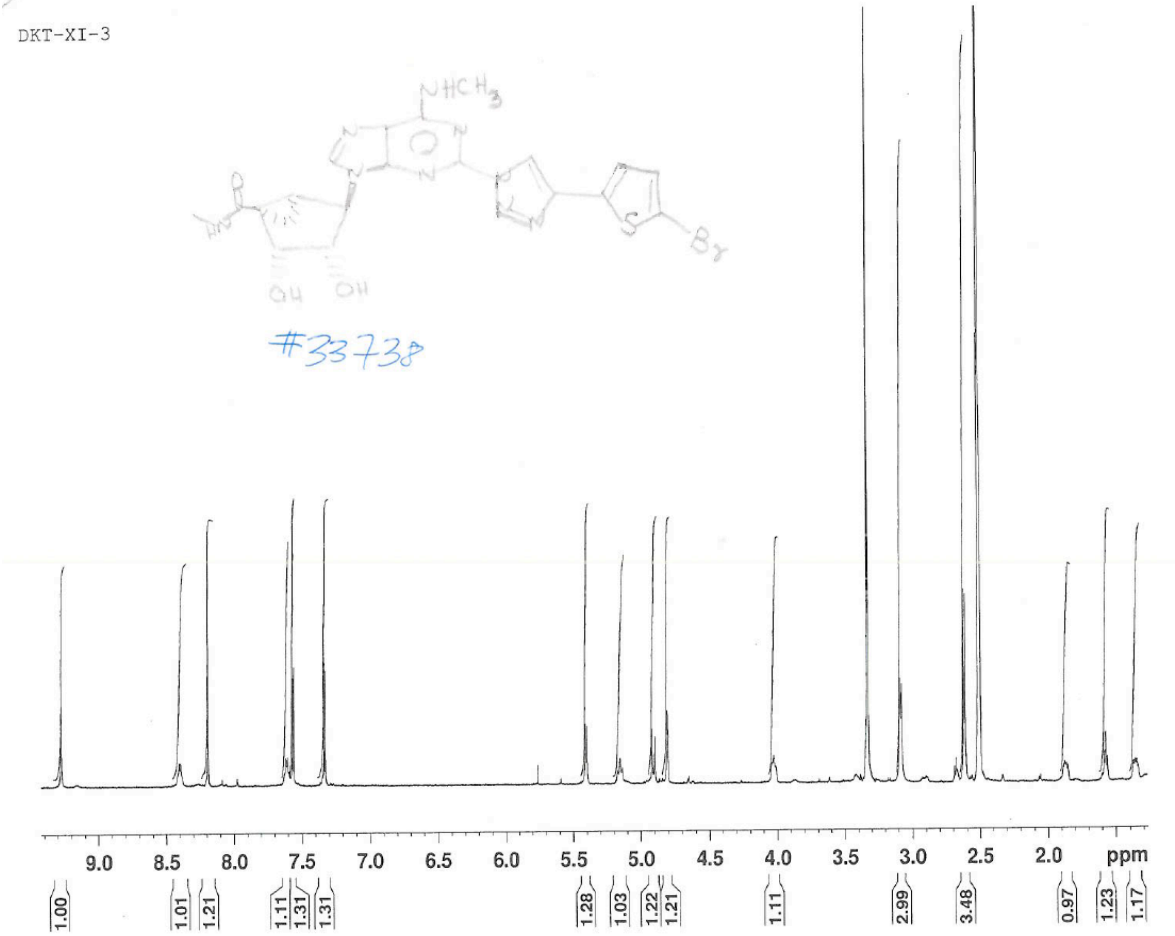
m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
496.1610	496.1607	0.51	10.0	$C_{23}H_{29}O_8N_2Cl$
	496.1607	0.52	15.5	$C_{22}H_{23}O_3N_9Cl$
	496.1615	-1.19	25.0	$C_{26}H_{16}N_{12}$
	496.1615	-1.20	19.5	$C_{27}H_{22}O_5N_5$
	496.1602	1.50	14.5	$C_{26}H_{26}O_9N$
	496.1602	1.51	20.0	$C_{25}H_{20}O_4N_8$
	496.1620	-2.18	15.0	$C_{24}H_{25}O_4N_6Cl$
	496.1625	-3.20	2.5	$C_{10}H_{27}O_{10}N_{11}Cl$
	496.1594	3.22	10.5	$C_{21}H_{27}O_7N_5Cl$
	496.1593	3.23	16.0	$C_{20}H_{21}O_2N_{12}Cl$

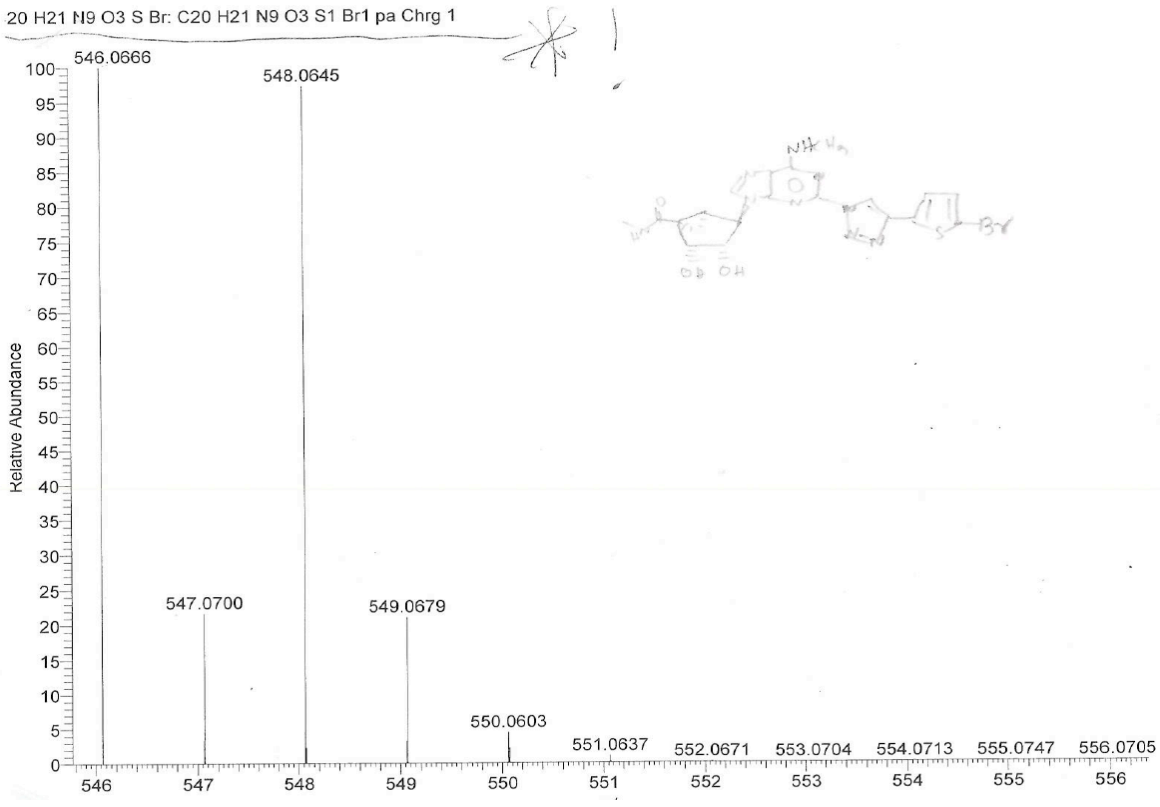
Compound 7


DKT-XI-1-1
#33735
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
1.00 0.91 2.35 1.13 2.13 1.03 1.00 1.00 1.09 1.09 2.93 3.33 1.01 1.09 1.06


D:\jrl-data\dkt-xi-1
05/13/14 13:22:59
dkt-xi-1 #68 RT: 0.91 AV: 1 SB: 2 1.78 , 1.78 NL: 1.98E7
T: FTMS + p ESI Full lock ms [300.00-1200.00]
498.1811
C22 H22 O3 N9 F2 = 498.1808
0.6092 ppm
Relative Abundance
m/z
400 420 440 460 480 500 520 540 560

Compound 19


DKT-XI-3
#33738
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
1.00
1.01
1.21
1.11
1.31
1.31
1.28
1.03
1.22
1.21
1.11
2.99
3.48
0.97
1.23
1.17

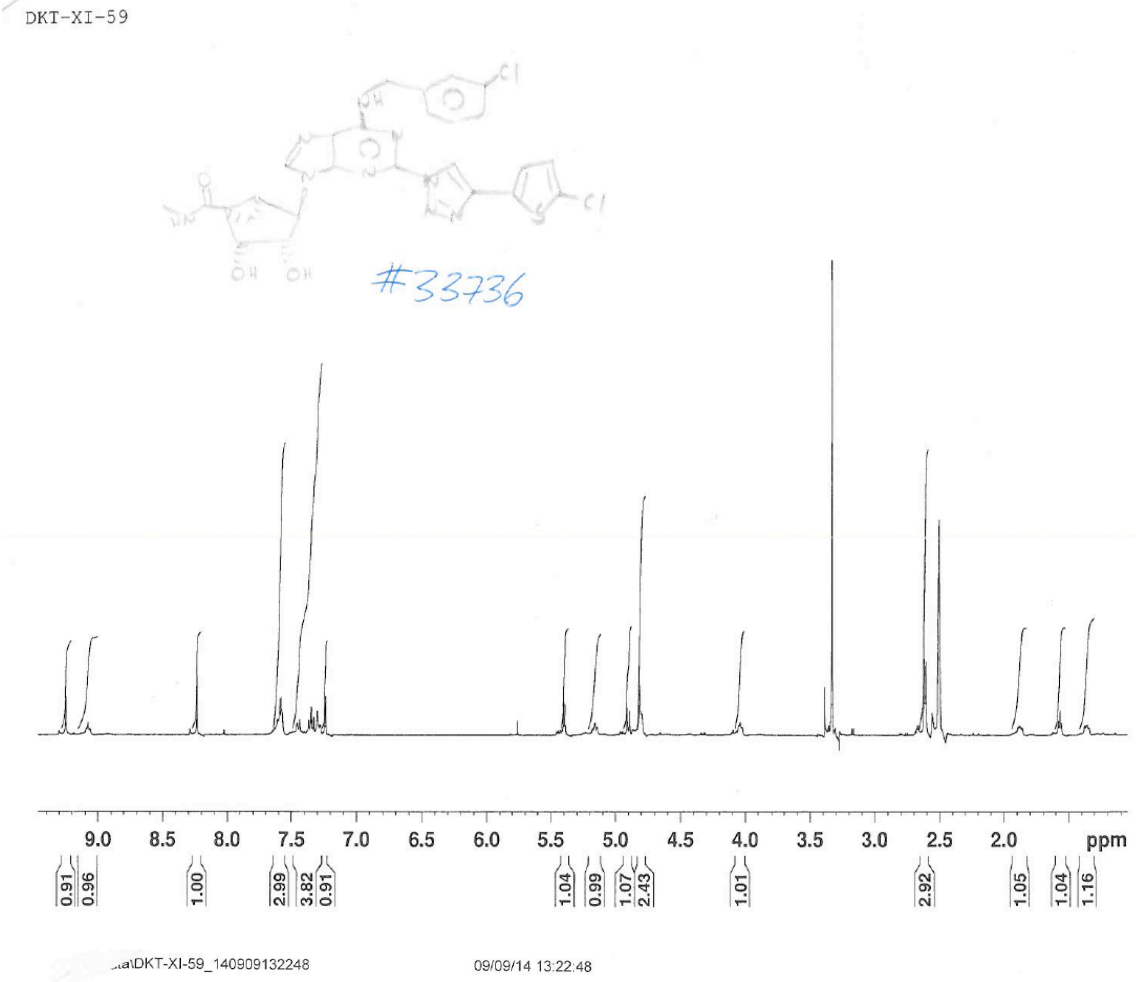

20 H21 N9 O3 S Br: C20 H21 N9 O3 S1 Br1 pa Chrg 1
546.0666
548.0645
547.0700
549.0679
550.0603
551.0637
552.0671
553.0704
554.0713
555.0747
556.0705
Relative Abundance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
546
547
548
549
550
551
552
553
554
555
556

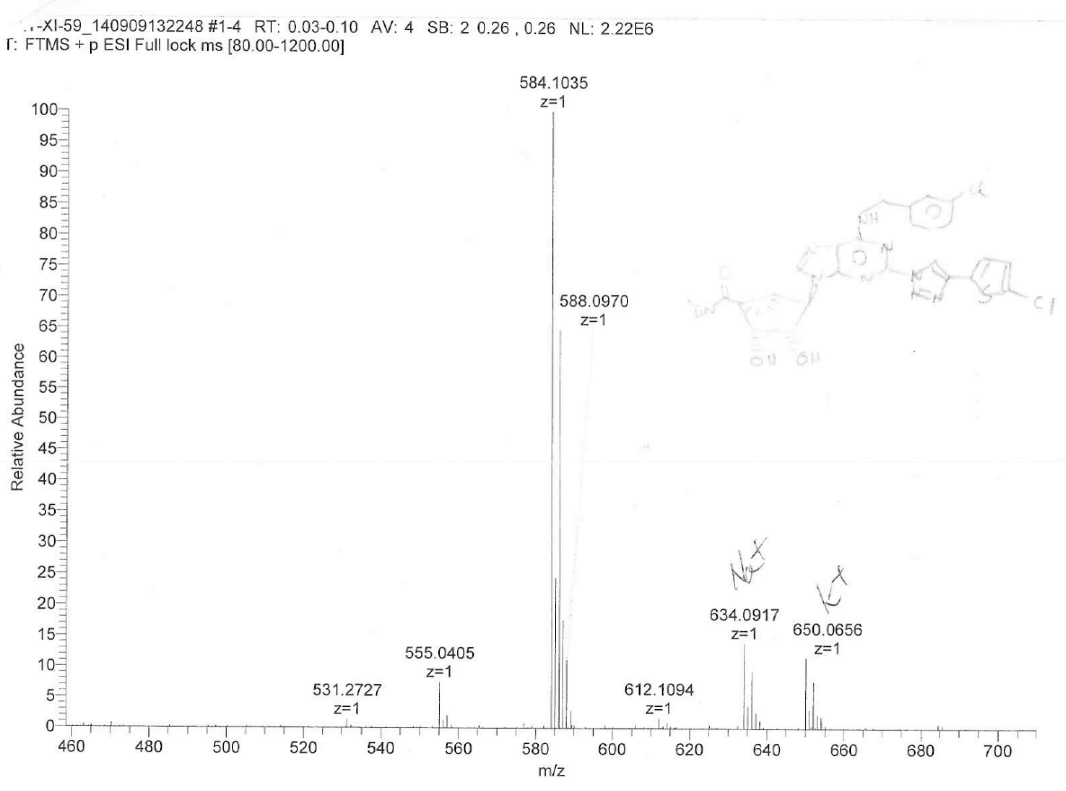
Elemental composition search on mass 546.07

m/z= 541.07-551.07

m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
546.0667	546.0666	0.23	14.5	$C_{20}H_{21}O_3N_9BrS$
	546.0664	0.55	6.0	$C_{13}H_{23}O_{11}N_8Br$
	546.0664	0.56	11.5	$C_{12}H_{17}O_6N_{15}Br$
	546.0671	-0.70	2.0	$C_6H_{23}O_9N_{14}BrS$
	546.0671	-0.71	-3.5	$C_7H_{29}O_{14}N_7BrS$
	546.0672	-0.97	23.5	$C_{28}H_{17}ON_7Br$
	546.0659	1.48	18.5	$C_{27}H_{21}O_5N_3Br$
	546.0659	1.49	24.0	$C_{26}H_{15}N_{10}Br$
	546.0658	1.75	-3.0	$C_5H_{27}O_{13}N_{10}BrS$
	546.0678	-1.90	11.0	$C_{14}H_{19}O_7N_{12}Br$
	546.0678	-1.90	5.5	$C_{15}H_{25}O_{12}N_5Br$
	546.0679	-2.23	14.0	$C_{22}H_{23}O_4N_6BrS$
	546.0653	2.68	9.5	$C_{19}H_{25}O_7N_5BrS$
	546.0653	2.69	15.0	$C_{18}H_{19}O_2N_{12}BrS$
	546.0651	3.00	1.0	$C_{12}H_{27}O_{15}N_4Br$

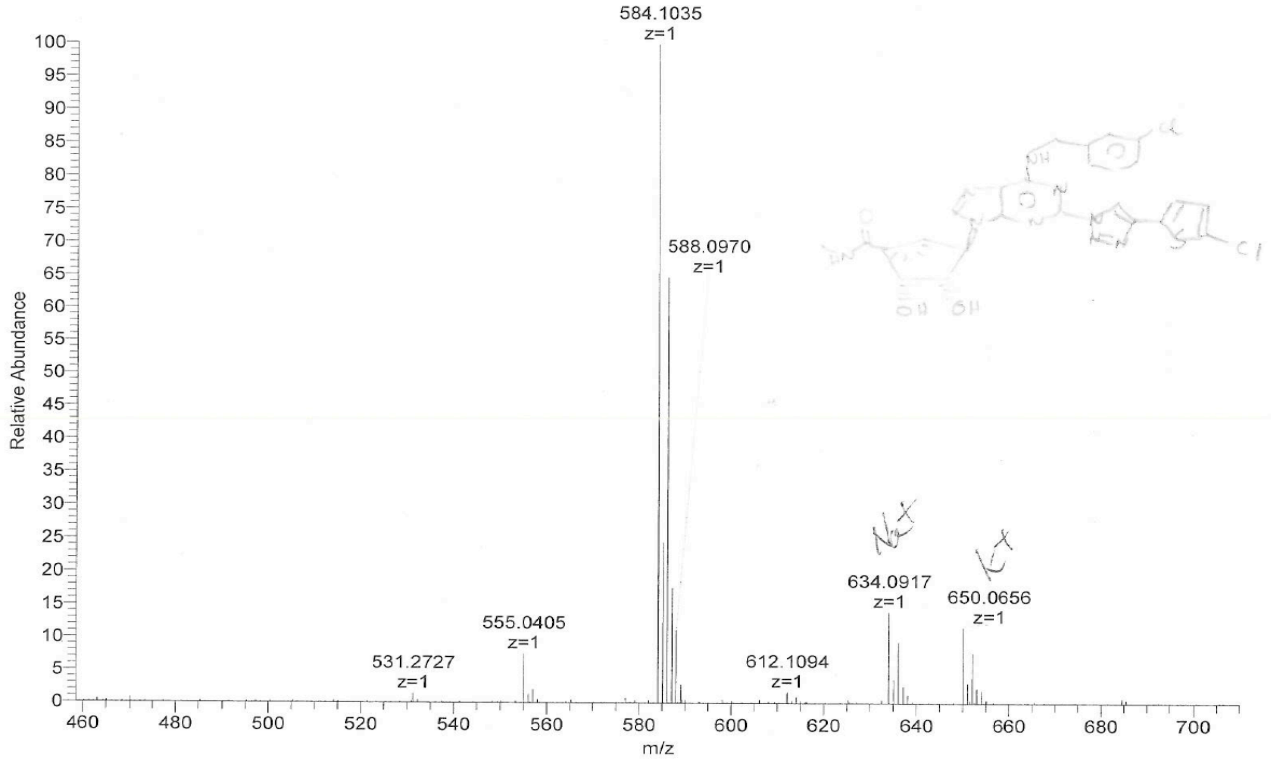
Compound 28


DKT-XI-59
#33736
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
0.91
0.96
1.00
2.99
3.82
0.91
1.04
0.99
1.07
2.43
1.01
2.92
1.05
1.04
1.16


09/09/14 13:22:48
-XI-59_140909132248 #1-4 RT: 0.03-0.10 AV: 4 SB: 2 0.26 , 0.26 NL: 2.22E6
T: FTMS + p ESI Full lock ms [80.00-1200.00]
584.1035
z=1
588.0970
z=1
634.0917
z=1
650.0656
z=1
555.0405
z=1
531.2727
z=1
612.1094
z=1
Relative Abundance
m/z

...a\DKT-XI-59_140909132248 09/09/14 13:22:48

...-XI-59_140909132248 #1-4 RT: 0.03-0.10 AV: 4 SB: 2 0.26 , 0.26 NL: 2.22E6
...: FTMS + p ESI Full lock ms [80.00-1200.00]



...omposition search on mass 650.07

...= 645.07-655.07

m/z	Theo. Mass	Delta (mmu)	RDB equiv.	Composition
650.07	650.07	-0.00	14.5	$C_{28}H_{28}O_5N_3Cl_2KNaS$
	650.07	0.07	37.5	$C_{36}H_9N_{11}NaS$
	650.07	-0.08	32.5	$C_{33}H_{13}ON_{11}KS$
	650.07	-0.14	31.5	$C_{32}H_{13}O_2N_{11}ClS$
	650.07	-0.22	32.5	$C_{37}H_{15}N_7Cl_2Na$
	650.07	0.28	18.5	$C_{26}H_{23}O_3N_9Cl_2KS$
	650.07	-0.36	28.5	$C_{35}H_{18}O_3N_5KNaS$
	650.07	-0.37	27.5	$C_{34}H_{19}ON_7Cl_2K$
	650.07	-0.42	27.5	$C_{34}H_{18}O_4N_5ClNaS$
	650.07	0.43	23.5	$C_{29}H_{19}O_2N_9Cl_2NaS$