Supporting information

Structure-Based Design, Synthesis by Click Chemistry and in Vivo Activity of Highly Selective A₃ Adenosine Receptor Agonists


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Molecular Modeling Methods

A₃AR 3D Structure
To perform docking studies, we used a previously reported homology model of the hA₃AR built, based on a hybrid template, using the alignment and the homology modeling tools implemented in the MOE suite. To build this model, an agonist-bound hA₂AAR crystal structure (PDB ID: 3QAK) was used as a template for the entire A₃AR structure except for the extracellular terminus of TM2 and EL1. The X-ray structure of the β₂ adrenergic receptor in complex with the Gs protein (PDB ID: 3SN6), after superimposition with the hA₂AAR 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.

Molecular Docking
Structures of potential A₃AR ligands were built and prepared for docking using the Builder and the LigPrep tools implemented in the Schrödinger suite. 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 hA₃AR model was performed by means of the Glide package from the Schrödinger suite. 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 hA3AR. The positions of the terminal phenyl rings overlap to a large degree.

References

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


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

\[
\text{%Analgesic effect} = \frac{[\text{PWT (g)} \text{t}_{\text{h}} - \text{PWT (g)} \text{t}_{\text{D7/BL}}]}{[\text{PWT (g)} \text{t}_{\text{D0}} - \text{PWT (g)} \text{t}_{\text{D7/BL}}]} \times 100;
\]

where, PWT (g) \text{t}_{\text{h}} = \text{PWT (g) at 1 h (max) or 3 h post treatment; PWT (g) t}_{\text{D7/BL}} = \text{PWT (g) at D7/BL; and PWT (g) t}_{\text{D0}} = \text{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.\textsuperscript{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 \( \mu \text{M} \)) for 12 and 14 were found at the following sites: 5HT\(_1\)A, 5HT\(_1\)B, 5HT\(_1\)D, 5HT\(_1\)E, 5HT\(_5\)A, \( \alpha_{1A}, \beta_1, \beta_2, \beta_3 \), 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 \( \mu \text{M} \) were with H\(_2\) histamine (12, 50% inhibition at 10 \( \mu \text{M} \)) 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: \( K_i <1.0 \ \mu \text{M} \) +++; 1-10 \( \mu \text{M} \) ++; >10 \( \mu \text{M} \) +.

For comparison, off-target interactions of earlier reported compounds are listed here.\textsuperscript{1,2}

\textbf{1. MRS5698} (PDSP 26565)
\begin{align*}
\alpha_{2A} & \quad ++ (4.8 \ \mu \text{M}) \\
\alpha_{2B} & \quad ++ (2.9 \ \mu \text{M}) \\
\alpha_{2C} & \quad ++ (2.0 \ \mu \text{M}) \\
\beta_3 & \quad ++ (1.5 \ \mu \text{M}) \\
5\text{HT}_1\text{A} & \quad ++ (7.6 \ \mu \text{M}) \\
5\text{HT}_2\text{B} & \quad ++ (2.6 \ \mu \text{M}) \\
5\text{HT}_2\text{C} & \quad ++ (5.8 \ \mu \text{M}) \\
\text{H}_4 & \quad ++ (9.4 \ \mu \text{M}) \\
\text{M}_2 & \quad ++ (7.7 \ \mu \text{M}) \\
\text{DOR} & \quad ++ (2.4 \ \mu \text{M}) \\
\sigma_2 & \quad +++ (0.91 \ \mu \text{M}) \\
\text{PBR} & \quad +++ (0.34 \ \mu \text{M})
\end{align*}

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

\textbf{4. MRS5979} (PDSP 32163)
Significant interactions (<10 \( \mu \text{M} \), Ki values in \( \mu \text{M} \) in parentheses) at 5HT\(_2\)A (0.42), 5HT\(_2\)B (0.318), 5HT\(_2\)C (0.277), 5HT\(_3\) (2.62), 5HT\(_6\) (0.365), 5HT\(_7\) (0.898), \( \alpha_{2B} \) (0.571), \( \alpha_{2C} \) (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 \( \mu \text{M} \)) at others.

\textbf{12. MRS7112} (PDSP 33692)
Ki values were measured at H\(_2\) histamine (Ki 2.21 \( \mu \text{M} \)) and Sigma-2 (Ki 2.35 \( \mu \text{M} \)) receptors.

\textbf{14. MRS7111} (PDSP 33691)
Ki values were measured at PBR (>10 \( \mu \text{M} \)) and Sigma-2 (Ki 1.86 \( \mu \text{M} \)) receptors.
**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$_2$OD 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$_2$OD. 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 dihydrogenophosphate)–CH$_2$CN 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 monosubstituted 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 (Perrinville, NJ).

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

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$_2$Cl$_2$:MeOH = 20:1) to give the compound 5 (17 mg, 86%) as a colorless powder. $^1$H NMR (CD$_2$OD, 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$_{23}$H$_{24}$N$_9$O$_3$ (M + H)$^+$: 462.2002; found 462.2007.

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

Compound 6 (55%) was prepared from compound 30 following the same method for compound 5. $^1$H NMR (CD$_2$OD, 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$_9$O$_3$Cl (M + H)$^+$: 496.1607; found 496.1610.

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

Compound 7 (84%) was prepared from compound 30 following the same method for compound 5. $^1$H NMR (DMSO-d$_6$, 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
H, 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_{23}H_{22}N_{9}O_{3}F_{2} (M + H)^{+}: 498.1808; found 498.1811.

(1S,2R,3S,4R,5S)-2,3-dihydroxy-N-methyl-4-(6-(methylamino)-2-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)-9H-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_{3}OD, 400 MHz) \( \delta \) 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.

(1S,2R,3S,4R,5S)-2,3-dihydroxy-N-methyl-4-(6-(methylamino)-2-(4-(pyrimidin-2-yl)-1H-1,2,3-triazol-1-yl)-9H-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_{3}OD, 400 MHz) \( \delta \) 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.

(1S,2R,3S,4R,5S)-2,3-dihydroxy-N-methyl-4-(6-(methylamino)-2-(4-(pyrazin-2-yl)-1H-1,2,3-triazol-1-yl)-9H-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-d_{6}, 400 MHz) \( \delta \) 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.

(1S,2R,3S,4R,5S)-2,3-dihydroxy-N-methyl-4-(2-(4-(1-methyl-1H-pyrazol-4-yl)-1H-1,2,3-triazol-1-yl)-6-(methylamino)-9H-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-d_{6}, 400 MHz) \( \delta \) 9.89 (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_{22}N_{11}O_{3} (M + Na)^{+}: 488.1883; found 488.1878.

(1S,2R,3S,4R,5S)-4-(2-(furan-2-yl)-1H-1,2,3-triazol-1-yl)-6-(methylamino)-9H-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_{3}OD, 400 MHz) \( \delta \) 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.

(1S,2R,3S,4R,5S)-4-(2-(benzofuran-2-yl)-1H-1,2,3-triazol-1-yl)-6-(methylamino)-9H-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-d_{6}, 400 MHz) \( \delta \) 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_{6}O_{4} (M + H)^{+}: 502.1946;
found 502.1947.

(1S,2R,3S,4R,5S)-4-(2-(4-(5-chlorothiophen-2-yl)-1H-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-d$_6$, 400 MHz) $\delta$ 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$_{25}$N$_6$O$_5$S (M + H) $^+$: 516.1328; found 516.1331.

(1S,2R,3S,4R,5S)-4-(2-(4-(5-chlorothiophen-2-yl)-1H-1,2,3-triazol-1-yl)-6-(ethylamino)-9H-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-d$_6$, 400 MHz) $\delta$ 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$_{23}$H$_{23}$N$_6$O$_5$SCl (M + H) $^+$: 516.1328; found 516.1331.

(1S,2R,3S,4R,5S)-4-(2-(4-(5-chlorothiophen-2-yl)-1H-1,2,3-triazol-1-yl)-6-(cyclobutylamino)-9H-purin-9-yl)-2,3-dihydroxy-N-methylbicyclo[3.1.0]hexane-1-carboxamide (16)

Compound 16 (93%) was prepared from compound 32 following the same method for compound 5. 

$^1$H NMR (DMSO-d$_6$, 400 MHz) $\delta$ 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$_{23}$N$_6$O$_5$SClNa (M + Na) $^+$: 564.1309; found 564.1300.

(1S,2R,3S,4R,5S)-4-(6-((3-chlorobenzyl)amino)-2-(4-(5-chlorothiophen-2-yl)-1H-1,2,3-triazol-1-yl)-9H-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-d$_6$, 400 MHz) $\delta$ 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$_{27}$N$_6$O$_5$SClNa (M + Na) $^+$: 634.0914; found 634.0917.

(1S,2R,3S,4R,5S)-4-(2-(4-(5-chlorothiophen-2-yl)-1H-1,2,3-triazol-1-yl)-6-(phenethylamino)-9H-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-d$_6$, 400 MHz) $\delta$ 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$_{26}$H$_{27}$N$_6$O$_5$SClNa (M + H) $^+$: 592.1646; found 592.1644.

(1S,2R,3S,4R,5S)-4-(2-(4-(5-bromothiophen-2-yl)-1H-1,2,3-triazol-1-yl)-6-(methylamino)-9H-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-d$_6$, 400 MHz) $\delta$ 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_{3}O_{3}SBr (M + H)^+ : 546.0666; found 546.0667.

(1S,2R,3S,4R,5S)-4-(2-(4-(ferrocene-2-yl)-1H-1,2,3-triazol-1-yl)-6-(methylamino)-9H-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. 1H 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_{20}H_{17}N_{3}O_{3}Fe (M) ^+: 569.1586; found 569.1589.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(2-iodo-6-(methylamino)-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-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. 1H NMR (CD_{3}OD, 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_{19}H_{22}N_{3}O_{4} (M + H)^+ : 500.1072; found 500.1075.

Ethyl(3aR,3bS,4aS,5R,5aS)-5-(6-(ethylamino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (23b)

Compound 23b (89%) was prepared from compound 22 following the same method for compound 23a. 1H NMR (CD_{3}OD, 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_{22}N_{3}O_{4} (M + H)^+ : 514.0946; found 514.0948.

Ethyl(3aR,3bS,4aS,5R,5aS)-5-(6-(cyclobutylamino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (23c)

Compound 23c (85%) was prepared from compound 22 following the same method for compound 23a. 1H NMR (CD_{3}OD, 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}N_{3}O_{4} (M + H)^+ : 540.1102; found 540.1105.

(3aR,3bS,4aS,5R,5aS)-5-(2-iodo-6-(methylamino)-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (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_{2}Cl_{2}:MeOH=40:1) to give the compound 24a (0.360 g, 79%) as a white powder. 1H NMR (CD_{3}OD, 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_{21}H_{27}N_{3}O_{3} (M + H)^+ : 485.0798; found 485.0803.

(3aR,3bS,4aS,5R,5aS)-5-(6-(ethylamino)-2-iodo-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (24b)
Compound 24b (75%) was prepared from compound 23b following the same method for compound 24a. $^1$H NMR (CD$_3$OD, 400 MHz) $\delta$ 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$_2$O$_3$ (M + H)$^+$: 499.0949; found 499.0952.

(3aR,3bS,4aS,5S,5aS)-5-(6-(cyclobutylamino)-2-ido-9H-purin-9-yl)-N,2,2-trimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxamide (24c) Compound 24c (78%) was prepared from compound 23c following the same method for compound 24a. $^1$H NMR (CD$_3$OD, 400 MHz) $\delta$ 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$_3$O$_3$ (M + H)$^+$: 525.1111; found 525.1100.

(1S,2R,3S,4R,5S)-2,3-dihydroxy-4-(2-ido-6-(methylamino)-9H-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% trifluoroethanesulfonic acid (2 mL) was heated at 70 °C for 5 h. Solvent was evaporated under vacuum, and the residue was purified on flash silica gel column chromatography (CH$_2$Cl$_2$:MeOH = 25:1) to give the compound 25 (13 mg, 88%) as a white powder. $^1$H NMR (CD$_3$OD, 400 MHz) $\delta$ 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$_6$O$_3$ (M + H)$^+$: 445.0485; found 445.0489.

(1S,2R,3S,4R,5S)-4-(6-(ethylamino)-2-ido-9H-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$_3$OD, 400 MHz) $\delta$ 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$_6$O$_3$ (M + H)$^+$: 459.0637.

(1S,2R,3S,4R,5S)-4-(6-(cyclobutylamino)-2-ido-9H-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$_3$OD, 400 MHz) $\delta$ 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$_6$O$_3$ (M + H)$^+$: 485.0798; found 485.0794.

(1S,2R,3S,4R,5S)-2,3-dihydroxy-4-(2-ido-6-(phenethylamino)-9H-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$_3$OD, 400 MHz) $\delta$ 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$_6$O$_3$ (M + H)$^+$: 535.0955; found 535.0957.

(1S,2R,3S,4R,5S)-4-(2-azido-6-(methylamino)-9H-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$_2$O (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$_2$CO$_3$ (3.5 mg, 0.03 mmol) in $^1$BuOH (1 mL)-H$_2$O (1 mL) and heated at 65 °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$_2$Cl$_2$:MeOH = 15:1) to give the azido derivative 30 (55 mg, 91%) as a colorless powder. $^1$H NMR (CD$_3$OD, 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$_{14}$H$_{18}$N$_5$O$_3$ (M + H)$^+$: 360.1533; found 360.1538.

(1S,2R,3S,4R,5S)-4-(2-azido-6-((ethylamino)-9H-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$_3$OD, 400 MHz) δ 7.98 (s, 1H), 5.02 (d, J = 5.6 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$_5$O$_3$ (M + H)$^+$: 374.1684; found 374.1682.

(1S,2R,3S,4R,5S)-4-(2-azido-6-(cyclobutylamino)-9H-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$_3$OD, 400 MHz) δ 7.96 (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$_{17}$H$_{22}$N$_5$O$_3$ (M + H)$^+$: 400.1846; found 400.1846.

(1S,2R,3S,4R,5S)-4-(2-azido-6-((3-chlorobenzyl)amino)-9H-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$_3$OD, 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$_5$O$_3$Cl (M + H)$^+$: 470.1456; found 470.1461.

(1S,2R,3S,4R,5S)-4-(2-azido-6-((phenethylamino)-9H-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$_3$OD, 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$_{24}$H$_{24}$N$_5$O$_3$ (M + H)$^+$: 450.2002; found 450.2009.
Representative $^1$H-NMR and Mass Spectra

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Compound 7

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Relative Abundance

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Compound 19

DKT-XI-3

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Elemental composition search on mass 546.07

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Composition search on mass 650.07

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