

Supporting Information

Discovery of Highly Potent Pinanamine-Based Inhibitors against Amantadine- and Oseltamivir-Resistant Influenza A Viruses

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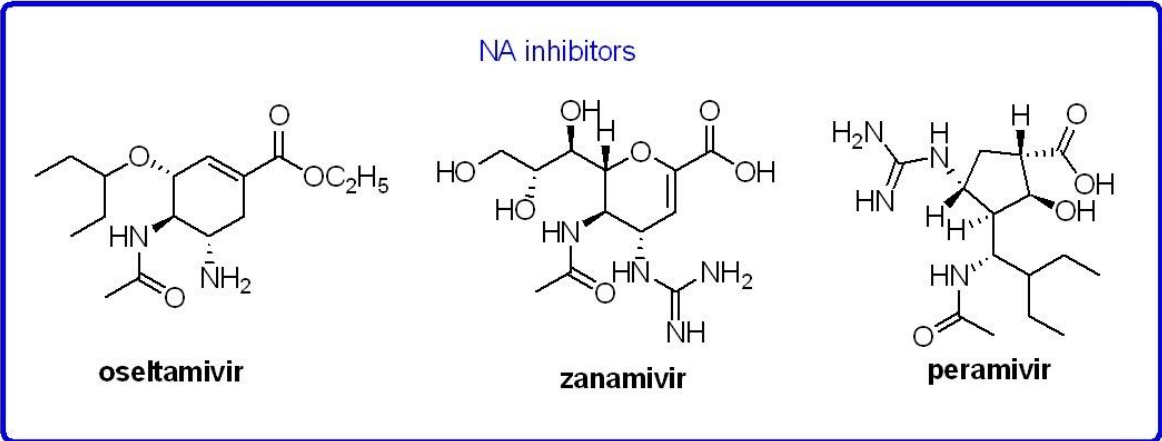
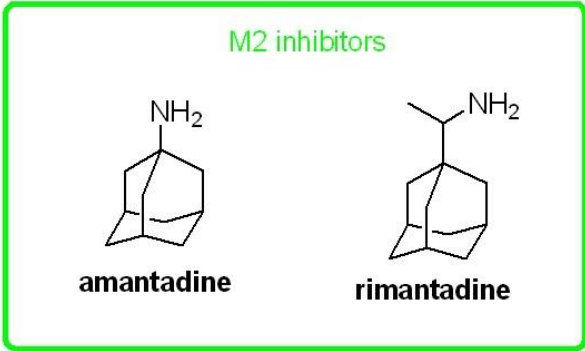
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Chart S1. Anti-influenza A drugs.



A

M090 μ M

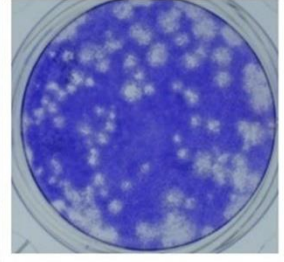
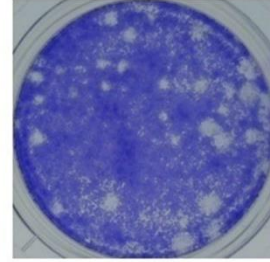
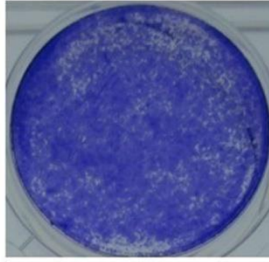
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15

7.5

Virus

**A/PR/8/34
(NA-H274Y)**



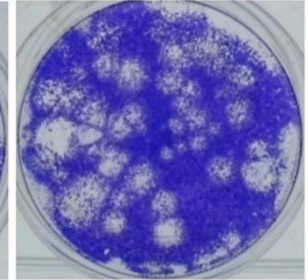
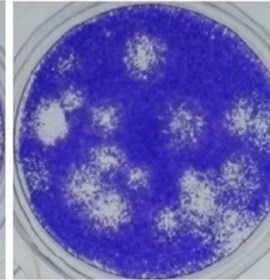
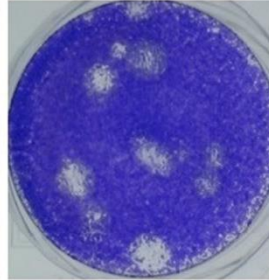
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13

6

Virus

A/PR/8/34



M090 μ M

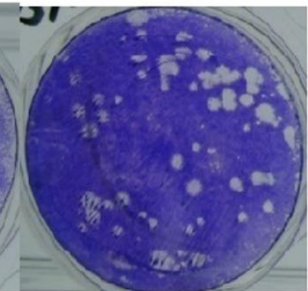
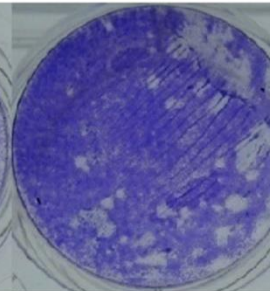
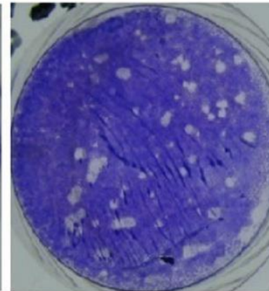
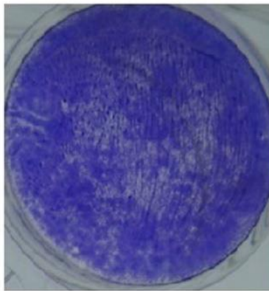
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13

6

Virus

A/Hong Kong/68



M090 μ M

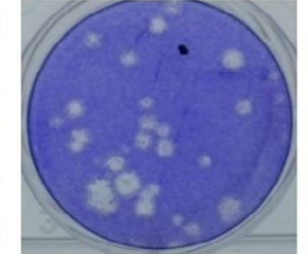
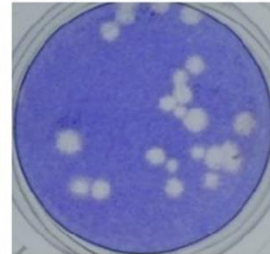
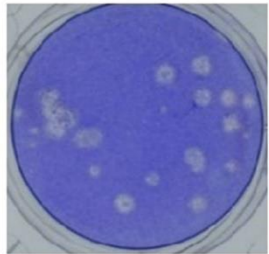
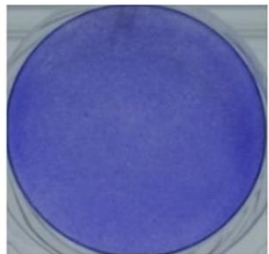
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3

1.5

Virus

A/WSN/33



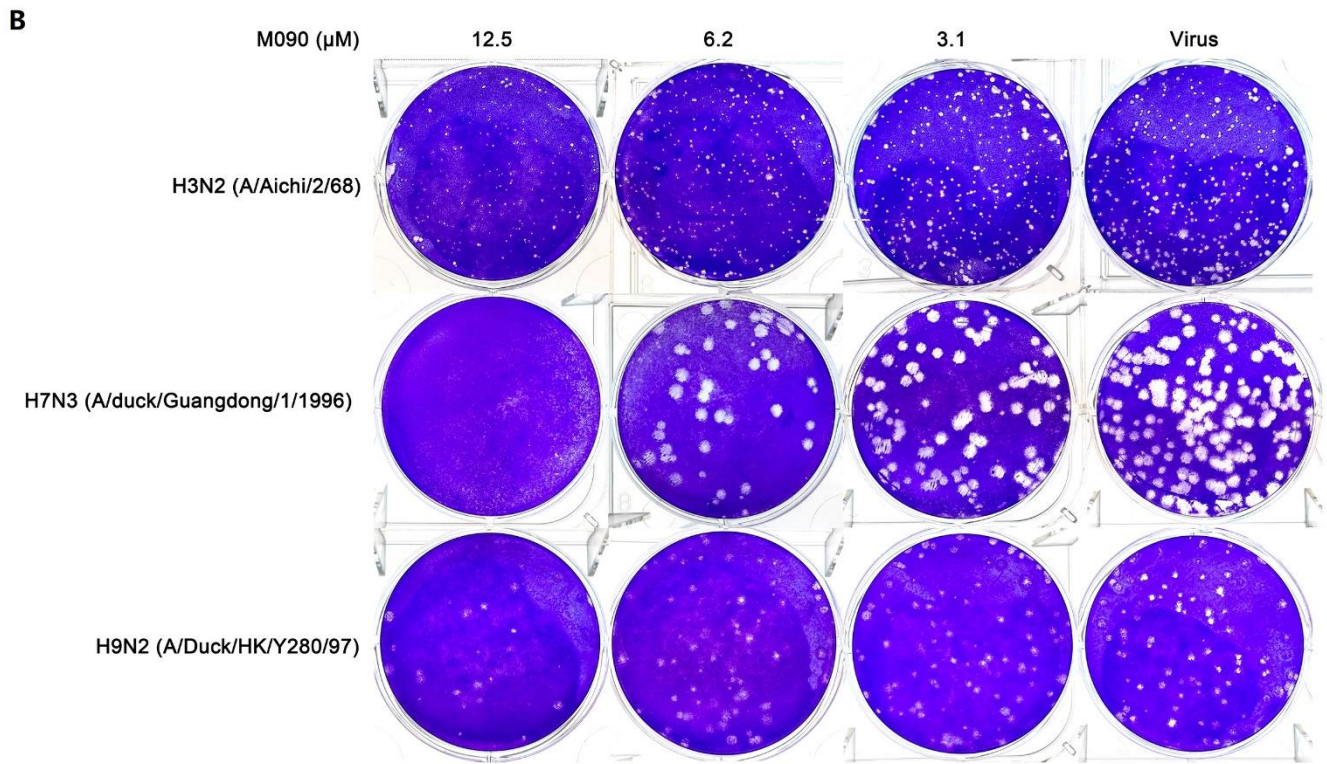


Figure S1. The plaque reduction assay of M090. Multiple influenza A strains were assayed for plaque formation treated with gradient concentration of **M090** on MDCK cells.

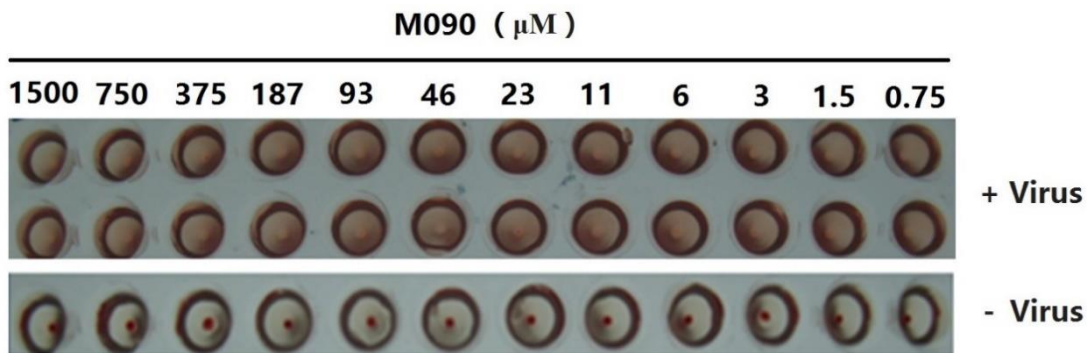


Figure S2. Hemagglutination inhibition assay. M090 did not inhibit the virus-induced aggregation of chicken erythrocytes of any concentrations.

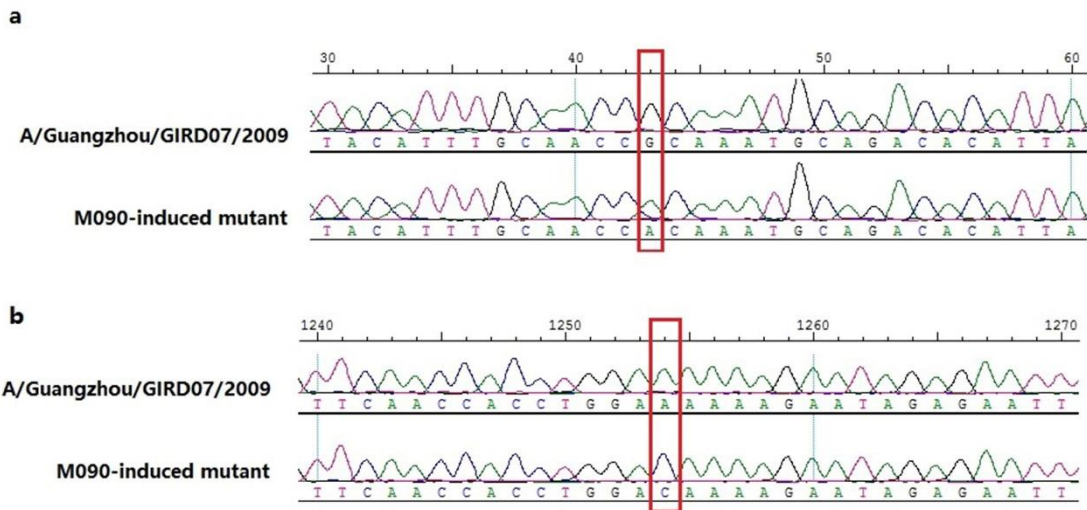


Figure S3. Changes in basic groups of M090-induced mutant. (a) HA segment, basic group 43 (G→A), residue 15 (A→T). (b) HA segment, basic group 1254 (A→C), residue 418 (E→D).

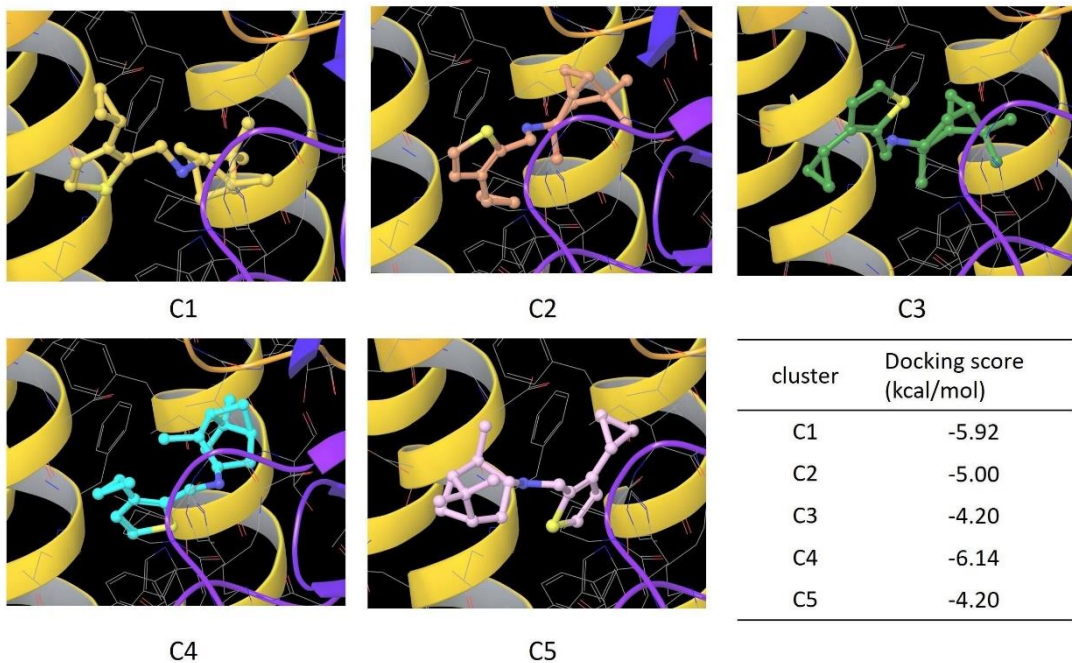


Figure S4. Molecular docking and clusters scoring. Conformations of M090 were docked into active sites of HA. Poses in this binding site were clustered and scored.

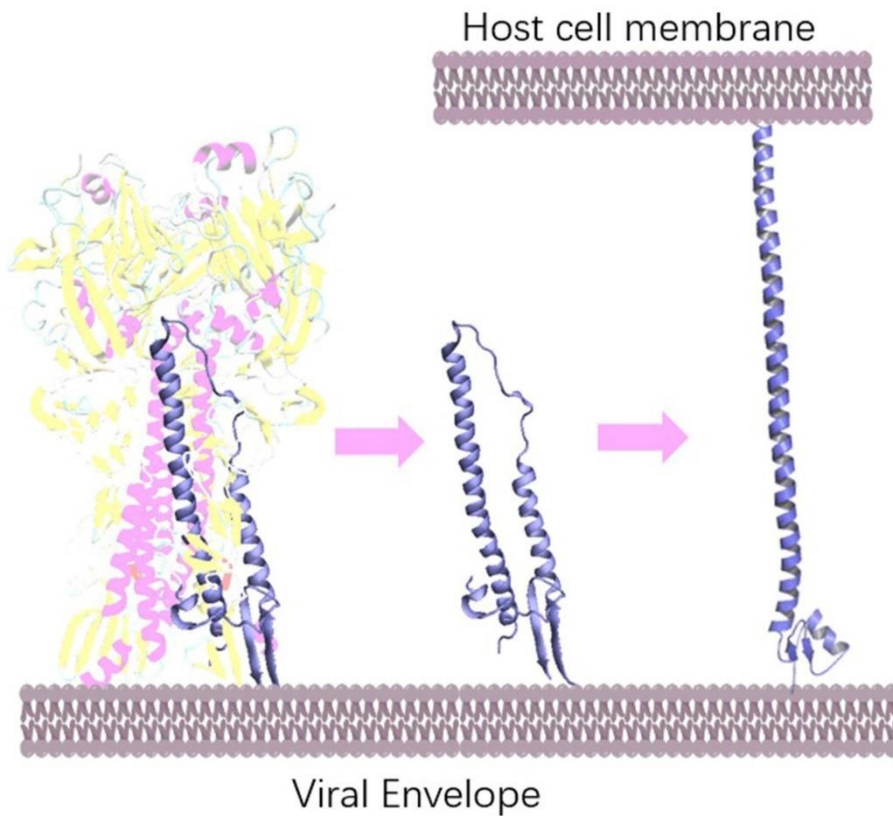


Figure S5. Conformational rearrangements of HA₂ monomer in membrane fusion¹.

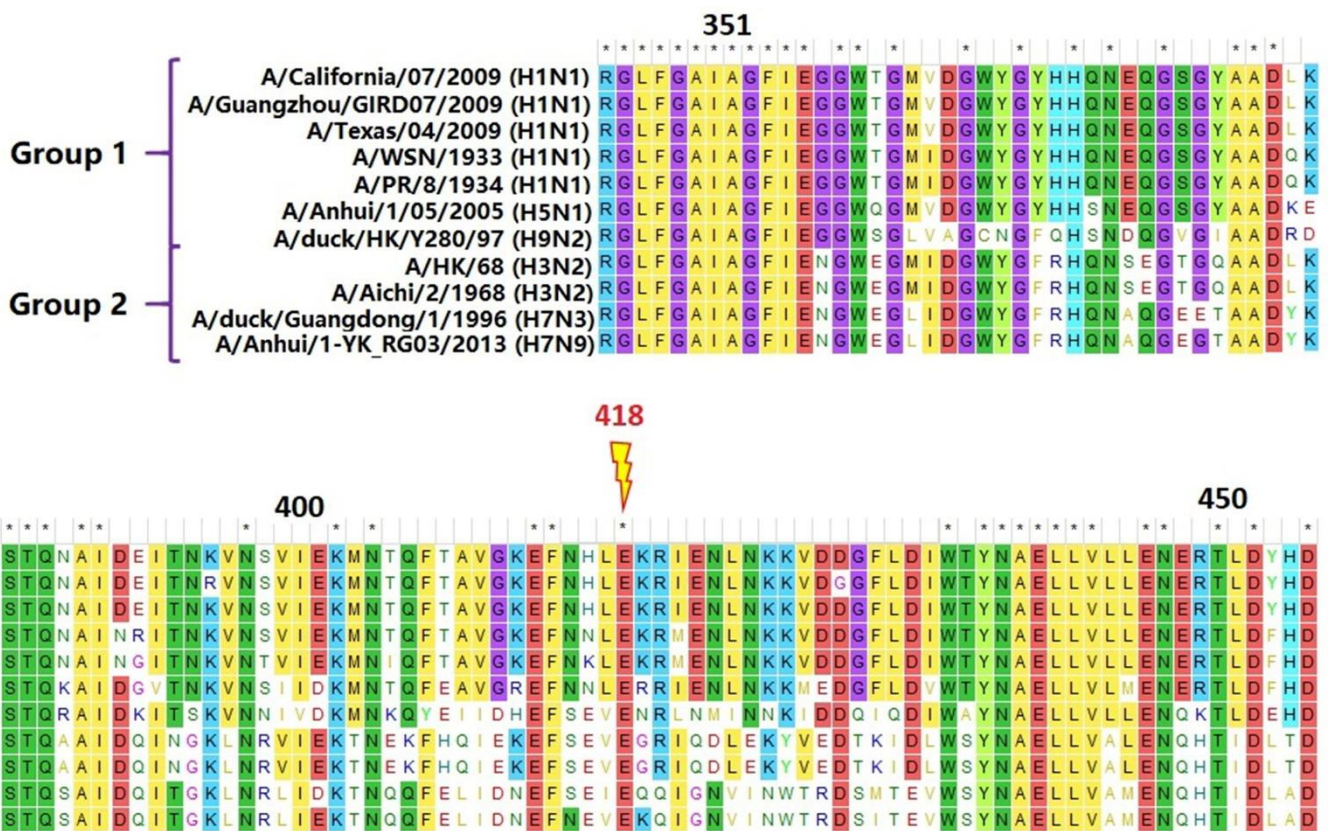


Figure S6. HA sequence analysis. HA protein sequences of influenza virus were obtained from the Influenza Research Database (<http://www.fludb.org>). Residues 350-450 of HA sequences from different strains were aligned by MEGA 7 (www.megasoftware.net) using the ClustalW method.

Table S1. Inhibitory activity of compounds on M2 ion channel conductance detected by two-electrode voltage clamp (TEVC)

Compd.	M2 ion channel inhibition (%) ^a	
	S31N	WT
M090	12.97 ± 0.74	2.70 ± 1.46
11	11.10 ± 0.38	17.57 ± 2.61
12	5.25 ± 1.45	13.80 ± 1.18
13	3.10 ± 3.10	9.10 ± 2.86
23	2.60 ± 1.47	15.97 ± 2.28
24	7.27 ± 0.33	42.23 ± 3.07
37	2.55 ± 0.65	38.60 ± 1.61
40	0	15.30 ± 1.78
Amantadine	36.40 ± 2.00	93.80 ± 1.21

^a Inhibition (%) for each of the compounds were measured after 2 minutes of drug exposure at pH 5.5 and drug concentration, 100 μM.

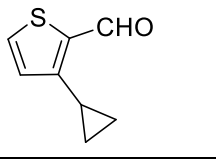
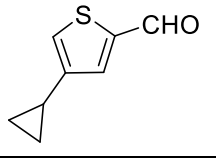
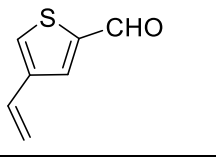
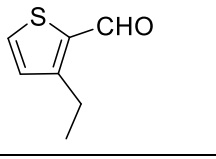
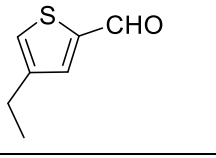
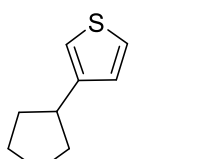
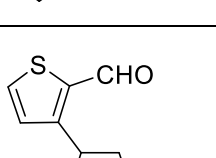
Table S2. Primer sequence for segments of influenza virus (A/Guangzhou/GIRD/07/2009).

PCR	Forward	Reverse
HA-1	ATACGACTAGCAAAAGCAGGGG	TGCTCATTTTGATGGTGATAACCG
HA-2	ATCCGATCACAATTGGAAAATGTCC	GTGTCAGTAGAAACAAGGGTGTTT
MP-1	AGCAAAAGCAGGTAG	AGTAGMAACAAGGTAGT

Reference:

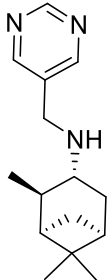
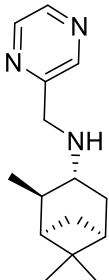
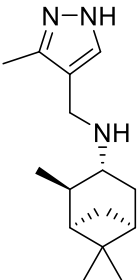
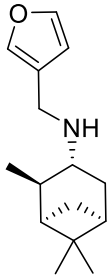
- (1) Kalani, M. R., Moradi, A., Moradi, M. & Tajkhorshid, E. Characterizing a histidine switch controlling ph-dependent conformational changes of the influenza virus hemagglutinin. *Biophys. J.* **2013**, *105*, 993–1003.

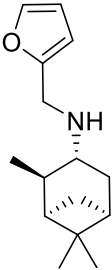
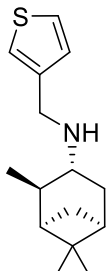
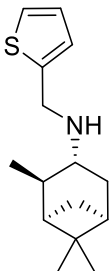
Synthesis and characterization of intermediates

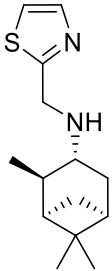
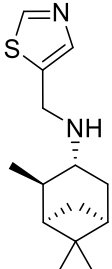
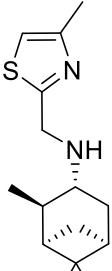
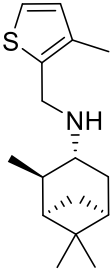
	Method D. Yield, 21%. ¹ H NMR (400 MHz, CDCl ₃) δ 10.19 (d, J = 0.8 Hz, 1H), 7.58 (d, J = 4.0 Hz, 1H), 6.63 (d, J = 5.2 Hz, 1H), 2.51–2.44 (m, 1H), 1.17–1.12 (m, 2H), 0.86–0.83 (m, 2H).
	Method D. Yield, 15%. ¹ H NMR (400 MHz, CDCl ₃) δ 9.84 (d, J = 1.2 Hz, 1H), 7.49 (d, J = 1.2 Hz, 1H), 7.31 (s, 1H), 1.95–1.91 (m, 1H), 1.00–0.95 (m, 2H), 0.68–0.64 (m, 2H).
	Method D. Yield, 12%. ¹ H NMR (400 MHz, CDCl ₃) δ 9.90 (s, 1H), 7.86 (s, 1H), 7.57 (s, 1H), 6.70–6.63 (m, 1H), 5.68 (d, J = 17.6 Hz, 1H), 5.31 (d, J = 11.2 Hz, 1H).
	Method B. Yield, 20%. ¹ H NMR (400 MHz, CDCl ₃) δ 10.04 (d, J = 0.8 Hz, 1H), 7.65 (d, J = 4.8 Hz, 1H), 7.03 (d, J = 4.8 Hz, 1H), 3.02–2.97 (q, 2H), 1.32–1.28 (t, 2H).
	Method C. Yield, 25%. ¹ H NMR (400 MHz, CDCl ₃) δ 9.77 (s, 1H), 7.54 (s, 1H), 7.29 (s, 1H), 2.58 (q, 2H), 1.18–1.41 (t, 2H).
	Method A. Yield, 16%. ¹ H NMR (400 MHz, CDCl ₃) δ: 7.24 (dd, J = 5.2, 3.2 Hz, 1H), 6.98 (dd, J = 5.2, 1.2 Hz, 1H), 6.94 (dt, J = 3.2, 1.2 Hz, 1H), 3.06 (p, J = 8.8 Hz, 1H), 2.11–2.00 (m, 2H), 1.83–1.72 (m, 2H), 1.72–1.63 (m, 2H), 1.62–1.55 (m, 2H).
	Method B. Yield, 23%. ¹ H NMR (400 MHz, CDCl ₃) δ: 10.09 (s, 1H), 7.63 (d, J = 1.2 Hz, 1H), 7.09 (d, J = 1.2 Hz, 1H), 3.29–3.22 (m, 1H), 1.98–1.92 (m, 2H), 1.88–1.82 (m, 2H), 1.79–1.73 (m, 2H), 1.53–1.46 (m, 2H).

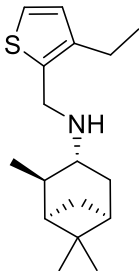
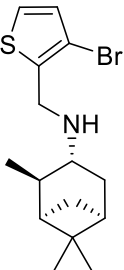
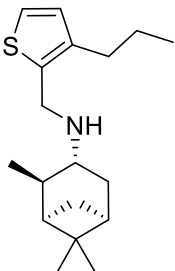
Other intermediates were used directly for next step without separation and purification.

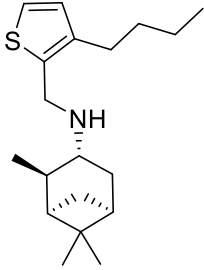
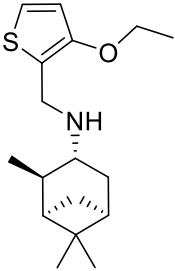
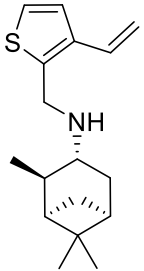
Final compounds synthesis and characterization.

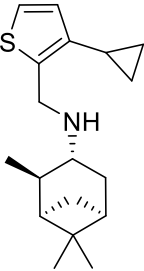
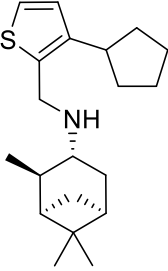
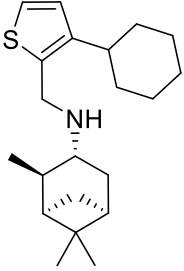
 <p>Compound 1</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(pyrimidin-5-ylmethyl) bicyclo [3.1.1] heptan-3-amine (1. HCl). Method E. Yield, 60%. ¹H NMR (400 MHz, DMSO-d₆) δ 9.65 (br s, 1H), 9.28 (br s, 1H), 9.21 (s, 1H), 9.06 (s, 2H), 4.27 (m, 2H), 3.49 (m, 1H), 2.40 (t, J = 12.0 Hz, 1H), 2.34 – 2.24 (m, 1H), 2.20 (m, 1H), 2.03 – 1.99 (m, 2H), 1.81 (t, J = 5.8 Hz, 1H), 1.39 (d, J = 10.0 Hz, 1H), 1.22 (s, 3H), 1.18 (d, J = 7.1 Hz, 3H), 0.93 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 159.28, 158.74, 56.70, 47.52, 44.16, 40.78, 40.22, 38.86, 32.17, 27.68, 23.68, 21.24. HRMS: m/z (M + H⁺): calculated, 246.19, found, 246.19611. HPLC: gradient solvent, 10 % to 80% KH₂PO₄ in H₂O, flow rate, 1.0 mL/min, retention time 9.14 min, purity 98.39 %.</p>
 <p>Compound 2</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(pyrazin-2-ylmethyl) bicyclo [3.1.1] heptan-3-amine (2. HCl). Method E. Yield, 47%. ¹H NMR (400 MHz, DMSO-d₆) δ 9.69 (br s, 1H), 9.32 (br s, 1H), 8.91 (s, 1H), 8.74 (s, 1H), 8.71 (s, 1H), 4.53 – 4.34 (m, 2H), 3.53 (m, 1H), 2.38 (t, J = 11.0 Hz, 1H), 2.33 – 2.14 (m, 2H), 1.97 (m, 2H), 1.85 – 1.74 (m, 1H), 1.40 (d, J = 9.9 Hz, 1H), 1.21 (s, 3H), 1.16 (d, J = 7.1 Hz, 3H), 0.90 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 148.79, 145.80, 145.05, 144.33, 56.32, 47.49, 47.10, 40.77, 40.23, 38.85, 32.18, 31.28, 27.70, 23.67, 21.07. HRMS: m/z (M + H⁺): calculated, 246.19, found, 246.19626. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 8.45 min, purity 95.08 %.</p>
 <p>Compound 3</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-((3-methyl-1H-pyrazol-4-yl)methyl) bicyclo [3.1.1] heptan-3-amine (3.2HCl). Method E. Yield, 61%. ¹H NMR (400 MHz, DMSO-d₆) δ 9.61 (br s, 1H), 9.17 (br s, 1H), 8.01 (s, 1H), 7.63 (br s, 2H), 4.09 – 3.92 (m, 2H), 3.37 (m, 1H), 2.37 (m, 1H), 2.33 (s, 3H), 2.29 – 2.21 (m, 1H), 2.16 (m, 1H), 1.98 (m, 2H), 1.78 (t, J = 5.0 Hz, 1H), 1.47 (d, J = 9.9 Hz, 1H), 1.20 (s, 3H), 1.13 (d, J = 7.1 Hz, 3H), 0.90 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 142.38, 136.42, 108.77, 54.90, 47.00, 40.33, 38.41, 38.11, 31.75, 30.86, 27.27, 23.20, 20.68, 9.83. HRMS: m/z (M + H⁺): calculated, 248.20, found, 248.21194. This compound was purified using preparative HPLC, purity 99.68 %.</p>
	<p>(1R,2R,3R,5S)-N-(furan-3-ylmethyl)-2,6,6-trimethylbicyclo [3.1.1] heptan-3-amine (4. HCl). Method E. Yield, 69%. ¹H NMR (400 MHz, DMSO-d₆) δ 9.73 (br s, 1H), 9.30 (br s, 1H), 7.90 (s, 1H), 7.72 (s, 1H), 6.85 (s, 1H), 4.02 (m, 2H), 3.24 (m, 1H), 2.28 (m, 2H), 2.16 (m, 1H), 2.03 – 1.89 (m, 2H), 1.78 (t, J = 5.0 Hz, 1H), 1.43 (d, J = 9.6 Hz, 1H), 1.19 (s, 3H), 1.10 (d, J = 7.1 Hz, 3H), 0.85 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ</p>

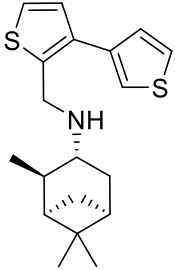
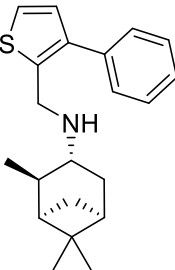
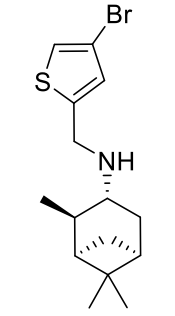
<p>Compound 4</p>	<p>143.80, 143.28, 116.27, 111.55, 54.40, 46.98, 40.27, 39.79, 38.79, 38.37, 31.80, 30.57, 27.23, 23.19, 20.59. HRMS: m/z ($M + H^+$): calculated, 234.18, found, 234.18500. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 4.89 min, purity 99.83 %.</p>
<p>Compound 5</p> 	<p>(1R,2R,3R,5S)-N-(furan-2-ylmethyl)-2,6,6-trimethylbicyclo [3.1.1] heptan-3-amine (5. HCl). Method E. Yield, 55%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.79 (br s, 1H), 9.33 (br s, 1H), 7.79 (d, <i>J</i> = 1.8 Hz, 1H), 6.73 (d, <i>J</i> = 3.3 Hz, 1H), 6.54 (dd, <i>J</i> = 3.3, 1.8 Hz, 1H), 4.23 (br s, 2H), 3.26 (m, 1H), 2.29 (m, 2H), 2.13 (m, 1H), 2.03 – 1.87 (m, 2H), 1.78 (t, <i>J</i> = 4.9 Hz, 1H), 1.39 (d, <i>J</i> = 9.9 Hz, 1H), 1.19 (s, 3H), 1.09 (d, <i>J</i> = 7.1 Hz, 3H), 0.87 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 145.73, 143.75, 112.06, 110.83, 55.06, 46.98, 40.45, 40.24, 38.18, 31.68, 30.43, 27.09, 22.93, 20.40. HRMS: m/z ($M + H^+$): calculated, 234.18, found, 234.18510. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 5.00 min, purity 99.87 %.</p>
<p>Compound 6</p> 	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(thiophen-3-ylmethyl) bicyclo [3.1.1] heptan-3-amine (6. HCl). Method E. Yield, 69%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.80 (br s, 1H), 9.37 (br s, 1H), 7.83 (dd, <i>J</i> = 3.0, 1.2 Hz, 1H), 7.61 (dd, <i>J</i> = 5.0, 3.0 Hz, 1H), 7.46 (dd, <i>J</i> = 5.0, 1.2 Hz, 1H), 4.15 (m, 2H), 3.30 – 3.13 (m, 1H), 2.38 – 2.11 (m, 3H), 2.06 – 1.87 (m, 2H), 1.77 (t, <i>J</i> = 4.9 Hz, 1H), 1.45 (d, <i>J</i> = 9.9 Hz, 1H), 1.19 (s, 3H), 1.09 (d, <i>J</i> = 7.1 Hz, 3H), 0.83 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 132.53, 128.96, 127.06, 126.86, 54.67, 47.00, 42.66, 40.29, 39.76, 38.41, 31.78, 30.60, 27.25, 23.18, 20.61. HRMS: m/z ($M + H^+$): calculated, 250.16, found, 250.16216. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 7.09 min, purity 97.62 %.</p>
<p>Compound 7</p> 	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(thiophen-2-ylmethyl) bicyclo [3.1.1] heptan-3-amine (7. HCl). Method E. Yield, 74%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.76 (br s, 1H), 9.29 (br s, 1H), 7.64 (dd, <i>J</i> = 5.1, 1.2 Hz, 1H), 7.44 (dd, <i>J</i> = 3.5, 1.2 Hz, 1H), 7.11 (dd, <i>J</i> = 5.1, 3.5 Hz, 1H), 4.39 (m, 2H), 3.32 – 3.21 (m, 1H), 2.38 – 2.22 (m, 2H), 2.15 (m, 1H), 2.04 – 1.91 (m, 2H), 1.78 (t, <i>J</i> = 5.7 Hz, 1H), 1.40 (d, <i>J</i> = 9.8 Hz, 1H), 1.19 (s, 3H), 1.08 (d, <i>J</i> = 7.1 Hz, 3H), 0.85 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 133.29, 131.31, 128.63, 127.74, 54.99, 47.44, 42.54, 40.76, 40.26, 38.84, 32.30, 31.05, 27.69, 23.61, 20.97. HRMS: m/z ($M + H^+$): calculated, 250.16, found, 250.16252. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 7.19 min, purity 99.50 %.</p>

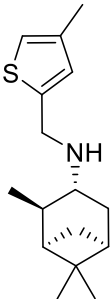
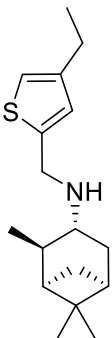
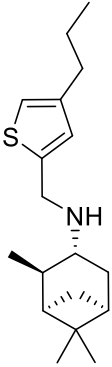
 <p>Compound 8</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(thiazol-2-ylmethyl) bicyclo [3.1.1] heptan-3-amine (8. HCl). Method E. Yield, 13%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.93 (br s, 1H), 9.53 (br s, 1H), 7.94 (d, <i>J</i> = 3.2 Hz, 1H), 7.89 (d, <i>J</i> = 3.2 Hz, 1H), 4.61 (m, 2H), 3.47 (m, 1H), 2.35 (t, <i>J</i> = 10.8 Hz, 1H), 2.31 – 2.22 (m, 1H), 2.17 (m, 1H), 1.97 (m, 2H), 1.79 (t, <i>J</i> = 5.2 Hz, 1H), 1.40 (d, <i>J</i> = 10.0 Hz, 1H), 1.20 (s, 3H), 1.12 (d, <i>J</i> = 7.1 Hz, 3H), 0.88 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 160.36, 143.09, 123.30, 55.87, 47.53, 44.79, 40.79, 38.86, 32.24, 31.10, 27.71, 23.64, 21.00. HRMS: <i>m/z</i> (M + H⁺): calculated, 251.15, found, 251.15752. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 3.18 min, purity 99.08 %.</p>
 <p>Compound 9</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(thiazol-5-ylmethyl) bicyclo [3.1.1] heptan-3-amine (9. HCl). Method E. Yield, 78%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.81 (br s, 1H), 9.41 (br s, 1H), 9.17 (s, 1H), 8.15 (s, 1H), 4.50 (t, <i>J</i> = 5.4 Hz, 2H), 3.41 – 3.25 (m, 1H), 2.40 – 2.21 (m, 2H), 2.21 – 2.11 (m, 1H), 2.05 – 1.90 (m, 2H), 1.79 (t, <i>J</i> = 5.2 Hz, 1H), 1.40 (d, <i>J</i> = 9.8 Hz, 1H), 1.20 (s, 3H), 1.12 (d, <i>J</i> = 7.1 Hz, 3H), 0.87 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 157.09, 146.49, 128.80, 55.56, 47.46, 40.74, 40.24, 38.83, 32.25, 31.12, 27.67, 23.64, 21.06. HRMS: <i>m/z</i> (M + H⁺): calculated, 251.15, found, 251.15733. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 2.51 min, purity 95.21 %.</p>
 <p>Compound 10</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-((4-methylthiazol-2-yl)methyl) bicyclo [3.1.1] heptan-3-amine (10. HCl). Method E. Yield, 62%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.89 (br s, 1H), 9.49 (br s, 1H), 7.42 (s, 1H), 4.54 (m, 2H), 3.47 (m, 1H), 2.41 (s, 3H), 2.34 (m, 1H), 2.30 – 2.22 (m, 1H), 2.16 (m, 1H), 1.98-1.93 (m, 2H), 1.84 – 1.73 (m, 1H), 1.39 (d, <i>J</i> = 9.9 Hz, 1H), 1.20 (s, 3H), 1.12 (d, <i>J</i> = 7.1 Hz, 3H), 0.88 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 159.70, 152.49, 117.55, 55.87, 47.52, 44.87, 40.80, 40.23, 38.92, 32.24, 31.09, 27.76, 23.68, 21.04, 16.99. HRMS: <i>m/z</i> (M + H⁺): calculated, 265.17, found, 265.17349. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 4.92 min, purity 98.79 %.</p>
 <p>Compound 11</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-((3-methylthiophen-2-yl)methyl) bicyclo [3.1.1] heptan-3-amine (11. HCl). Method E. Yield, 41%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.77 (br s, 1H), 9.17 (br s, 1H), 7.56 (d, <i>J</i> = 5.1 Hz, 1H), 6.95 (d, <i>J</i> = 5.1 Hz, 1H), 4.29 (br t, <i>J</i> = 5.4 Hz, 2H), 3.50 – 3.36 (m, 1H), 2.36 (m, 1H), 2.29 (s, 3H), 2.25 (m, 1H), 2.18 (m, 1H), 2.05-1.94 (m, 2H), 1.78 (td, <i>J</i> = 5.8, 1.9 Hz, 1H), 1.46 (d, <i>J</i> = 9.8 Hz, 1H), 1.20 (s, 3H), 1.11 (d, <i>J</i> = 7.1 Hz, 3H), 0.89 (s, 3H). ¹³C NMR (126 MHz,</p>

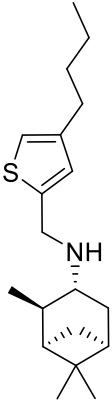
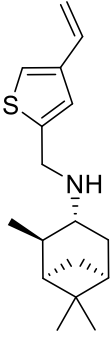
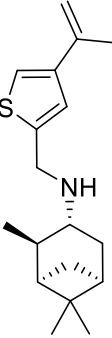
	DMSO) δ 139.07, 130.00, 126.72, 126.49, 55.13, 46.99, 40.60, 40.36, 39.83, 38.42, 31.73, 30.72, 27.26, 23.16, 20.61, 13.81. HRMS: m/z ($M + H^+$): calculated, 264.17, found, 264.17807. HPLC: solvent, H ₂ O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 5.76 min, purity 99.87 %.
 <p>Compound 12</p>	(1R,2R,3R,5S)-N-((3-ethylthiophen-2-yl) methyl) -2,6,6-trimethyl bicyclo [3.1.1] heptan-3-amine (12 . HCl). Method B, then Method E. Yield, 12%. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.66 (br s, 1H), 9.08 (br s, 1H), 7.59 (d, $J = 5.2$ Hz, 1H), 7.03 (d, $J = 5.2$ Hz, 1H), 4.44 – 4.17 (m, 2H), 3.42 (m, 1H), 2.66 (q, $J = 7.5$ Hz, 2H), 2.41 – 2.31 (m, 1H), 2.26 (m, 1H), 2.14 (m, 1H), 2.05 – 1.91 (m, 2H), 1.78 (td, $J = 5.8, 1.9$ Hz, 1H), 1.43 (d, $J = 9.9$ Hz, 1H), 1.20 (s, 3H), 1.17 (t, $J = 7.6$ Hz, 3H), 1.11 (d, $J = 7.1$ Hz, 3H), 0.89 (s, 3H). ¹³ C NMR (126 MHz, DMSO) δ 145.34, 128.23, 127.08, 125.94, 55.15, 46.96, 40.43, 40.35, 39.88 (overlap with DMSO peak, 38.40, 31.76, 30.69, 27.25, 23.14, 20.93, 20.56, 14.98. HRMS: m/z ($M + H^+$): calculated, 278.19, found, 278.19382. HPLC: solvent, H ₂ O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.16 min, purity 97.44 %.
 <p>Compound 13</p>	(1R,2R,3R,5S)-N-((3-bromothiophen-2-yl) methyl) -2,6,6-trimethyl bicyclo [3.1.1] heptan-3-amine (13 . HCl). Method E. Yield, 86%. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.77 (br s, 1H), 9.35 (br s, 1H), 7.84 (d, $J = 5.4$ Hz, 1H), 7.19 (d, $J = 5.3$ Hz, 1H), 4.35 (br s, 2H), 3.38 (br s, 1H), 2.44 (t, $J = 11.7$ Hz, 1H), 2.28 (m, 1H), 2.12 (m, 1H), 2.06 – 1.93 (m, 2H), 1.80 (td, $J = 5.7, 2.0$ Hz, 1H), 1.35 (d, $J = 9.9$ Hz, 1H), 1.20 (s, 3H), 1.13 (d, $J = 7.1$ Hz, 3H), 0.90 (s, 3H). ¹³ C NMR (126 MHz, DMSO) δ 130.00, 129.47, 128.43, 113.93, 55.02, 46.88, 41.71, 40.35, 40.00, 38.38, 31.77, 30.66, 27.22, 23.16, 20.55. HRMS: m/z ($M + H^+$): calculated, 328.07, found, 328.07306. HPLC: solvent, H ₂ O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 5.87 min, purity 99.87 %.
 <p>Compound 14</p>	(1R,2R,3R,5S)-2,6,6-trimethyl-N-((3-propylthiophen-2-yl) methyl) bicyclo [3.1.1] heptan-3-amine (14 . HCl). Method B, then Method E. Yield, 15%. ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.56 (br s, 1H), 9.02 (br s, 1H), 7.58 (d, $J = 5.2$ Hz, 1H), 7.01 (d, $J = 5.2$ Hz, 1H), 4.32 (m, 2H), 3.48 – 3.38 (m, 1H), 2.61 (dd, $J = 8.7, 6.7$ Hz, 2H), 2.41 – 2.31 (m, 1H), 2.27 (m, 1H), 2.13 (m, 1H), 2.05 – 1.91 (m, 2H), 1.79 (m, 1H), 1.64 – 1.51 (m, 2H), 1.40 (d, $J = 9.9$ Hz, 1H), 1.20 (s, 3H), 1.11 (d, $J = 7.0$ Hz, 3H), 0.92 (t, $J = 7.4$ Hz, 3H), 0.89 (s, 3H). ¹³ C NMR (126 MHz, DMSO) δ 144.23, 129.13, 127.38, 126.91, 55.56, 47.44, 40.95, 40.84, 40.38, 38.86, 32.24, 31.12, 30.11, 27.71, 23.85, 23.61, 21.02,

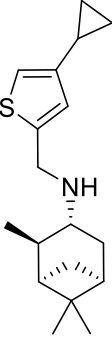
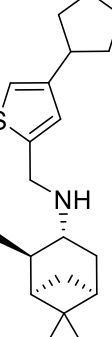
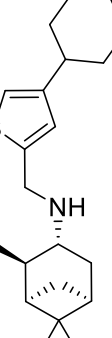
	14.18. HRMS: m/z ($M + H^+$): calculated, 292.20, found, 292.20941. HPLC: gradient solvent, 10 % to 100 % TFA in H_2O , flow rate, 1.0 mL/min, retention time 13.04 min, purity 100 %.
 <p>Compound 15</p>	(1R,2R,3R,5S)-N-((3-butylthiophen-2-yl)methyl)-2,6,6-trimethylbicyclo [3.1.1] heptan-3-amine (15 . HCl). Method B, then Method E. Yield, 22%. 1H NMR (400 MHz, DMSO- d_6) δ 9.62 (br s, 1H), 9.05 (br s, 1H), 7.58 (d, $J = 5.1$ Hz, 1H), 7.01 (d, $J = 5.2$ Hz, 1H), 4.31 (m, 2H), 3.40 (m, 1H), 2.64 (t, $J = 7.8$ Hz, 2H), 2.36 (t, $J = 11.7$ Hz, 1H), 2.31 – 2.23 (m, 1H), 2.13 (m, 1H), 2.06 – 1.92 (m, 2H), 1.85 – 1.74 (m, 1H), 1.53 (m, 2H), 1.41 (d, $J = 9.9$ Hz, 1H), 1.33 (q, $J = 7.4$ Hz, 2H), 1.20 (s, 3H), 1.11 (d, $J = 7.0$ Hz, 3H), 0.94 – 0.87 (m, 6H). ^{13}C NMR (126 MHz, DMSO) δ 144.41, 129.16, 127.43, 126.78, 55.64, 47.41, 41.02, 40.82, 40.41, 38.85, 32.87, 32.25, 31.20, 27.88, 27.70, 23.62, 22.40, 21.00, 14.23. HRMS: m/z ($M + H^+$): calculated, 306.22, found, 306.22501. HPLC: solvent, H_2O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.79 min, purity 99.73 %.
 <p>Compound 16</p>	(1R,2R,3R,5S)-N-((3-ethoxythiophen-2-yl)methyl)-2,6,6-trimethyl bicyclo [3.1.1] heptan-3-amine (16 . HCl). Method E. Yield, 66%. 1H NMR (400 MHz, DMSO- d_6) δ 9.56 (br s, 1H), 8.97 (br s, 1H), 7.61 (d, $J = 5.4$ Hz, 1H), 7.07 (d, $J = 5.4$ Hz, 1H), 4.17 (s, 2H), 4.12 (q, $J = 6.9$ Hz, 2H), 3.25 (m, 1H), 2.41 (t, $J = 11.7$ Hz, 1H), 2.28 (m, 1H), 2.07 (m, 1H), 2.02 – 1.88 (m, 2H), 1.78 (t, $J = 5.8$ Hz, 1H), 1.31 (t, $J = 7.3$ Hz, 4H), 1.19 (s, 3H), 1.03 (d, $J = 7.0$ Hz, 3H), 0.86 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 157.27, 127.27, 117.18, 108.67, 67.30, 54.56, 47.25, 40.81, 40.59, 39.01, 38.84, 32.49, 30.98, 27.70, 23.55, 20.79, 15.35. HRMS: m/z ($M + H^+$): calculated, 294.18, found, 294.18881. HPLC: solvent, H_2O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.12 min, purity 99.50 %.
 <p>Compound 17</p>	(1R,2R,3R,5S)-2,6,6-trimethyl-N-((3-vinylthiophen-2-yl)methyl) bicyclo [3.1.1] heptan-3-amine (17 . HCl). Method D, then Method E. Yield, 11%. 1H NMR (400 MHz, DMSO- d_6) δ 9.64 (br s, 1H), 9.09 (br s, 1H), 7.65 (d, $J = 5.3$ Hz, 1H), 7.42 (d, $J = 5.3$ Hz, 1H), 6.97 (dd, $J = 17.3, 11.0$ Hz, 1H), 5.79 (dd, $J = 17.2, 1.3$ Hz, 1H), 5.37 (dd, $J = 10.9, 1.3$ Hz, 1H), 4.45 (m, 2H), 3.38 (m, 1H), 2.41 – 2.20 (m, 2H), 2.19 – 2.06 (m, 1H), 2.05 – 1.92 (m, 2H), 1.83 – 1.72 (m, 1H), 1.37 (d, $J = 9.9$ Hz, 1H), 1.19 (s, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 0.86 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 140.91, 137.87, 129.19, 128.39, 125.49, 116.63, 55.60, 47.41, 40.80, 38.84, 32.30, 31.18, 27.70, 23.55, 20.95. HRMS: m/z ($M + H^+$): calculated, 276.17, found, 276.17809. HPLC: solvent, H_2O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.26 min, purity 99.80 %.

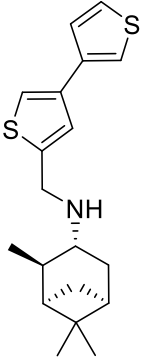
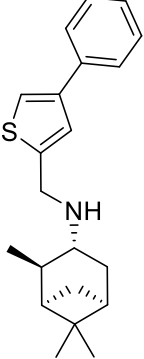
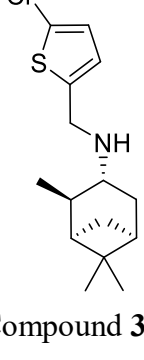
 <p>Compound 18</p>	<p>(1R,2R,3R,5S)-N-(3-cyclopropylthiophen-2-yl)methyl-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (M090. H₃PO₄). Method D, then Method E. Yield, 13%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.70 (br s, 1H), 9.09 (br s, 1H), 7.54 (d, <i>J</i> = 5.2 Hz, 1H), 6.67 (d, <i>J</i> = 5.3 Hz, 1H), 4.48-4.37 (m, 2H), 3.42 (m, 1H, overlap with H₂O peak), 2.44 – 2.34 (m, 1H), 2.27 (m, 1H), 2.18 – 2.06 (m, 2H), 2.05 – 1.92 (m, 2H), 1.80 – 1.76 (m, 1H), 1.38 (d, <i>J</i> = 9.9 Hz, 1H), 1.19 (s, 3H), 1.08 (d, <i>J</i> = 7.0 Hz, 3H), 0.99 – 0.94 (m, 2H), 0.87 (s, 3H), 0.72 (m, 1H), 0.64 (m, 1H). ¹³C NMR (126 MHz, DMSO) δ 145.75, 127.37, 126.15, 124.85, 54.75, 46.90, 40.53, 40.39, 39.76, 38.43, 31.91, 30.69, 27.28, 23.16, 20.52, 9.55, 8.86, 8.62. HRMS: <i>m/z</i> (M + H⁺): calculated, 290.19, found, 290.19376. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.33 min, purity 99.84 %.</p>
 <p>Compound 19</p>	<p>(1R,2R,3R,5S)-N-(3-cyclopentylthiophen-2-yl)methyl-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (19. HCl). Method A, Method B, then Method E. Yield, 4%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.74 (br s, 1H), 9.05 (br s, 1H), 7.59 (d, <i>J</i> = 5.2 Hz, 1H), 7.06 (d, <i>J</i> = 5.2 Hz, 1H), 4.45 – 4.16 (m, 2H), 3.37 (m, 1H), 3.20 (p, <i>J</i> = 8.8 Hz, 1H), 2.40 – 2.19 (m, 2H), 2.19 – 2.07 (m, 1H), 2.07 – 1.87 (m, 4H), 1.80-1.73 (m, 3H), 1.70 – 1.57 (m, 2H), 1.54-1.41 (m, 3H), 1.20 (s, 3H), 1.09 (d, <i>J</i> = 7.3 Hz, 3H), 0.87 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 148.60, 127.77, 126.96, 126.35, 55.39, 47.39, 40.83, 40.42, 38.85, 38.56, 34.97, 34.78, 32.31, 31.04, 27.70, 25.67, 23.58, 20.95. HRMS: <i>m/z</i> (M + H⁺): calculated, 318.22, found, 318.22491. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.66 min, purity 99.25 %.</p>
 <p>Compound 20</p>	<p>(1R,2R,3R,5S)-N-(3-cyclohexylthiophen-2-yl)methyl-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (20. HCl). Method A, Method B, then Method E. Yield, 7%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.76 (br s, 1H), 9.05 (br s, 1H), 7.58 (d, <i>J</i> = 5.2 Hz, 1H), 7.07 (d, <i>J</i> = 5.3 Hz, 1H), 4.43 – 4.24 (m, 2H), 3.33 (m, 1H), 2.86 – 2.69 (m, 1H), 2.43 – 2.22 (m, 2H), 2.14 (m, 1H), 2.08 – 1.93 (m, 2H), 1.85 – 1.61 (m, 6H), 1.47-1.35 (m, 5H), 1.24 (m, 1H), 1.20 (s, 3H), 1.08 (d, <i>J</i> = 7.0 Hz, 3H), 0.87 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 149.81, 127.72, 127.05, 125.74, 55.26, 47.33, 40.85, 40.64, 38.84, 37.32, 34.29, 34.21, 32.31, 31.03, 27.68, 26.56, 26.48, 25.84, 23.57, 20.91. HRMS: <i>m/z</i> (M + H⁺): calculated, 332.23, found, 332.24063. HPLC: gradient solvent, 10 % to 100 % TFA in H₂O, flow rate, 1.0 mL/min, retention time 14.03 min, purity 96.15 %.</p>

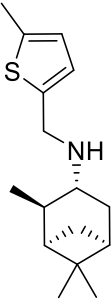
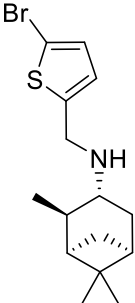
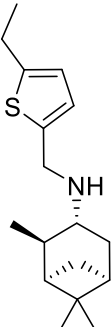
 <p>Compound 21</p>	<p>(1R,2R,3R,5S)-N-([3,3'-bithiophen]-2-ylmethyl)-2,6,6-trimethylbicyclo [3.1.1] heptan-3-amine (21. HCl). Method E. Yield, 70%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.70 (br s, 1H), 9.05 (br s, 1H), 7.76 (d, <i>J</i> = 5.0 Hz, 1H), 7.73-7.71 (m, 2H), 7.32 (d, <i>J</i> = 4.7 Hz, 1H), 7.23 (d, <i>J</i> = 5.0 Hz, 1H), 4.43 (m, 2H), 3.22 (m, 1H), 2.23 (m, 1H), 2.06 (m, 1H), 1.94 (m, 1H), 1.84 (m, 1H), 1.75 (m, 2H), 1.29 (d, <i>J</i> = 9.4 Hz, 1H), 1.16 (s, 3H), 1.02 (d, <i>J</i> = 6.9 Hz, 3H), 0.79 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 139.10, 135.73, 129.51, 128.84, 128.20, 128.15, 127.57, 124.37, 55.36, 47.31, 41.58, 40.82, 40.41, 38.85, 32.29, 30.63, 27.71, 23.72, 20.95. HRMS: <i>m/z</i> (M + H⁺): calculated, 332.14, found, 332.15005. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.53 min, purity 99.87 %.</p>
 <p>Compound 22</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(3-phenylthiophen-2-yl)methyl bicyclo [3.1.1] heptan-3-amine (22. HCl). Method E. 76%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.91 (br s, 1H), 9.14 (br s, 1H), 7.78 (d, <i>J</i> = 5.2 Hz, 1H), 7.51-7.40 (m, 5H), 7.19 (d, <i>J</i> = 5.2 Hz, 1H), 4.36 (m, 2H), 3.09 (m, 1H), 2.20 (m, 1H), 2.03 (m, 1H), 1.77-1.70 (m, 4H), 1.28 (d, <i>J</i> = 9.9 Hz, 1H), 1.14 (s, 3H), 1.00 (d, <i>J</i> = 7.0 Hz, 3H), 0.75 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 144.45, 135.36, 129.53, 129.33, 129.25, 128.33, 128.30, 128.21, 55.01, 47.21, 41.29, 40.71, 40.38, 38.75, 32.22, 30.36, 27.61, 23.66, 20.81. HRMS: <i>m/z</i> (M + H⁺): calculated, 326.19, found, 326.19363. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.68 min, purity 99.70 %.</p>
 <p>Compound 23</p>	<p>(1R,2R,3R,5S)-N-((4-bromothiophen-2-yl)methyl)-2,6,6-trimethylbicyclo [3.1.1] heptan-3-amine (23. HCl). Method E. 88%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.63 (br s, 1H), 9.26 (br s, 1H), 7.77 (d, <i>J</i> = 1.5 Hz, 1H), 7.47 (d, <i>J</i> = 1.6 Hz, 1H), 4.40 (m, 2H), 3.40 (m, 1H), 2.30 (m, 2H), 2.21 – 2.09 (m, 1H), 2.03 – 1.90 (m, 2H), 1.80 (m, 1H), 1.36 (d, <i>J</i> = 9.9 Hz, 1H), 1.20 (s, 3H), 1.12 (d, <i>J</i> = 7.1 Hz, 3H), 0.88 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 135.73, 133.31, 126.14, 108.84, 55.58, 47.54, 42.44, 40.81, 40.24, 38.91, 32.26, 31.14, 27.75, 23.71, 21.15. HRMS: <i>m/z</i> (M + H⁺): calculated, 328.07, found, 328.07288. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.07 min, purity 99.78 %.</p>

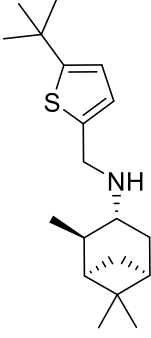
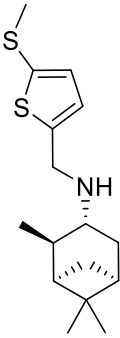
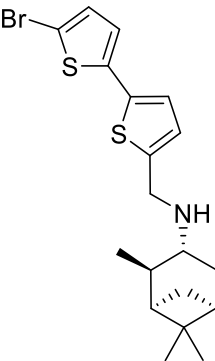
 <p>Compound 24</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(4-methylthiophen-2-yl)methyl bicyclo [3.1.1] heptan-3-amine (24. HCl). Method E. 80%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.45 (br s, 1H), 9.09 (br s, 1H), 7.21 (s, 2H), 4.34 (m, 2H), 3.38 (m, 1H), 2.39 – 2.25 (m, 2H), 2.21 (s, 3H), 2.16 – 2.06 (m, 1H), 1.96 (m, 2H), 1.80 (m, 1H), 1.34 (d, <i>J</i> = 9.9 Hz, 1H), 1.20 (s, 3H), 1.10 (d, <i>J</i> = 7.0 Hz, 3H), 0.87 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 137.11, 132.75, 123.10, 64.84, 54.62, 46.97, 42.36, 40.29, 38.36, 31.82, 30.66, 27.22, 23.15, 20.52, 15.25, 15.11. HRMS: <i>m/z</i> (M + H⁺): calculated, 264.17, found, 264.17810. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.15 min, purity 99.78 %.</p>
 <p>Compound 25</p>	<p>(1R,2R,3R,5S)-N-(4-ethylthiophen-2-yl)methyl-2,6,6-trimethylbicyclo [3.1.1] heptan-3-amine (25. HCl). Method C, then Method E. Yield, 10%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.78 (br s, 1H), 9.29 (br s, 1H), 7.31 (s, 1H), 7.22 (s, 1H), 4.30 (m, 2H), 3.28 (m, 1H), 2.57 (q, <i>J</i> = 7.5 Hz, 2H), 2.38 – 2.20 (m, 2H), 2.15 (m, 1H), 1.97 (m, 2H), 1.78 (t, <i>J</i> = 5.8 Hz, 1H), 1.42 (d, <i>J</i> = 9.8 Hz, 1H), 1.22 – 1.13 (m, 6H), 1.09 (d, <i>J</i> = 7.1 Hz, 3H), 0.85 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 144.16, 132.74, 131.69, 122.00, 64.92, 54.52, 46.99, 42.35, 40.31, 38.44, 31.87, 30.59, 27.30, 23.18, 22.94, 20.57, 14.76. HRMS (EI): <i>m/z</i> (M): calculated, 277.19, found, 277.1869. HPLC: gradient solvent, 10 % to 80% KH₂PO₄ in H₂O, flow rate, 1.0 mL/min, retention time 13.38 min, purity 99.07 %</p>
 <p>Compound 26</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(4-propylthiophen-2-yl)methyl bicyclo [3.1.1] heptan-3-amine (26. HCl). Method C, then Method E. Yield, 13%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.85 (br s, 1H), 9.31 (br s, 1H), 7.30 (s, 1H), 7.22 (s, 1H), 4.42 – 4.23 (m, 2H), 3.25 (m, 1H), 2.53 (t, <i>J</i> = 7.2 Hz, 2H), 2.28 (m, 2H), 2.15 (m, 1H), 2.05 – 1.92 (m, 2H), 1.78 (t, <i>J</i> = 5.8 Hz, 1H), 1.58 (m, 2H), 1.42 (d, <i>J</i> = 9.9 Hz, 1H), 1.19 (s, 3H), 1.08 (d, <i>J</i> = 7.1 Hz, 3H), 0.88 (t, <i>J</i> = 7.3 Hz, 3H), 0.84 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 142.91, 132.96, 132.38, 123.12, 54.78, 47.46, 42.71, 40.78, 40.23, 38.84, 32.32, 32.11, 30.94, 27.70, 23.56, 23.54, 20.92, 13.94. HRMS: <i>m/z</i> (M + H⁺): calculated, 292.20, found, 292.20929. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.49 min, purity 99.83 %.</p>

 <p>Compound 27</p>	<p>(1R,2R,3R,5S)-N-((4-butylthiophen-2-yl) methyl)-2,6,6-trimethyl bicyclo [3.1.1] heptan-3-amine (27. HCl). Method C, then Method E. 18%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.78 (br s, 1H), 9.26 (br s, 1H), 7.29 (s, 1H), 7.22 (s, 1H), 4.32 (m, 2H), 3.25 (m, 1H), 2.56 (t, <i>J</i> = 7.5 Hz, 2H), 2.36 – 2.21 (m, 2H), 2.14 (m, 1H), 2.04 – 1.90 (m, 2H), 1.79 (m, <i>J</i> = 5.8 Hz, 1H), 1.54 (m, 2H), 1.40 (d, <i>J</i> = 9.9 Hz, 1H), 1.29 (m, 2H), 1.19 (s, 3H), 1.07 (d, <i>J</i> = 7.0 Hz, 3H), 0.88 (t, <i>J</i> = 7.4 Hz, 3H), 0.84 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 143.06, 132.97, 132.34, 123.02, 54.81, 47.47, 42.75, 40.79, 40.26, 38.84, 32.53, 32.34, 30.98, 29.69, 27.71, 23.52, 22.01, 20.91, 14.10. HRMS: <i>m/z</i> (M + H⁺): calculated, 306.22, found, 306.22507. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.49 min, purity 99.94 %.</p>
 <p>Compound 28</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-((4-vinylthiophen-2-yl) methyl) bicyclo [3.1.1] heptan-3-amine (28. HCl). Method D, then Method E. Yield, 14%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.65 (br s, 1H), 9.24 (br s, 1H), 7.66 (s, 1H), 7.56 (s, 1H), 6.70 (dd, <i>J</i> = 17.6, 11.0 Hz, 1H), 5.61 (d, <i>J</i> = 17.6 Hz, 1H), 5.22 (d, <i>J</i> = 11.0 Hz, 1H), 4.35 (m, 2H), 3.35 (m, 1H), 2.33 (m, 2H), 2.15 (m, 1H), 2.06 – 1.88 (m, 2H), 1.79 (t, <i>J</i> = 5.8 Hz, 1H), 1.38 (d, <i>J</i> = 9.8 Hz, 1H), 1.20 (s, 3H), 1.11 (d, <i>J</i> = 7.1 Hz, 3H), 0.87 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 139.89, 133.78, 130.87, 128.34, 125.09, 114.19, 54.93, 46.98, 42.52, 40.29, 38.38, 31.80, 30.71, 27.23, 23.17, 20.57. HRMS: <i>m/z</i> (M + H⁺): calculated, 276.17, found, 276.17822. HPLC: gradient solvent, 10 % to 100 % TFA in H₂O, flow rate, 1.0 mL/min, retention time 12.12 min, purity 96.56 %</p>
 <p>Compound 29</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(4-(prop-1-en-2-yl) thiophen-2-yl) methyl) bicyclo [3.1.1] heptan-3-amine (29. HCl). Method D, then Method E. Yield, 10 %. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.87 (s, 1H), 9.39 (s, 1H), 7.73 (s, 1H), 7.54 (s, 1H), 5.37 (s, 1H), 5.05 (s, 1H), 4.34 (m, 2H), 3.33 (m, 1H), 2.40 – 2.12 (m, 3H), 2.05 (s, 3H), 2.00-1.94 (m, 2H), 1.78 (t, <i>J</i> = 5.9 Hz, 1H), 1.44 (d, <i>J</i> = 9.9 Hz, 1H), 1.19 (s, 3H), 1.10 (d, <i>J</i> = 7.0 Hz, 3H), 0.86 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 142.74, 138.11, 133.68, 129.50, 123.58, 112.29, 55.25, 47.48, 42.87, 40.77, 40.20, 38.86, 32.23, 31.07, 27.70, 23.62, 21.64, 21.05. HRMS: <i>m/z</i> (M + H⁺): calculated, 290.19, found, 290.19362. HPLC: gradient solvent, 10 % to 100 % TFA in H₂O, flow rate, 1.0 mL/min, retention time 12.53 min, purity 96.20 %</p>

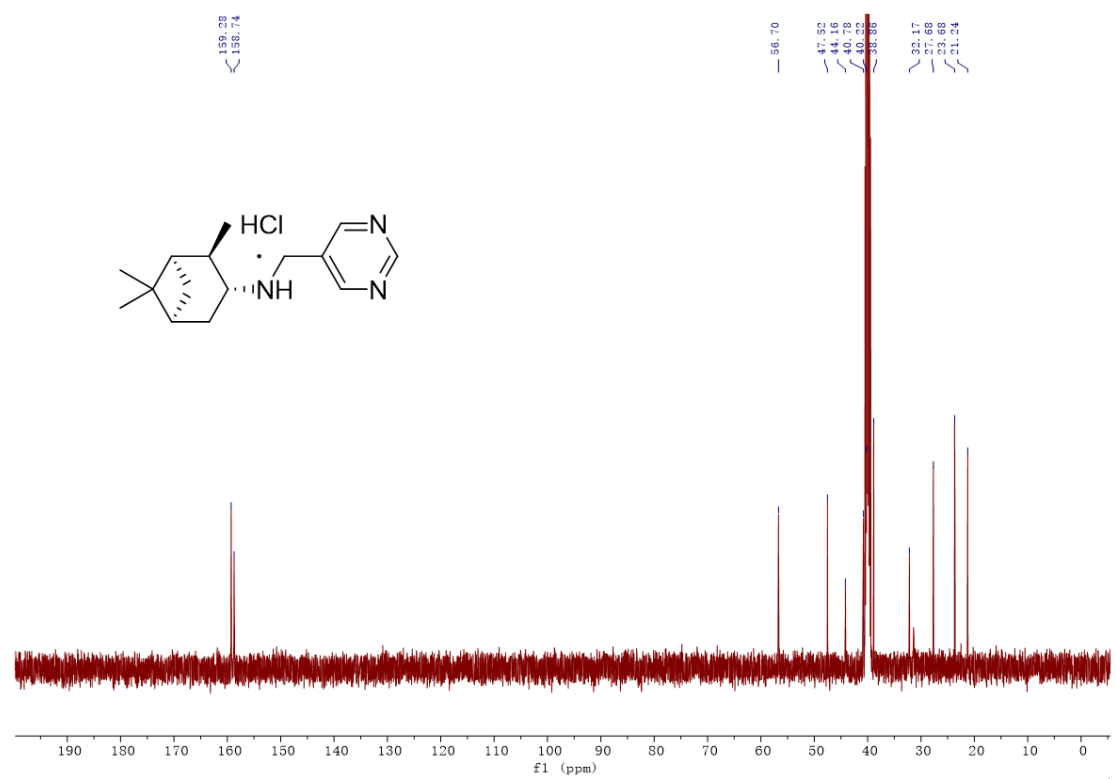
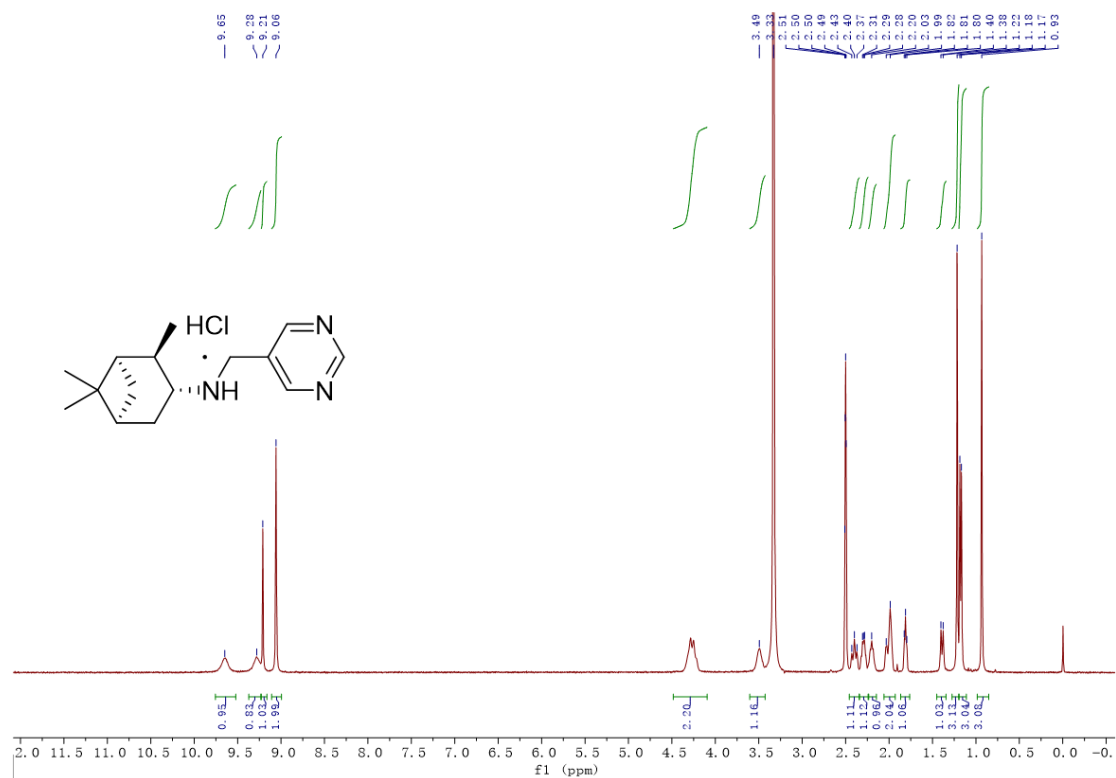
 <p>Compound 30</p>	<p>(1R,2R,3R,5S)-N-((4-cyclopropylthiophen-2-yl) methyl)-2,6,6-trimethyl bicyclo [3.1.1] heptan-3-amine (30. HCl). Method D, then Method E. Yield, 18%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.62 (br s, 1H), 9.18 (br s, 1H), 7.18 (s, 1H), 7.17 (s, 1H), 4.29 (m, 2H), 3.30 (m, 1H), 2.38 – 2.20 (m, 2H), 2.18 – 2.06 (m, 1H), 2.03 – 1.86 (m, 3H), 1.79 (t, <i>J</i> = 5.7 Hz, 1H), 1.38 (d, <i>J</i> = 9.9 Hz, 1H), 1.19 (s, 3H), 1.09 (d, <i>J</i> = 6.8 Hz, 3H), 0.89 (m, 2H), 0.85 (s, 3H), 0.58 (m, 2H). ¹³C NMR (126 MHz, DMSO) δ 144.73, 132.73, 129.57, 120.24, 54.67, 46.97, 42.45, 40.28, 39.78, 38.38, 31.82, 30.64, 27.23, 23.14, 20.53, 11.08, 8.55, 8.50. HRMS: <i>m/z</i> (M + H⁺): calculated, 290.19, found, 290.19379. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.28 min, purity 98.36 %.</p>
 <p>Compound 31</p>	<p>(1R,2R,3R,5S)-N-(4-cyclopentylthiophen-2-yl) methyl)-2,6,6-trimethyl bicyclo [3.1.1] heptan-3-amine (31. HCl). Method A, Method C, then Method E. Yield, 9%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.69 (br s, 1H), 9.22 (br s, 1H), 7.34 (s, 1H), 7.23 (s, 1H), 4.43 – 4.23 (m, 2H), 3.28 (m, 1H), 3.00 (m, 1H), 2.38 – 2.21 (m, 2H), 2.14 (m, 1H), 2.01-1.94 (m, 4H), 1.82 – 1.43 (m, 7H), 1.39 (d, <i>J</i> = 9.8 Hz, 1H), 1.19 (s, 3H), 1.09 (d, <i>J</i> = 7.1 Hz, 3H), 0.85 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 147.36, 133.14, 131.43, 121.71, 55.08, 47.47, 42.94, 41.05, 40.77, 40.22, 38.84, 34.02, 32.31, 31.07, 27.70, 25.07, 23.54, 20.96. HRMS: <i>m/z</i> (M + H⁺): calculated, 318.22, found, 318.22485. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.89 min, purity 99.74 %.</p>
 <p>Compound 32</p>	<p>(1R,2R,3R,5S)-N-(4-cyclohexylthiophen-2-yl) methyl)-2,6,6-trimethyl bicyclo [3.1.1] heptan-3-amine (32. HCl). Method A, Method C, then Method E. Yield, 8%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.67 (br s, 1H), 9.22 (br s, 1H), 7.36 (s, 1H), 7.22 (s, 1H), 4.44 – 4.22 (m, 2H), 3.27 (m, 1H), 2.55 (m, 1H), 2.41 – 2.21 (m, 2H), 2.14 (m, 1H), 2.02 – 1.63 (m, 8H), 1.45 – 1.26 (m, 5H), 1.19 (s, 4H), 1.08 (d, <i>J</i> = 7.1 Hz, 3H), 0.85 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 148.93, 132.91, 131.12, 121.46, 55.06, 47.46, 42.96, 40.76, 40.23, 39.27, 38.83, 34.09, 34.05, 32.32, 31.06, 27.70, 26.36, 26.01, 23.54, 20.96. HRMS: <i>m/z</i> (M + H⁺): calculated, 332.23, found, 332.24066. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 7.27 min, purity 99.47 %.</p>

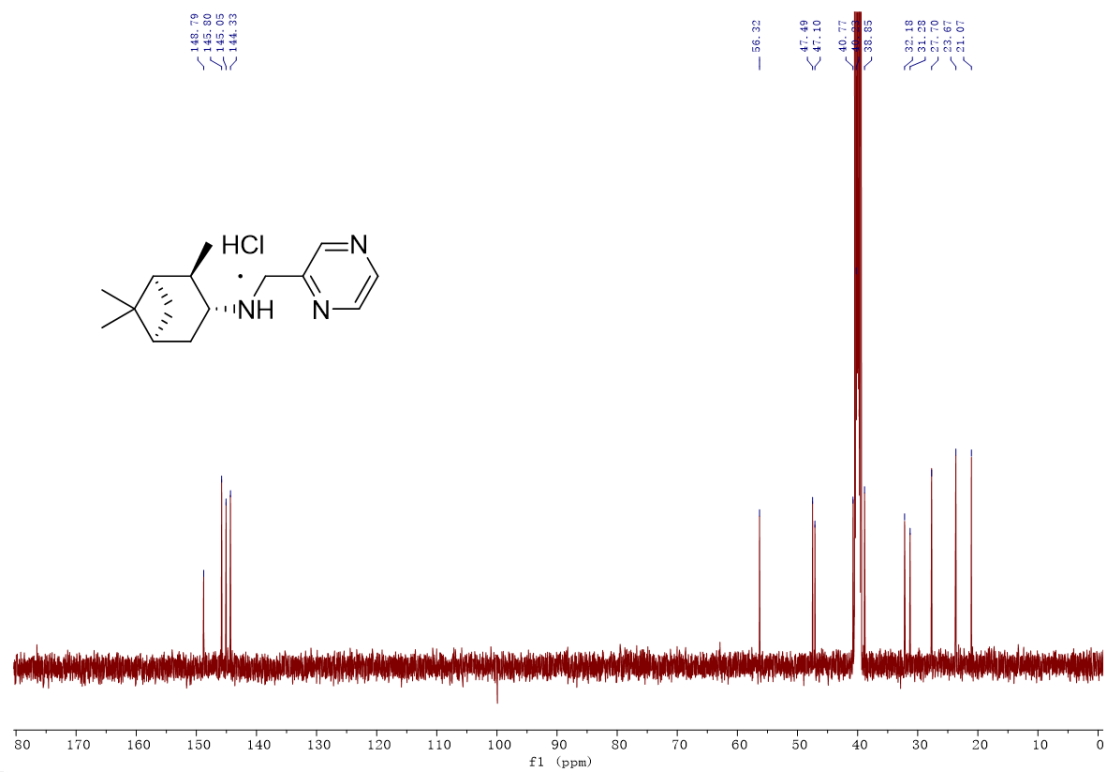
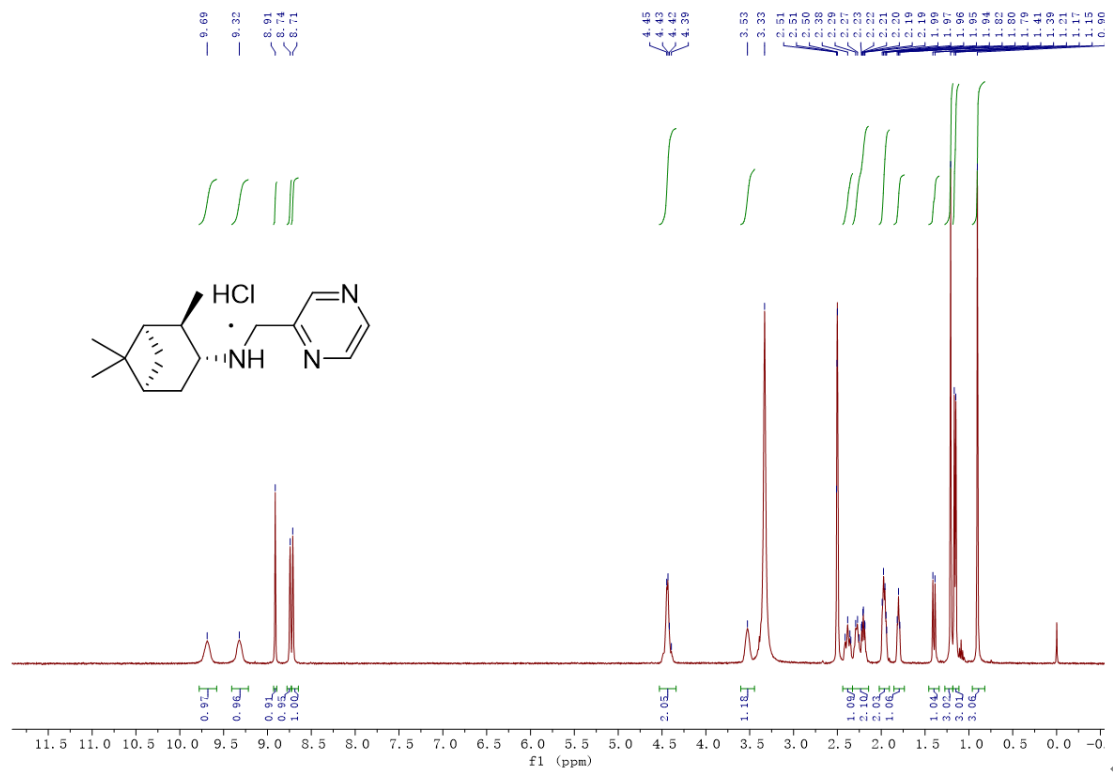
 <p>Compound 33</p>	<p>(1R,2R,3R,5S)-N-([3,3'-bithiophen]-5-ylmethyl)-2,6,6-trimethylbicyclo [3.1.1] heptan-3-amine (33. HCl). Method E. Yield, 71%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.78 (br s, 1H), 9.35 (br s, 1H), 7.85 (s, 1H), 7.83 (s, 1H), 7.72(d, <i>J</i> = 2.9 Hz, 1H), 7.62 (dd, <i>J</i> = 5.0, 2.9 Hz, 1H), 7.48 (d, <i>J</i> = 5.0 Hz, 1H), 4.39 (m, 2H), 3.36 (m, 1H), 2.36 (t, <i>J</i> = 11.6 Hz, 1H), 2.27 (m, 1H), 2.18 (m, 1H), 2.04-1.97 (m, 2H), 1.79 (t, <i>J</i> = 5.2 Hz, 1H), 1.42 (d, <i>J</i> = 9.9 Hz, 1H), 1.20 (s, 3H), 1.12 (d, <i>J</i> = 7.1 Hz, 3H), 0.87 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 136.99, 136.84, 134.13, 130.45, 127.54, 126.61, 122.68, 120.91, 55.32, 47.47, 42.93, 40.78, 38.86, 32.29, 31.14, 27.70, 23.65, 21.05. HRMS: <i>m/z</i> (M + H⁺): calculated, 332.14, found, 332.15018. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.59 min, purity 99.83 %.</p>
 <p>Compound 34</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(4-phenylthiophen-2-yl)methyl bicyclo [3.1.1] heptan-3-amine (34. HCl). Method E. Yield, 65%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.74 (br s, 1H), 9.34 (br s, 1H), 7.94 (s, 1H), 7.91 (s, 1H), 7.68 (d, <i>J</i> = 7.6 Hz, 2H), 7.44 (t, <i>J</i> = 7.6 Hz, 2H), 7.32 (t, <i>J</i> = 7.4 Hz, 1H), 4.64 – 4.23 (m, 2H), 3.39 (m, 1H), 2.38 (t, <i>J</i> = 11.9 Hz, 1H), 2.28 (m, 1H), 2.24 – 2.12 (m, 1H), 2.07 – 1.93 (m, 2H), 1.81 (t, <i>J</i> = 5.9 Hz, 1H), 1.42 (d, <i>J</i> = 9.9 Hz, 1H), 1.20 (s, 3H), 1.13 (d, <i>J</i> = 7.1 Hz, 3H), 0.88 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 141.59, 135.15, 134.44, 130.18, 129.44, 127.81, 126.26, 123.24, 55.43, 47.47, 43.02, 40.78, 38.85, 32.29, 31.20, 27.70, 23.64, 21.07. HRMS: <i>m/z</i> (M + H⁺): calculated, 326.19, found, 326.19358. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.75 min, purity 99.83 %.</p>
 <p>Compound 35</p>	<p>(1R,2R,3R,5S)-N-(5-chlorothiophen-2-yl)methyl-2,6,6-trimethyl bicyclo [3.1.1] heptan-3-amine (35. HCl). Method E. Yield, 66%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.82 (br s, 1H), 9.41 (br s, 1H), 7.31 (d, <i>J</i> = 3.8 Hz, 1H), 7.12 (d, <i>J</i> = 3.8 Hz, 1H), 4.35 (m, 2H), 3.30 (m, 1H), 2.38 – 2.22 (m, 2H), 2.16 (m, 1H), 2.06 – 1.90 (m, 2H), 1.79 (t, <i>J</i> = 5.8 Hz, 1H), 1.41 (d, <i>J</i> = 9.9 Hz, 1H), 1.20 (s, 3H), 1.12 (d, <i>J</i> = 7.0 Hz, 3H), 0.87 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 132.92, 131.53, 130.21, 127.11, 55.16, 47.49, 42.81, 40.77, 40.22, 38.85, 32.23, 31.01, 27.69, 23.65, 21.07. HRMS: <i>m/z</i> (M + H⁺): calculated, 284.12, found, 284.12357. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 5.93 min, purity 99.94 %.</p>

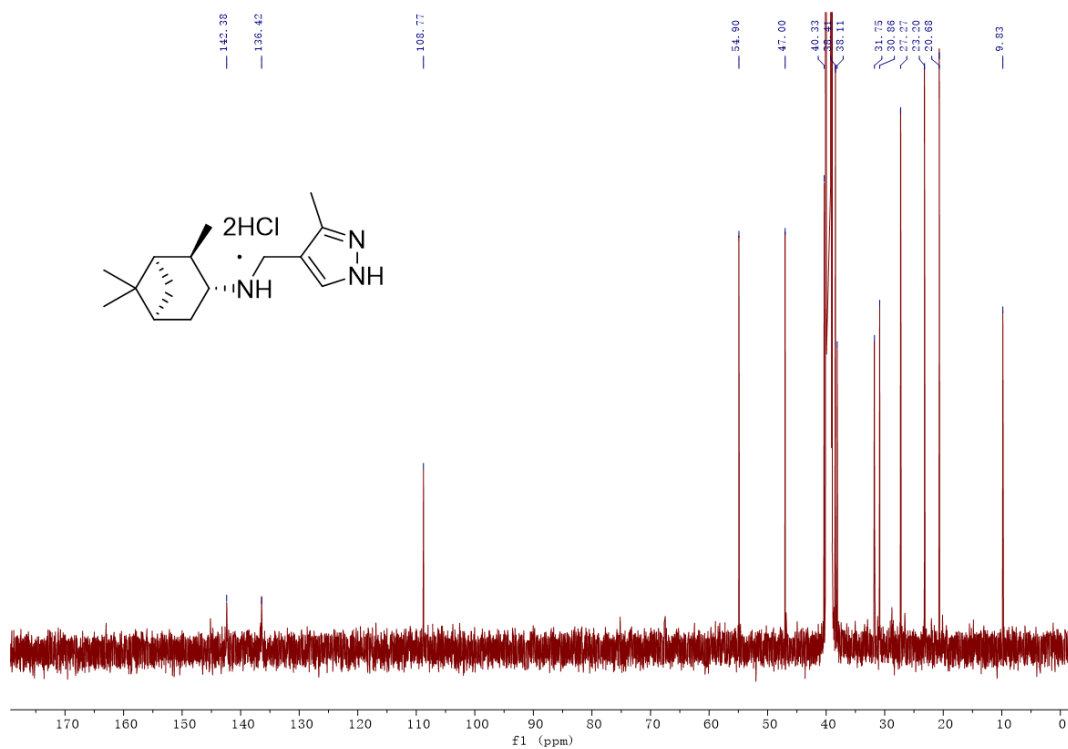
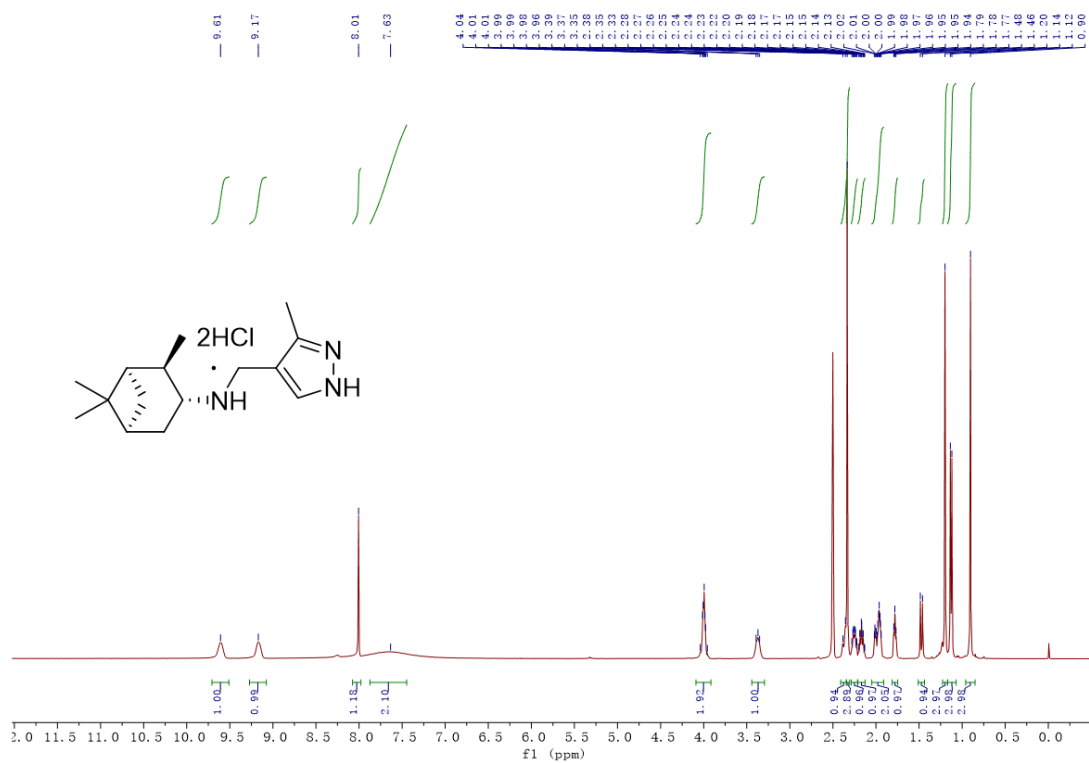
 <p>Compound 36</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-((5-methylthiophen-2-yl)methyl) bicyclo [3.1.1] heptan-3-amine (36. HCl). Method E. Yield, 72%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.68 (br s, 1H), 9.22 (br s, 1H), 7.19 (d, <i>J</i> = 3.5 Hz, 1H), 6.78 (dd, <i>J</i> = 3.4, 1.3 Hz, 1H), 4.29 (m, 2H), 3.28 (m, 1H), 2.45 (d, <i>J</i> = 1.0 Hz, 3H), 2.36 – 2.22 (m, 2H), 2.14 (m, 1H), 1.97 (m, 2H), 1.78 (m, 1H), 1.39 (d, <i>J</i> = 9.9 Hz, 1H), 1.19 (s, 3H), 1.08 (d, <i>J</i> = 7.1 Hz, 3H), 0.85 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 141.59, 130.91, 130.28, 125.51, 54.34, 46.96, 42.33, 40.29, 38.36, 31.85, 30.59, 27.22, 23.17, 20.51, 14.93. HRMS: <i>m/z</i> (M + H⁺): calculated, 264.17, found, 264.17810. HPLC: gradient solvent, 10 % to 100 % TFA in H₂O, flow rate, 1.0 mL/min, retention time 11.89 min, purity 99.61 %</p>
 <p>Compound 37</p>	<p>(1R,2R,3R,5S)-N-(5-bromothiophen-2-yl)methyl-2,6,6-trimethyl bicyclo [3.1.1] heptan-3-amine (37. HCl). Method E. Yield, 58%. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.98 (br s, 1H), 9.55 (br s, 1H), 7.30 (d, <i>J</i> = 3.8 Hz, 1H), 7.20 (d, <i>J</i> = 3.8 Hz, 1H), 4.35 (t, <i>J</i> = 5.1 Hz, 2H), 3.30 (m, 1H), 2.35 – 2.21 (m, 2H), 2.18 (m, 1H), 2.01 (m, 1H), 1.94 (m, 1H), 1.77 (td, <i>J</i> = 5.8, 1.9 Hz, 1H), 1.46 (d, <i>J</i> = 9.9 Hz, 1H), 1.19 (s, 3H), 1.11 (d, <i>J</i> = 7.1 Hz, 3H), 0.85 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 135.64, 132.51, 130.71, 113.64, 55.26, 47.55, 42.75, 40.83, 40.27, 38.91, 32.29, 31.07, 27.76, 23.72, 21.14. HRMS: <i>m/z</i> (M + H⁺): calculated, 328.07, found, 328.07285. HPLC: gradient solvent, 10 % to 80% KH₂PO₄ in H₂O, flow rate, 1.0 mL/min, retention time 12.86 min, purity 99.03 %.</p>
 <p>Compound 38</p>	<p>(1R,2R,3R,5S)-N-((5-ethylthiophen-2-yl)methyl)-2,6,6-trimethyl bicyclo [3.1.1] heptan-3-amine (38. HCl). Method E. Yield, 50%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.58 (br s, 1H), 9.16 (br s, 1H), 7.20 (d, <i>J</i> = 3.5 Hz, 1H), 6.82 (dd, <i>J</i> = 3.4, 1.1 Hz, 1H), 4.45 – 4.20 (m, 2H), 3.32 (m, 1H), 2.82 (m, 2H), 2.39 – 2.22 (m, 2H), 2.13 (m, 1H), 1.99-1.93 (m, 2H), 1.78 (td, <i>J</i> = 5.8, 1.9 Hz, 1H), 1.38 (d, <i>J</i> = 9.9 Hz, 1H), 1.23 (t, <i>J</i> = 7.5 Hz, 3H), 1.20 (s, 3H), 1.09 (d, <i>J</i> = 7.1 Hz, 3H), 0.86 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 149.09, 130.69, 130.03, 123.79, 54.55, 46.96, 42.49, 40.28, 38.36, 31.82, 30.65, 27.22, 23.14, 22.74, 20.53, 15.93. HRMS: <i>m/z</i> (M + H⁺): calculated, 278.19, found, 278.19360. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.51 min, purity 99.31 %.</p>

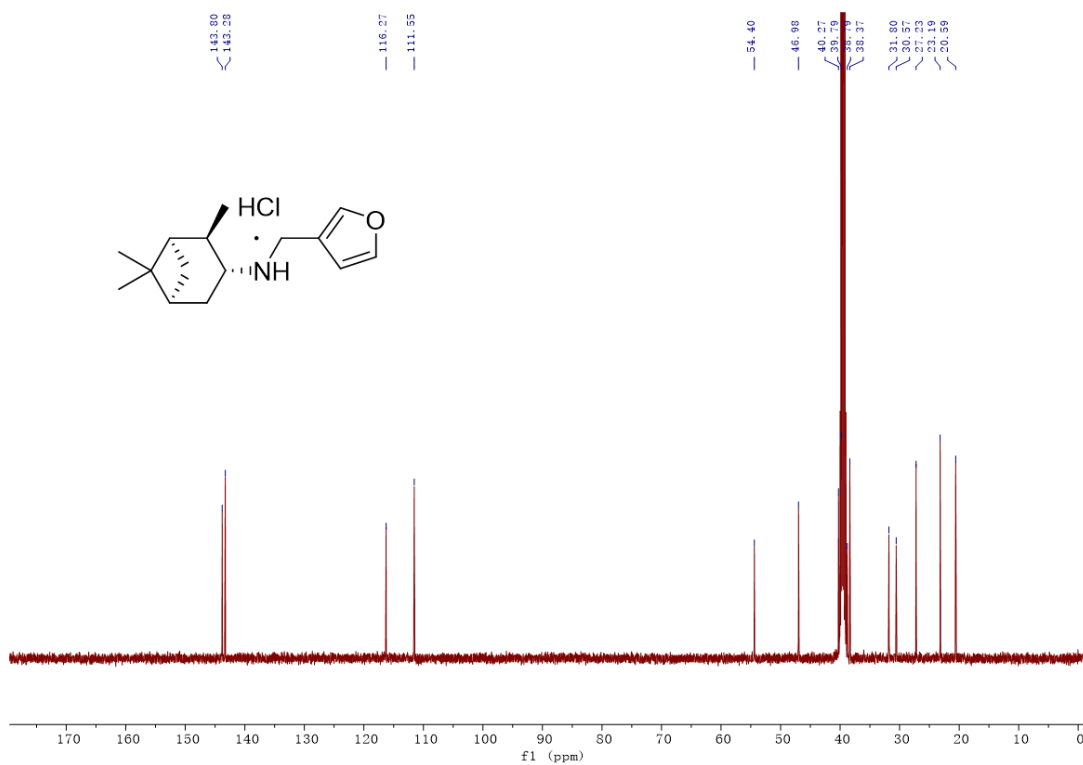
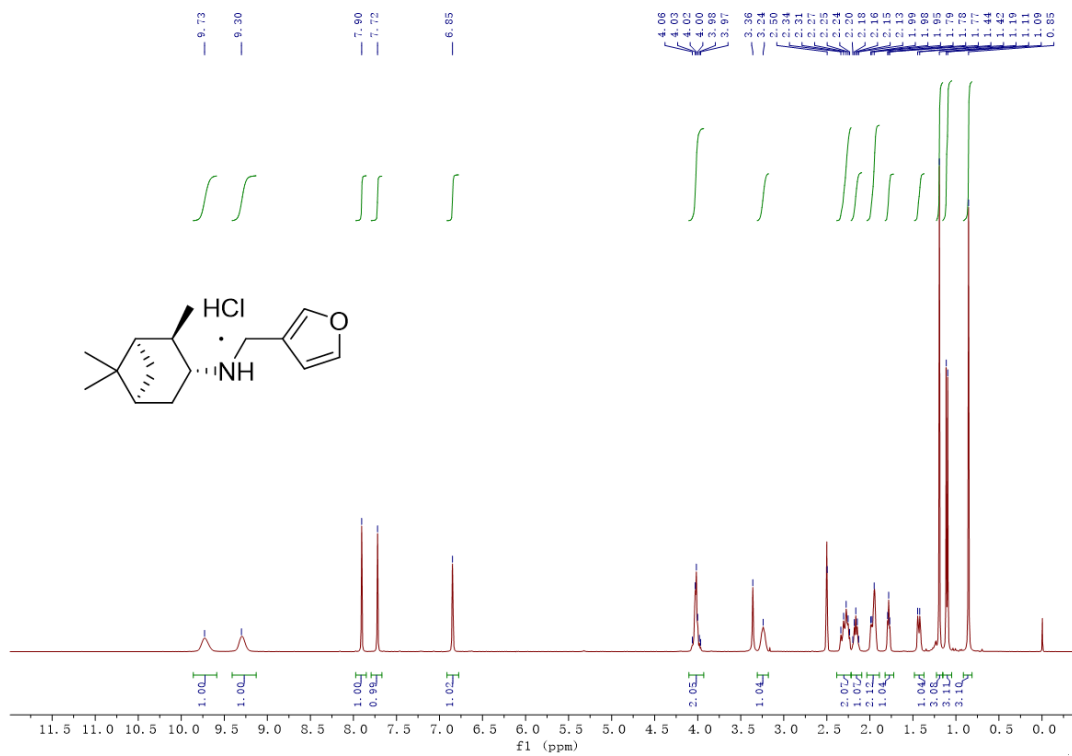
 <p>Compound 39</p>	<p>(1R,2R,3R,5S)-N-((5-(tert-butyl) thiophen-2-yl) methyl)-2,6,6-trimethyl bicyclo [3.1.1] heptan-3-amine (39. HCl). Method E. 71%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.57 (br s, 1H), 9.17 (br s, 1H), 7.21 (d, <i>J</i> = 3.6 Hz, 1H), 6.86 (d, <i>J</i> = 3.6 Hz, 1H), 4.42 – 4.20 (m, 2H), 3.35 (m, 1H), 2.40 – 2.21 (m, 2H), 2.14 (m, 1H), 1.99-1.94 (m, 2H), 1.82 – 1.75 (m, 1H), 1.39 (d, <i>J</i> = 9.9 Hz, 1H), 1.34 (s, 9H), 1.20 (s, 3H), 1.10 (d, <i>J</i> = 7.1 Hz, 3H), 0.87 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 158.83, 130.42, 129.70, 121.78, 54.85, 47.00, 42.63, 40.29, 39.77, 38.37, 34.20, 32.10, 31.78, 30.71, 27.24, 23.10, 20.56. HRMS: <i>m/z</i> (M + H⁺): calculated, 306.22, found, 306.22504. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.89 min, purity 99.87 %.</p>
 <p>Compound 40</p>	<p>(1R,2R,3R,5S)-2,6,6-trimethyl-N-(5-(methylthio) thiophen-2-yl) methyl bicyclo [3.1.1] heptan-3-amine (40. HCl). Method E. 45%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.70 (s, 1H), 9.29 (s, 1H), 7.30 (d, <i>J</i> = 3.6 Hz, 1H), 7.08 (d, <i>J</i> = 3.6 Hz, 1H), 4.34 (m, 2H), 3.31 (m, 1H), 2.50 (s, 3H), 2.34 – 2.31 (m, 2H), 2.14 (m, 1H), 1.98 – 1.94 (m, 2H), 1.84 – 1.71 (m, 1H), 1.39 (d, <i>J</i> = 9.8 Hz, 1H), 1.19 (s, 3H), 1.10 (d, <i>J</i> = 7.0 Hz, 3H), 0.86 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 138.99, 134.42, 131.58, 129.70, 54.82, 46.98, 42.43, 40.29, 39.81, 38.39, 31.81, 30.67, 27.23, 23.19, 20.77, 20.59. HRMS: <i>m/z</i> (M + H⁺): calculated, 296.14, found, 296.15008. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 6.18 min, purity 98.89 %.</p>
 <p>Compound 41</p>	<p>(1R,2R,3R,5S)-N-((5'-bromo-[2,2'-bithiophen]-5-yl) methyl)-2,6,6-trimethylbicyclo [3.1.1] heptan-3-amine (41. HCl). Method E. 40%. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.75 (br s, 1H), 9.34 (br s, 1H), 7.39 (d, <i>J</i> = 3.7 Hz, 1H), 7.29 (d, <i>J</i> = 3.7 Hz, 1H), 7.24 (d, <i>J</i> = 3.9 Hz, 1H), 7.18 (d, <i>J</i> = 3.9 Hz, 1H), 4.39 (m, 2H), 3.35 (m, 1H), 2.40 – 2.21 (m, 2H), 2.16 (m, 1H), 2.06 – 1.90 (m, 2H), 1.84 – 1.71 (m, 1H), 1.40 (d, <i>J</i> = 9.9 Hz, 1H), 1.20 (s, 3H), 1.12 (d, <i>J</i> = 7.0 Hz, 3H), 0.87 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 138.05, 137.44, 133.18, 132.56, 132.12, 125.46, 124.80, 111.08, 55.44, 47.46, 42.80, 40.76, 38.83, 32.26, 31.16, 27.68, 23.65, 21.06. HRMS: <i>m/z</i> (M + H⁺): calculated, 410.05, found, 410.06036. HPLC: solvent, H₂O (0.1 % HCOOH), flow rate, 0.8 mL/min, retention time 7.23 min, purity 99.73 %.</p>

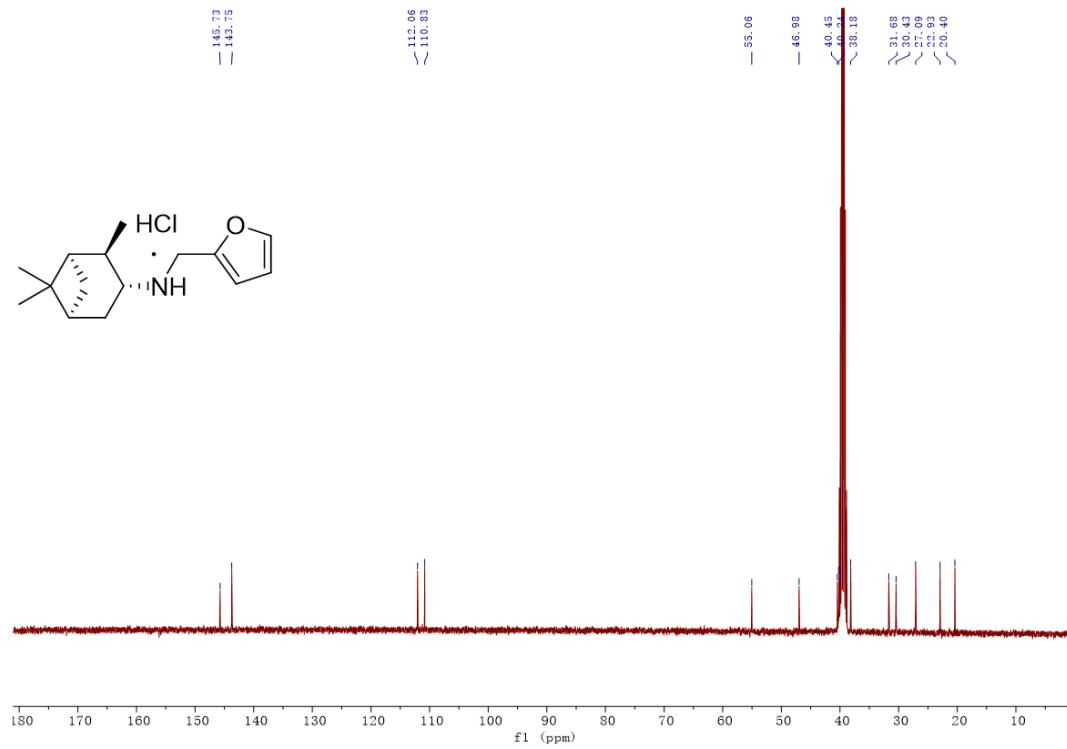
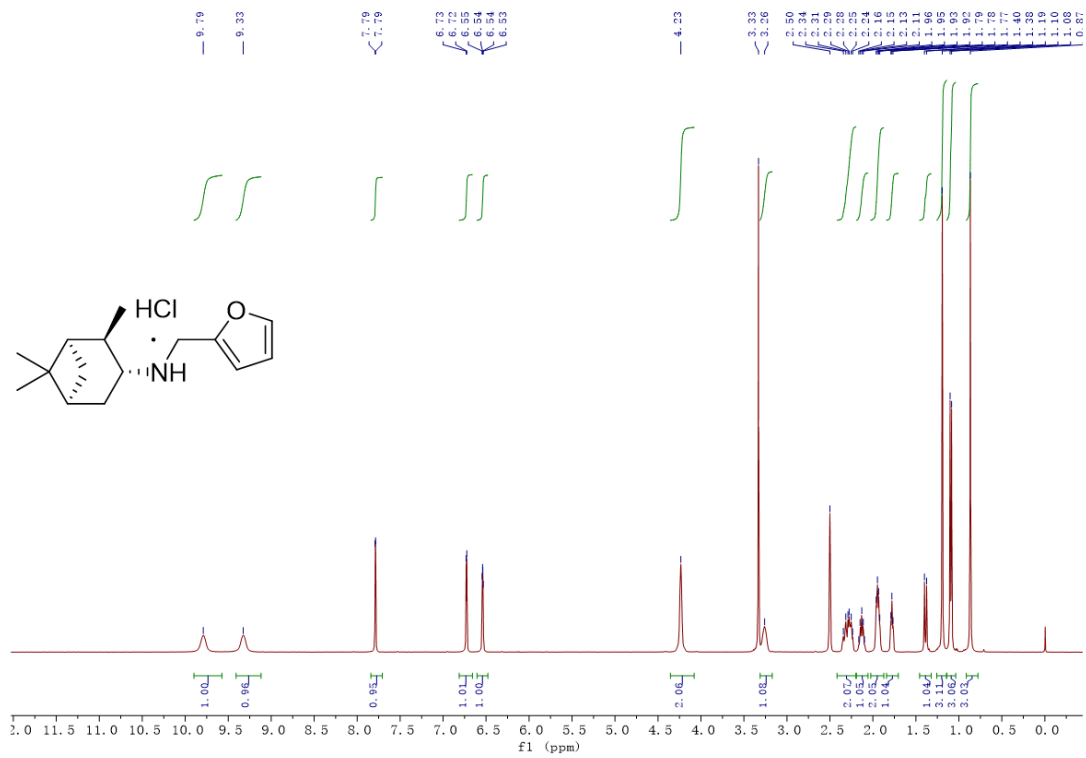
1H NMR and 13CNMR spectra of Compounds

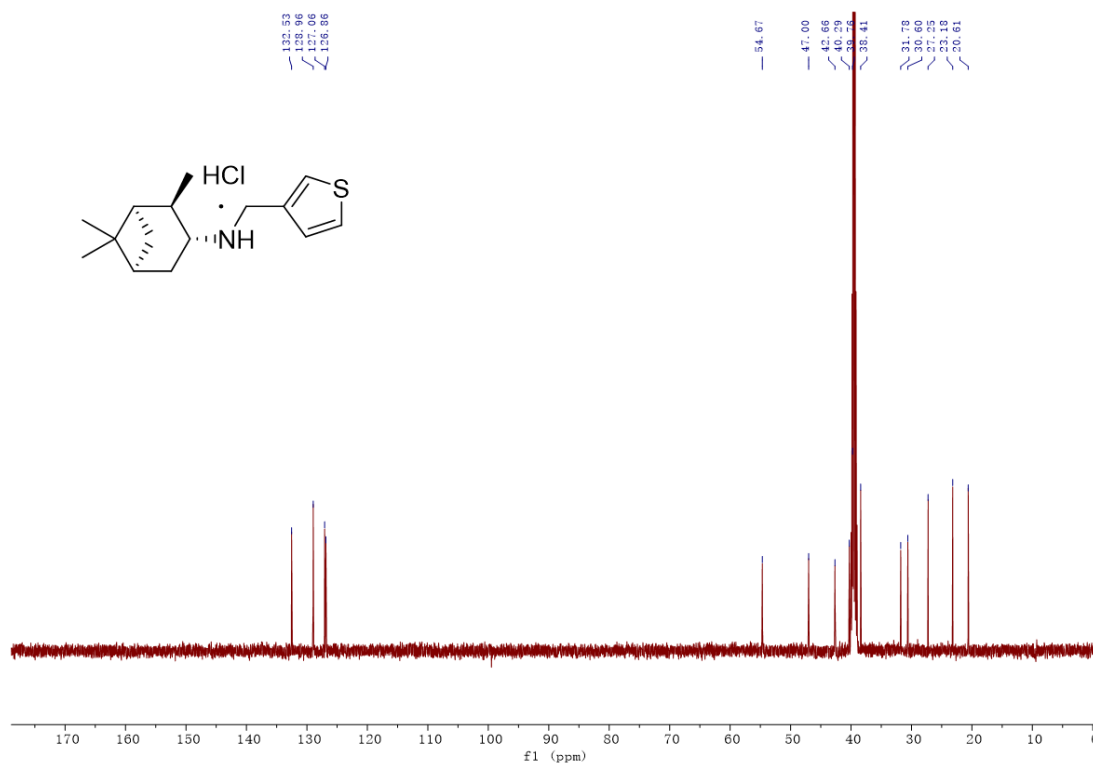
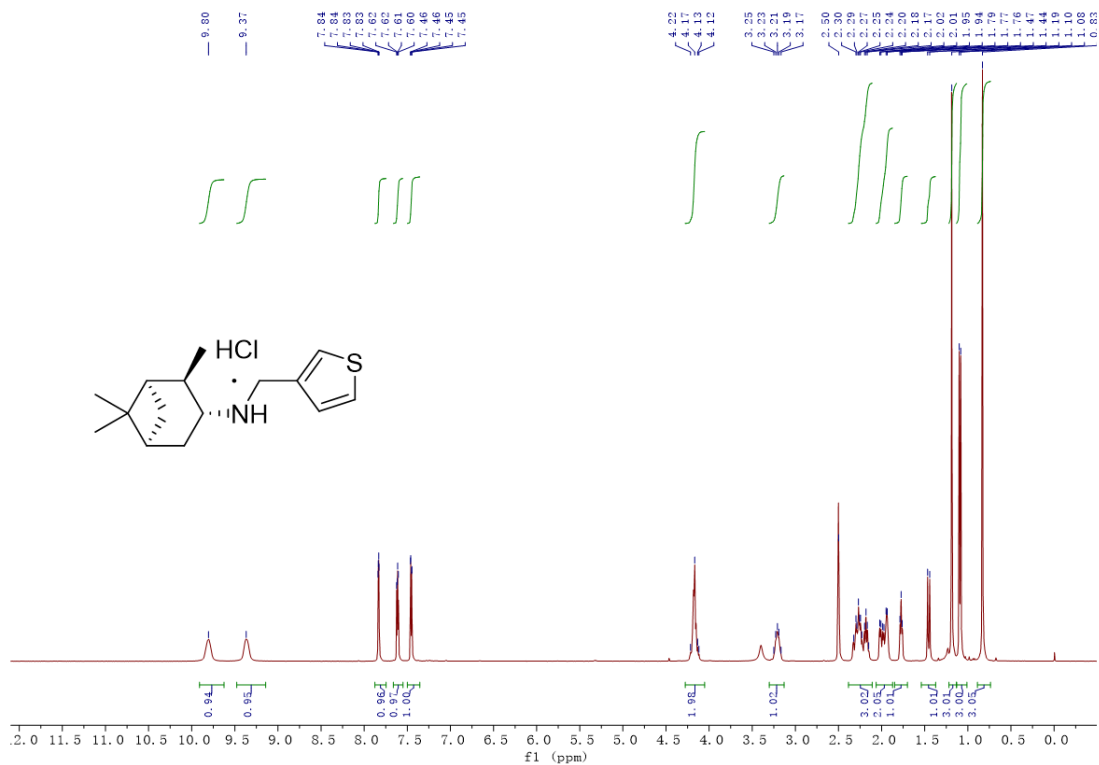


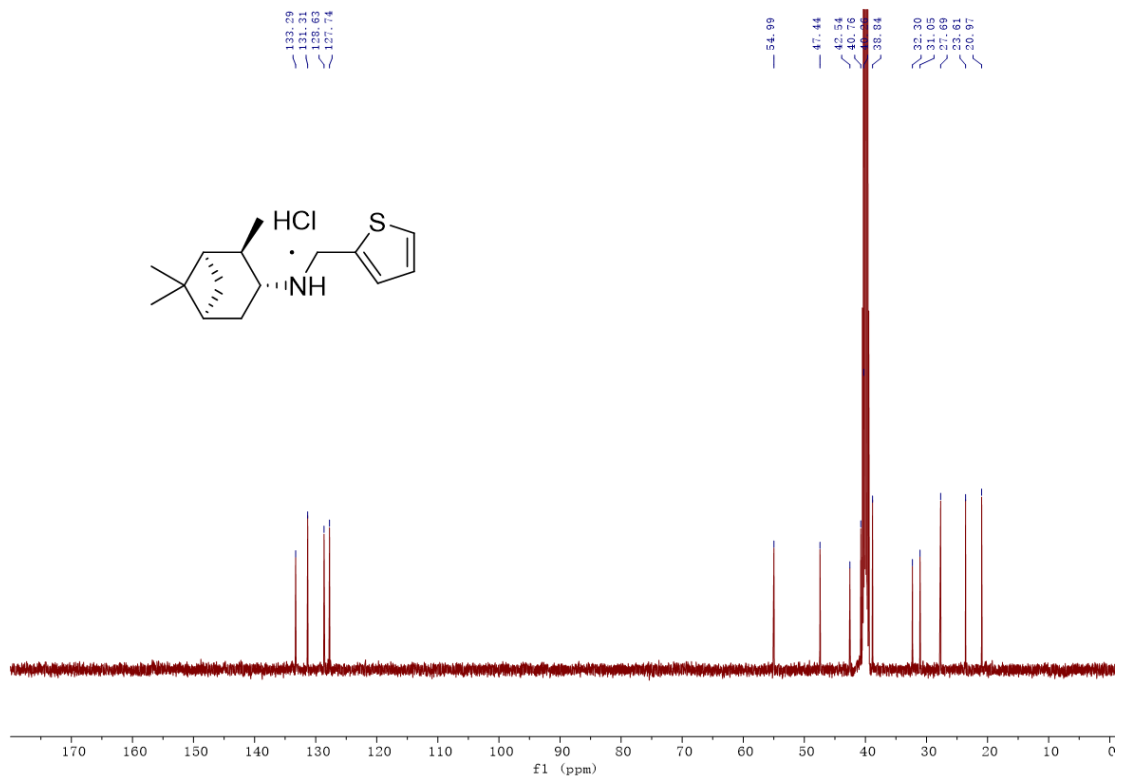
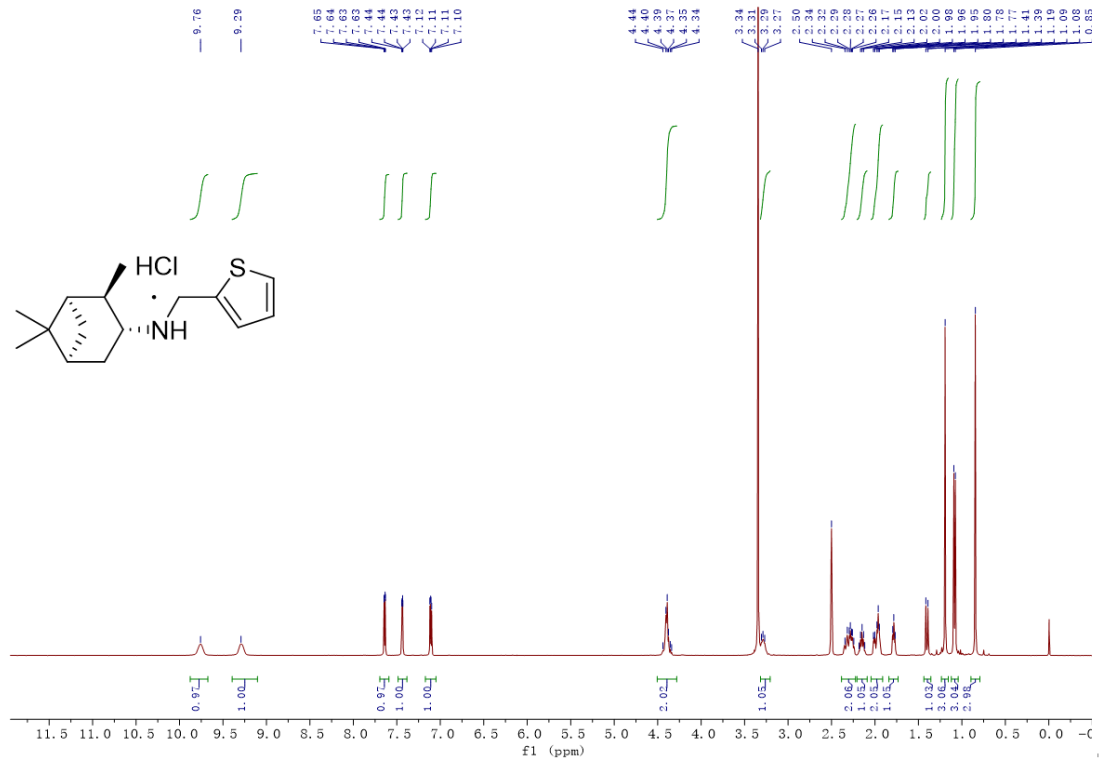


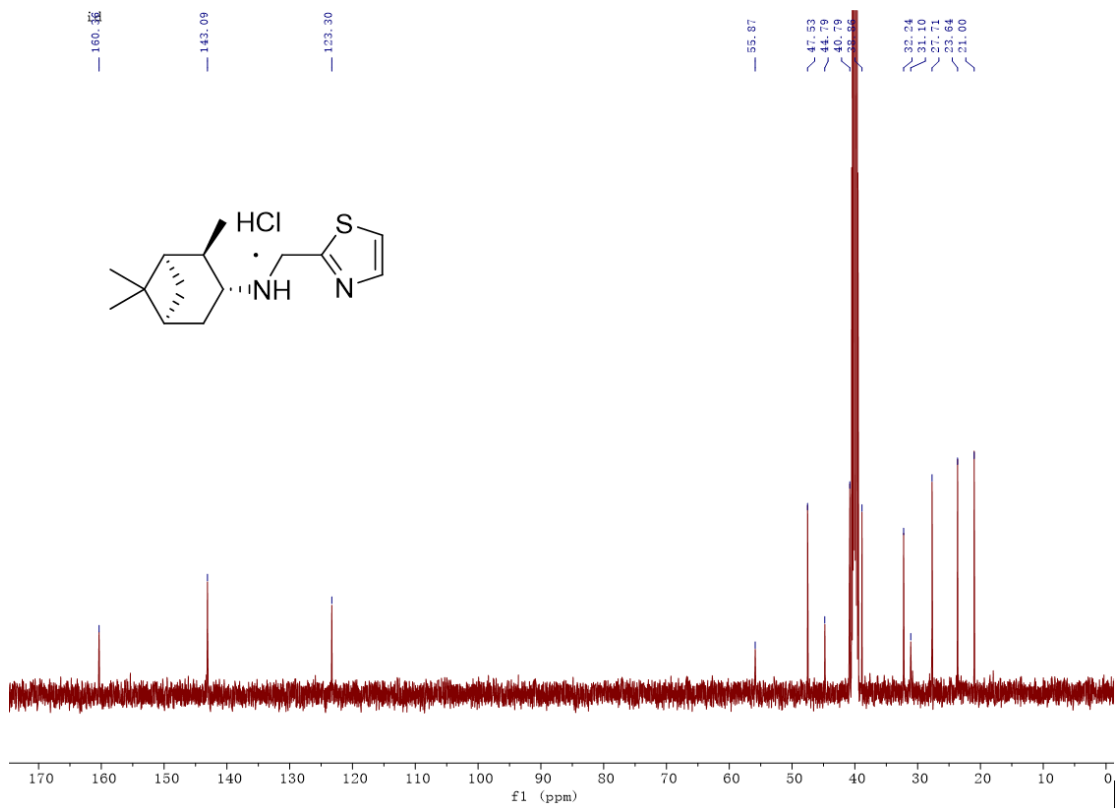
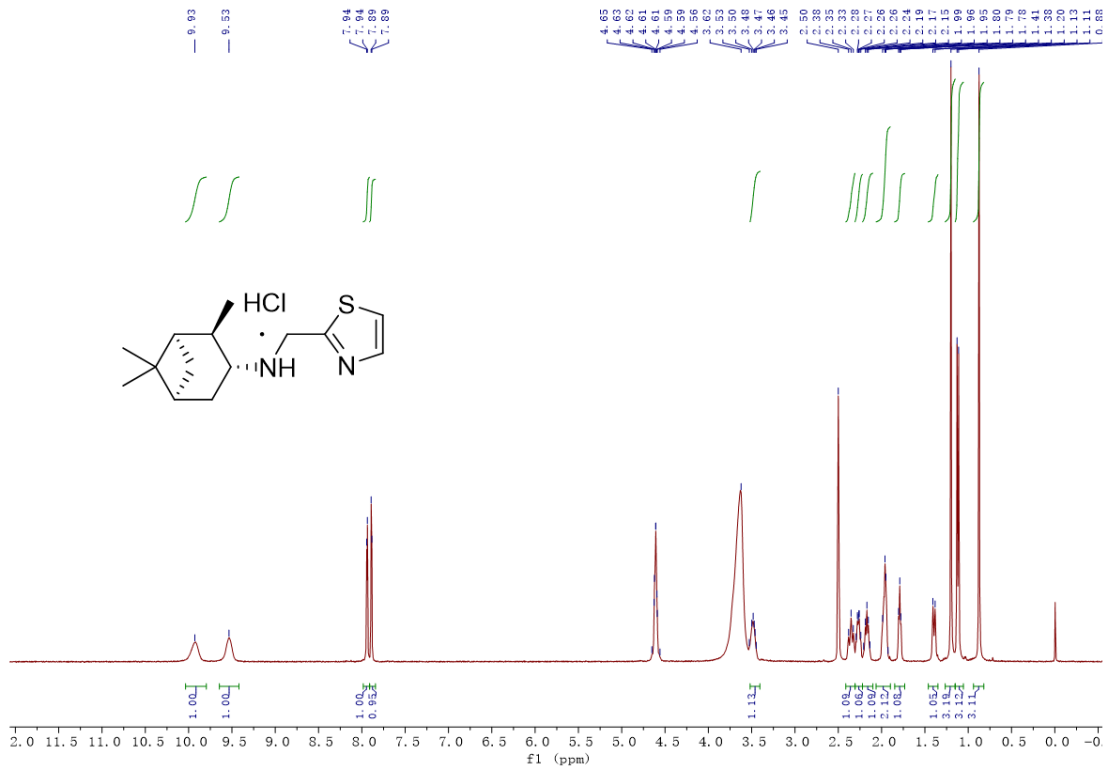


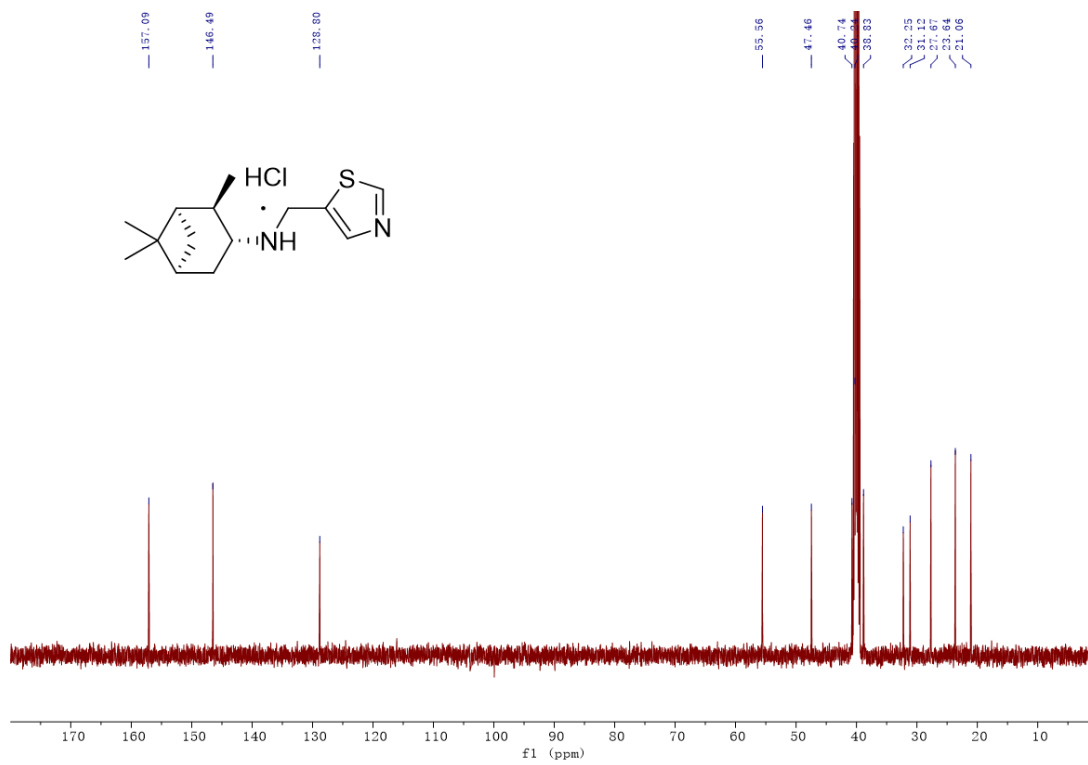
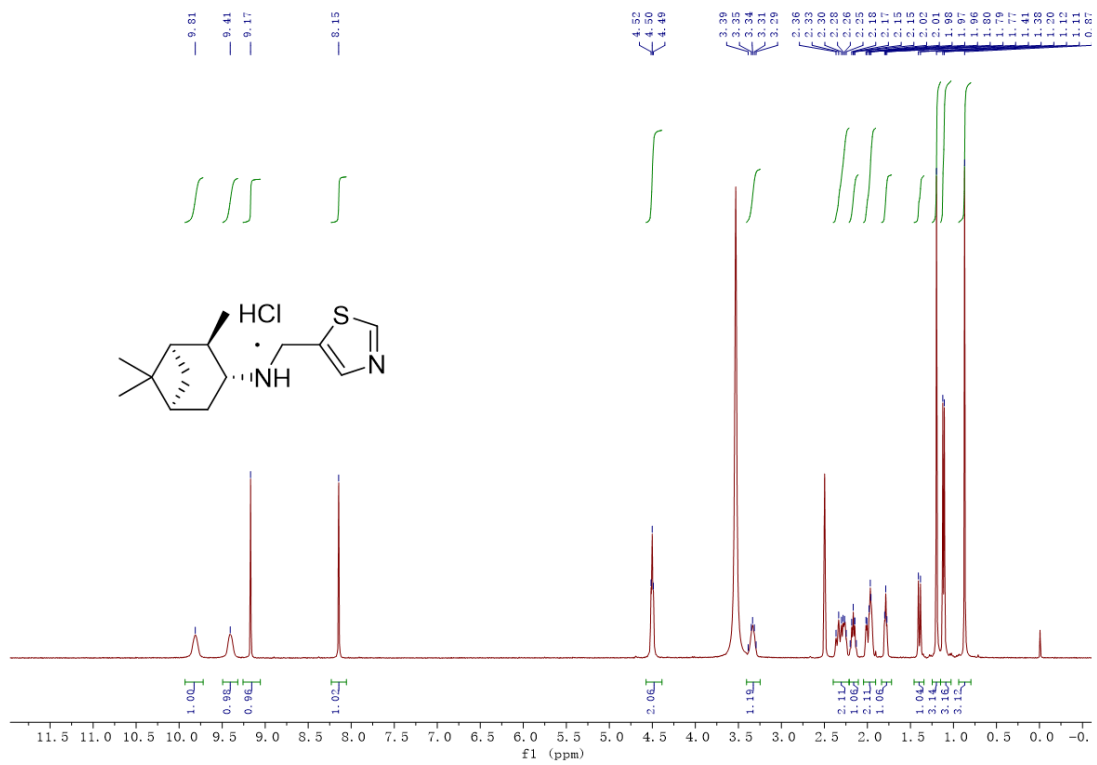


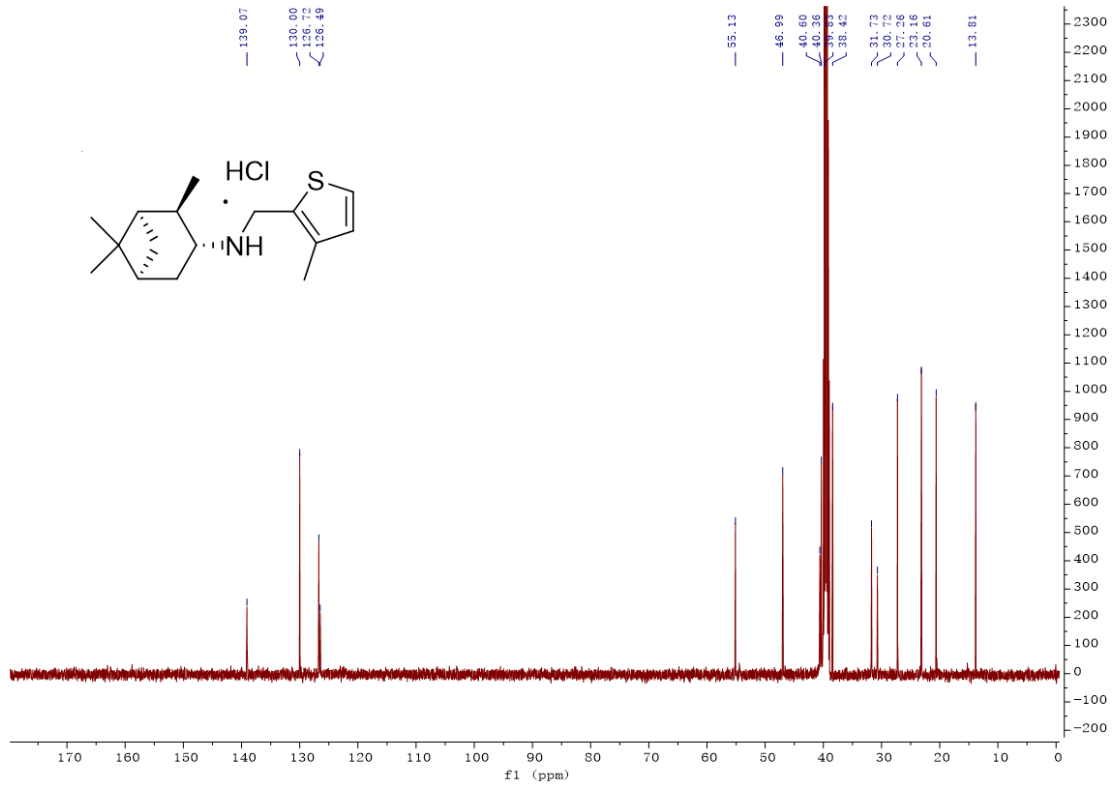
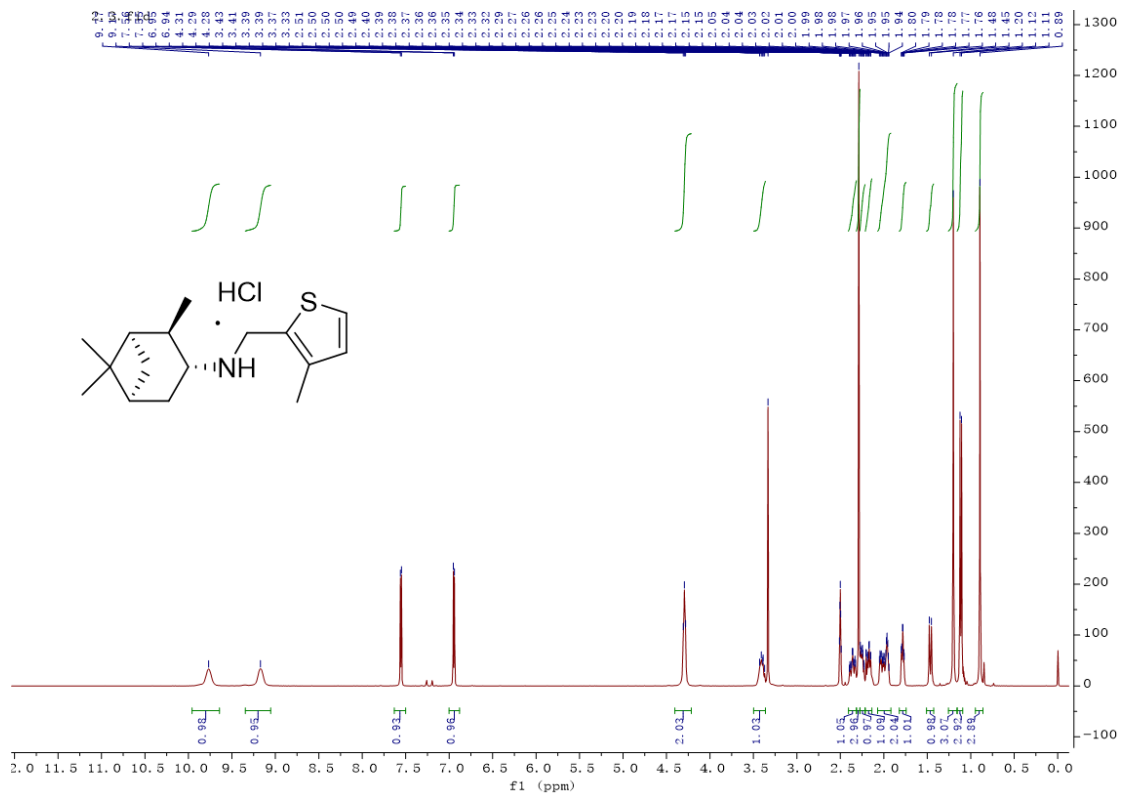


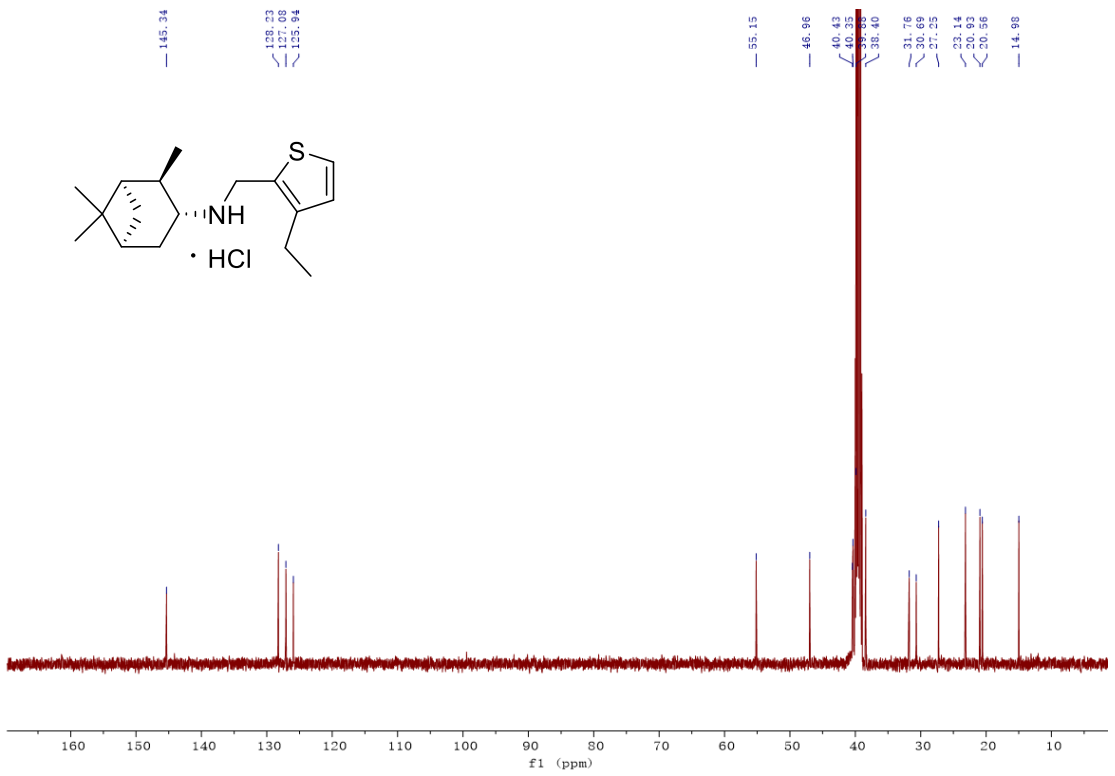
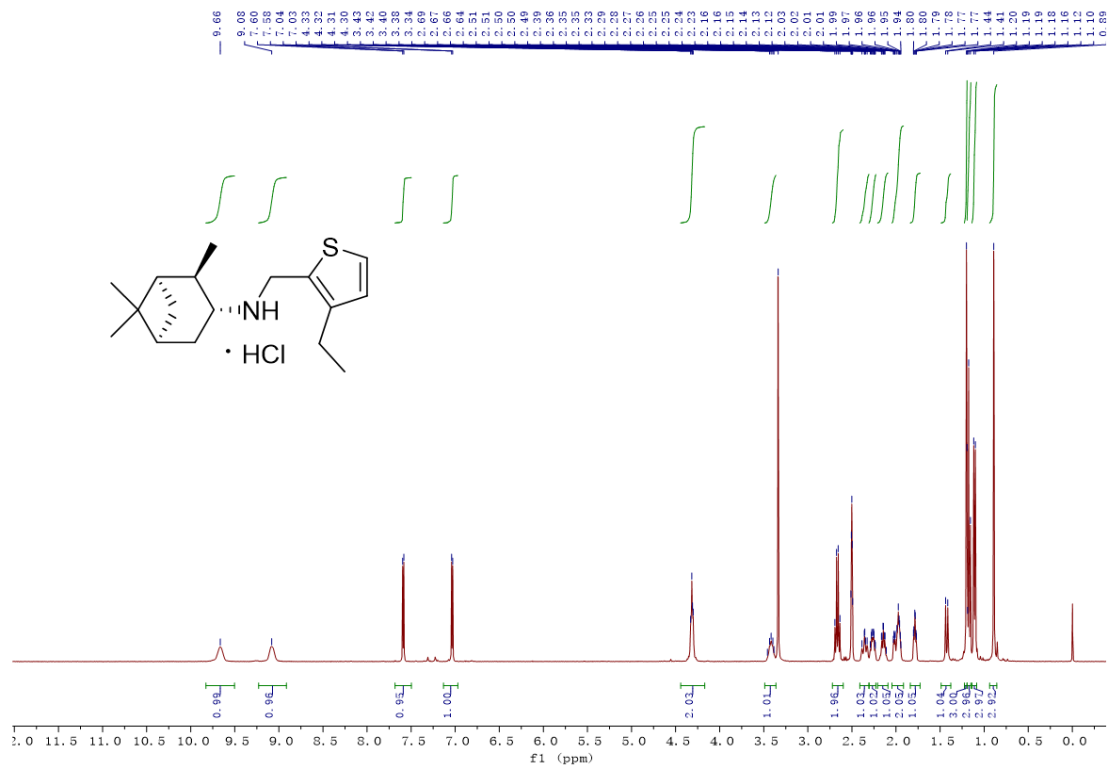


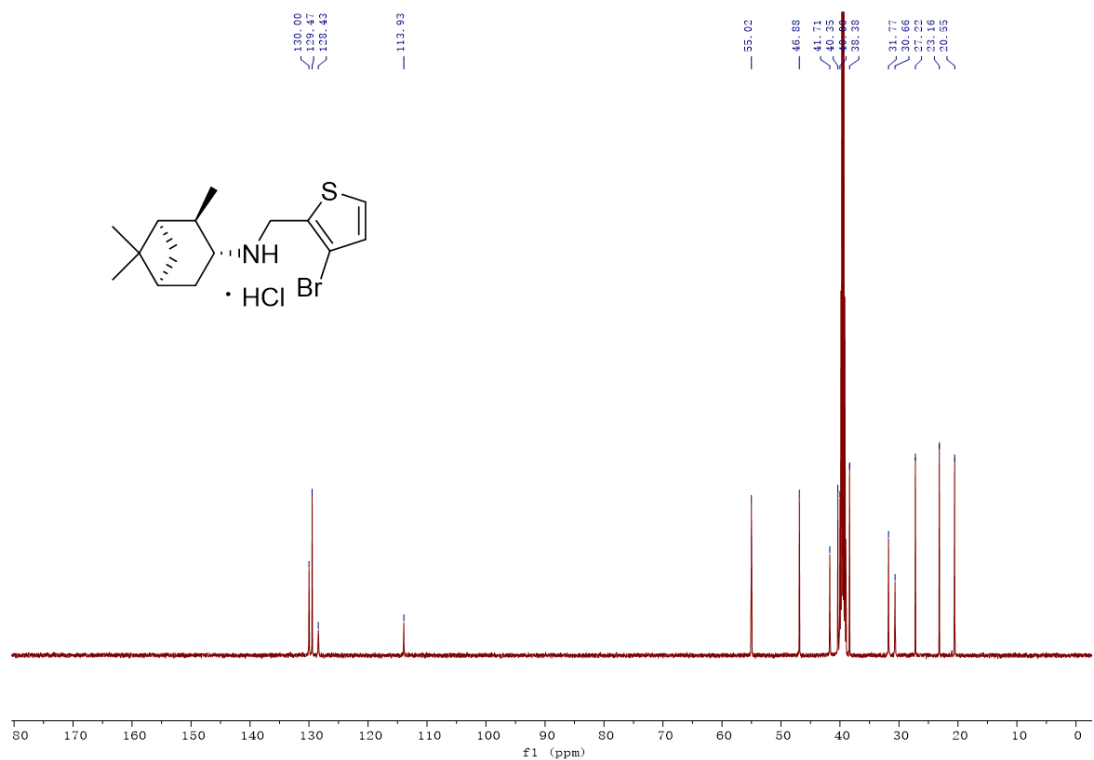
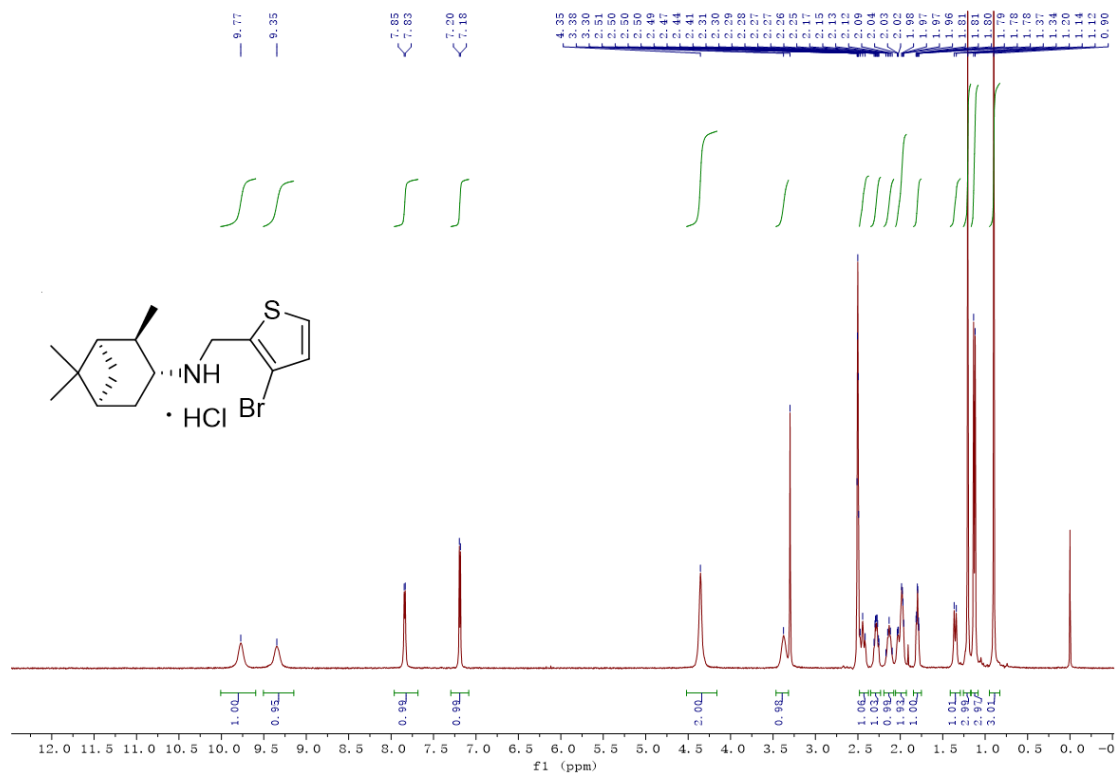


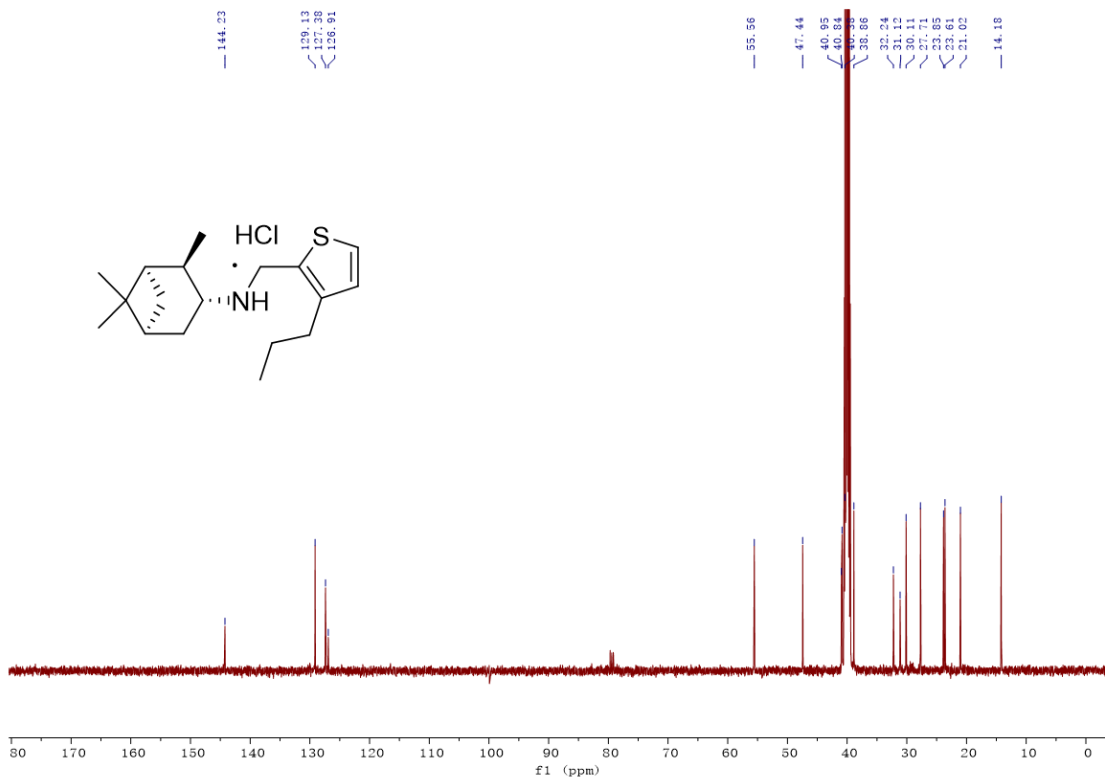
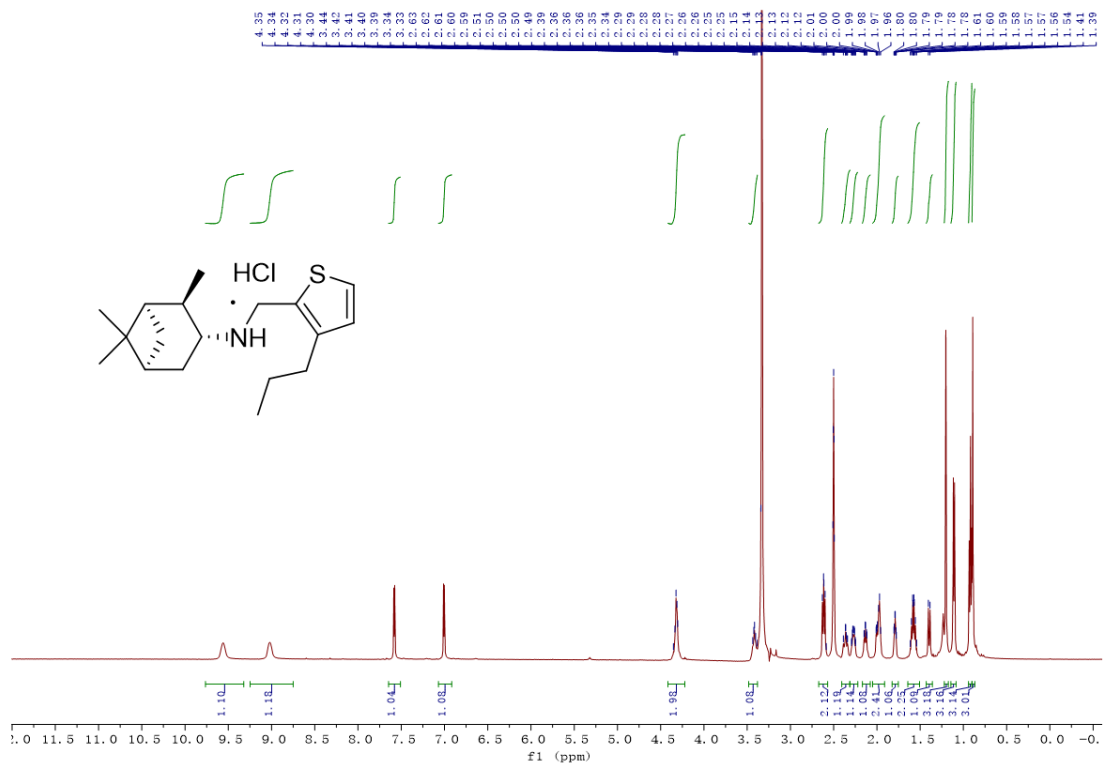


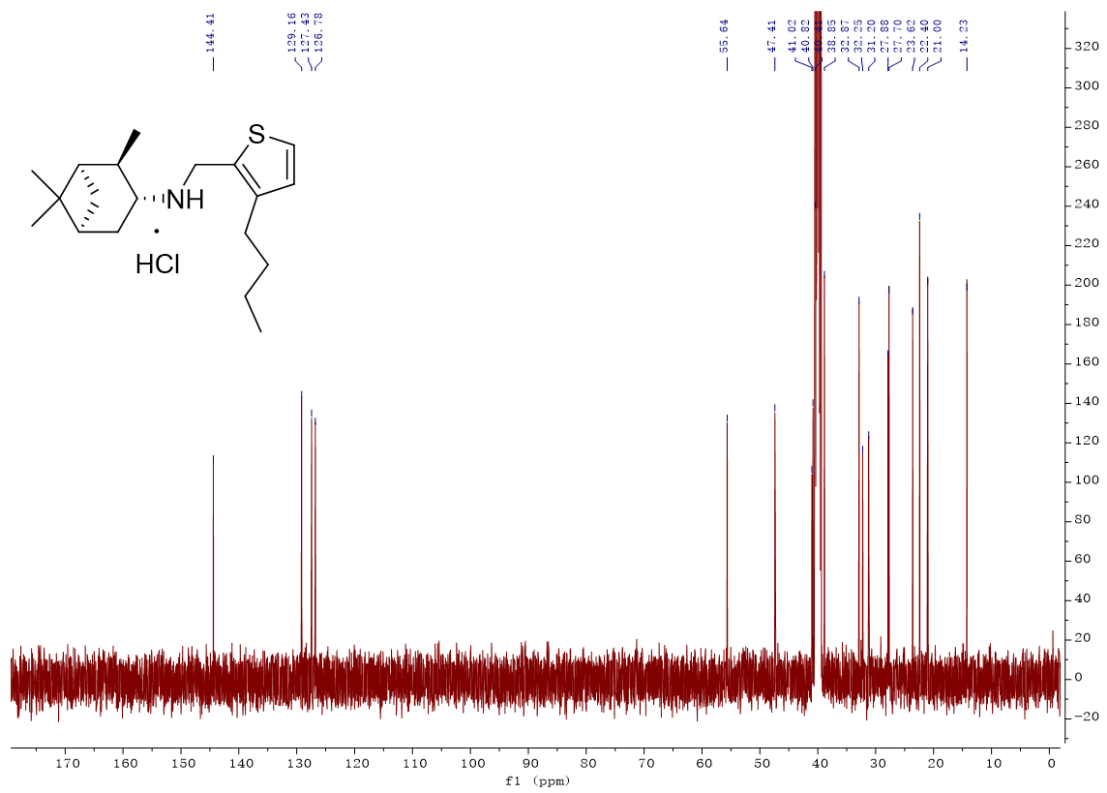
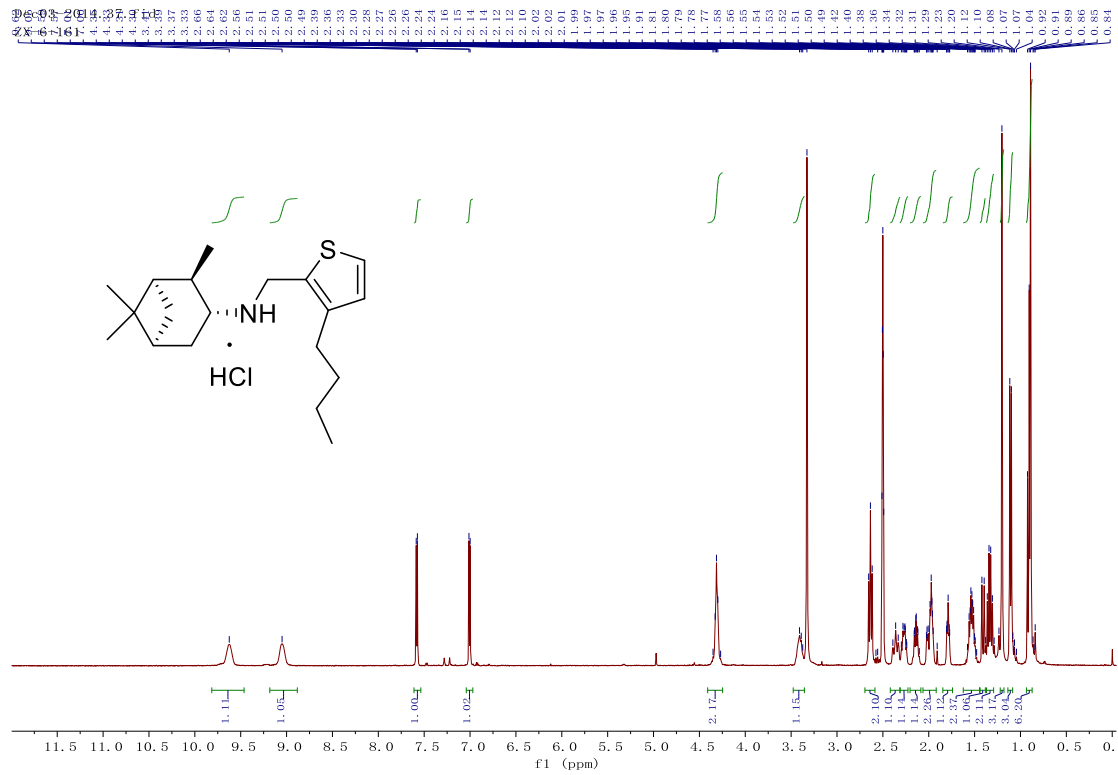


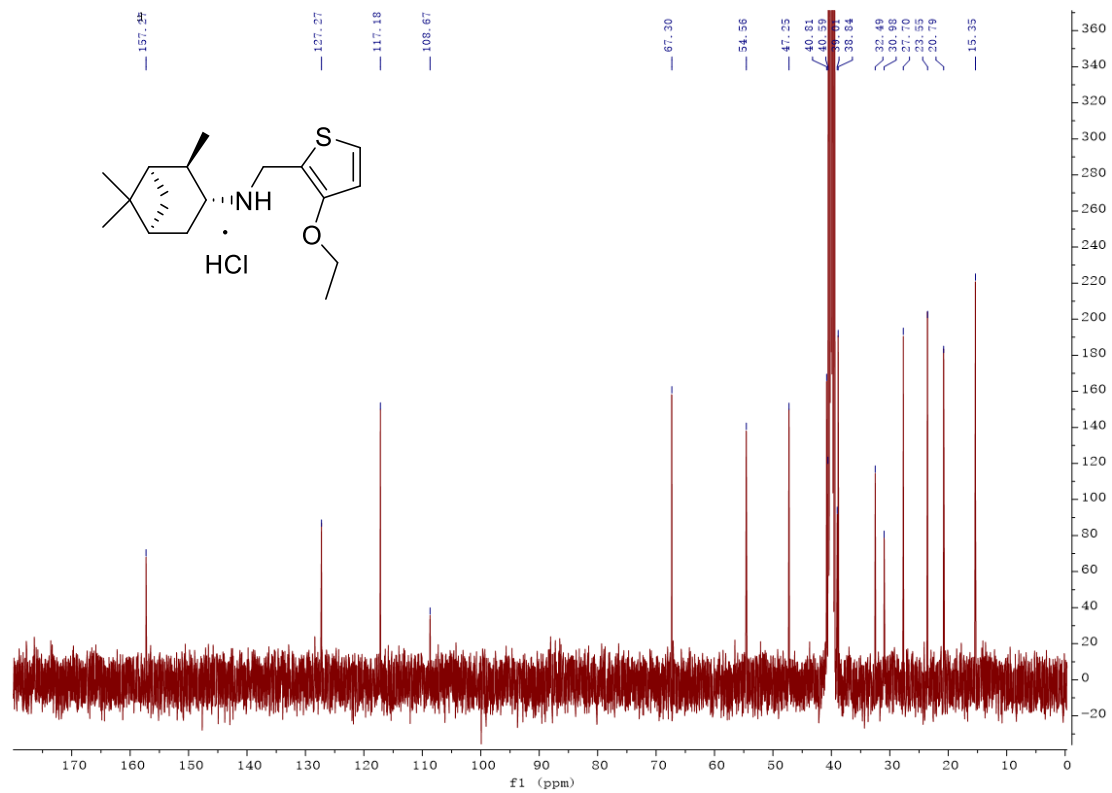
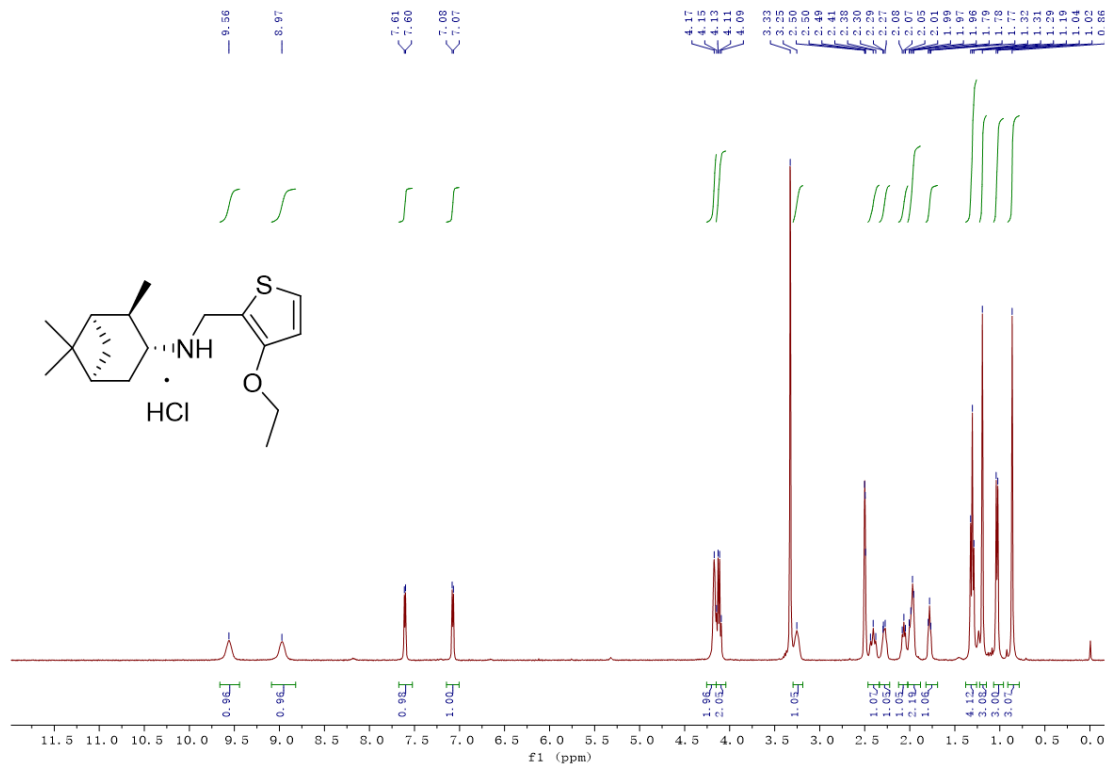


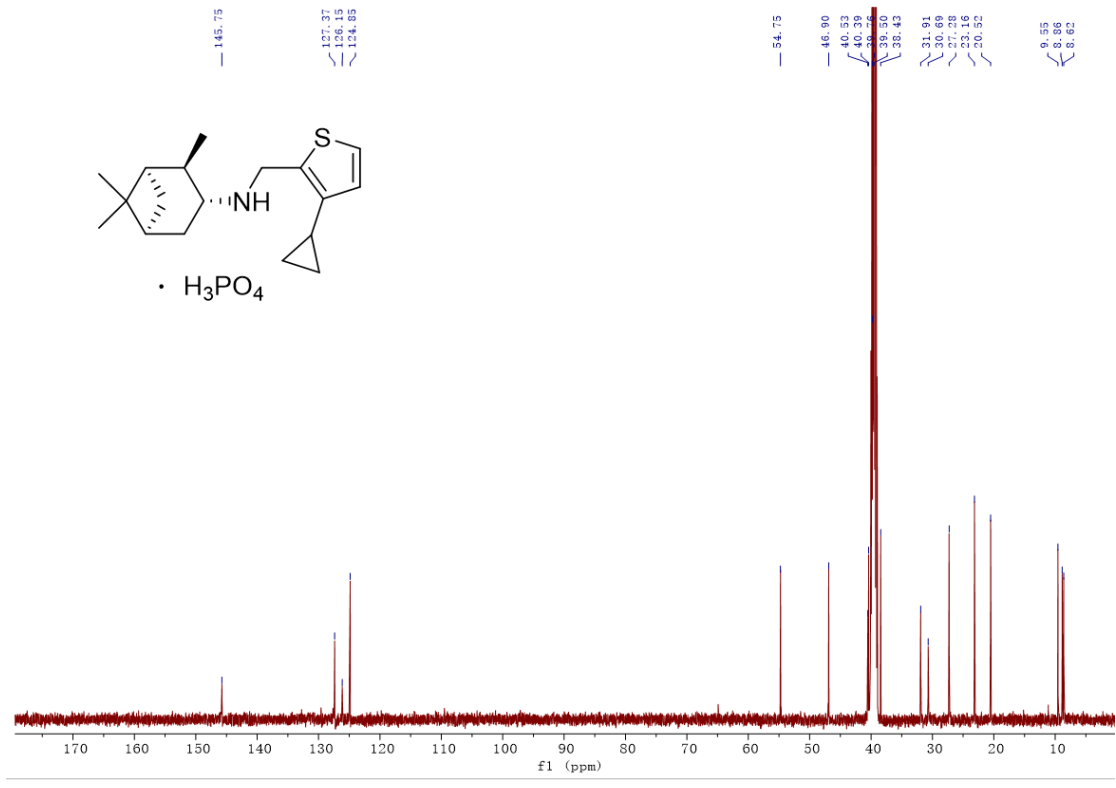
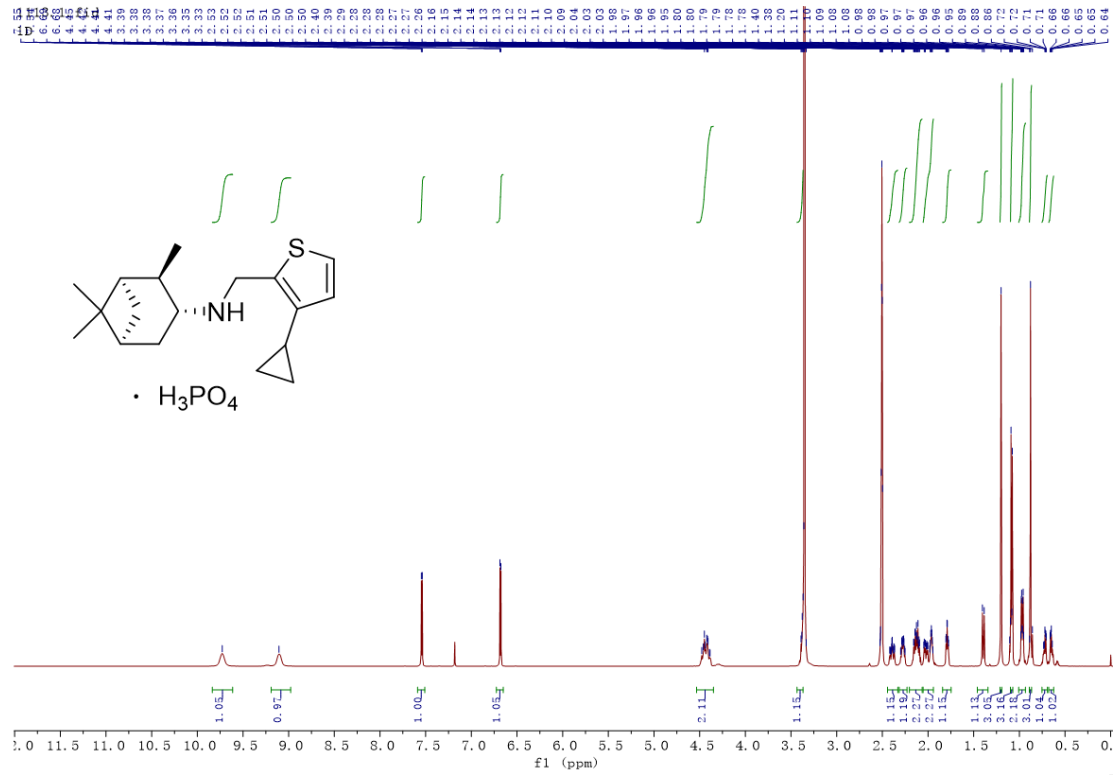




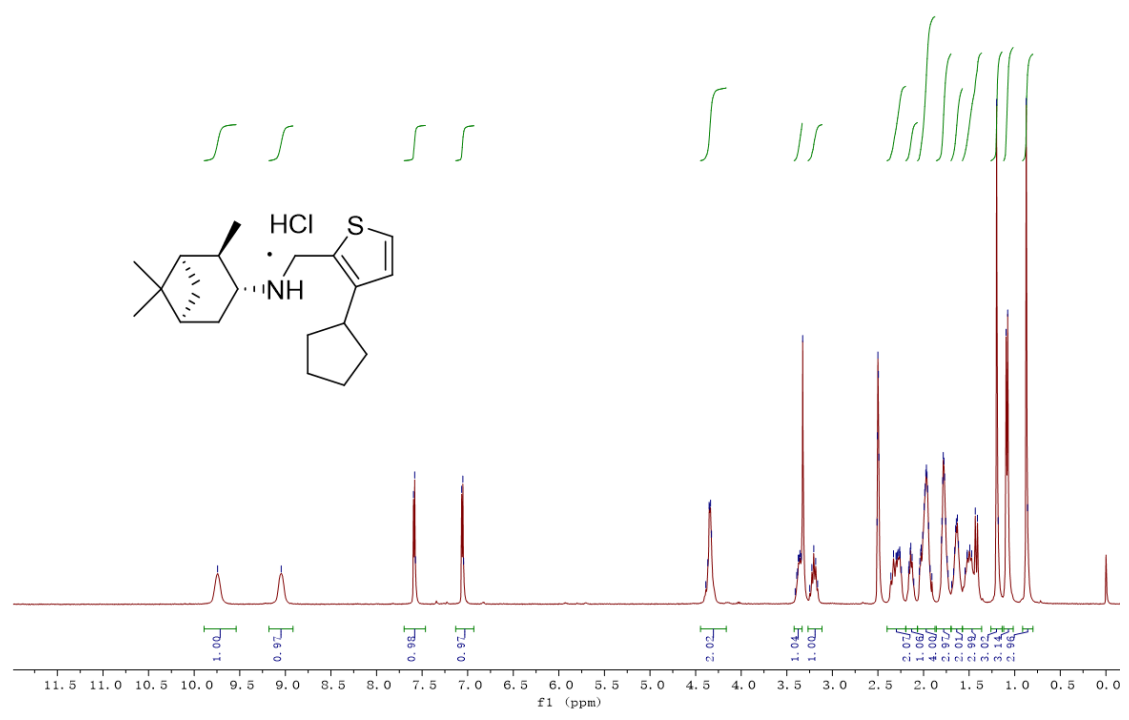
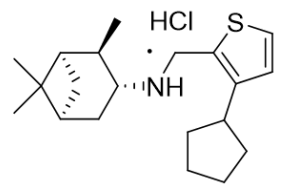








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148.60 137.77 136.96 136.35 55.39 47.39 40.83 38.85 38.56 34.97 32.30 32.33 31.04 27.70 25.67 23.58 23.35

