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New adamantane-containing compounds targeting rimantadine-resistant influenza virus A/PR/8/34: molecular design, synthesis and SAR study

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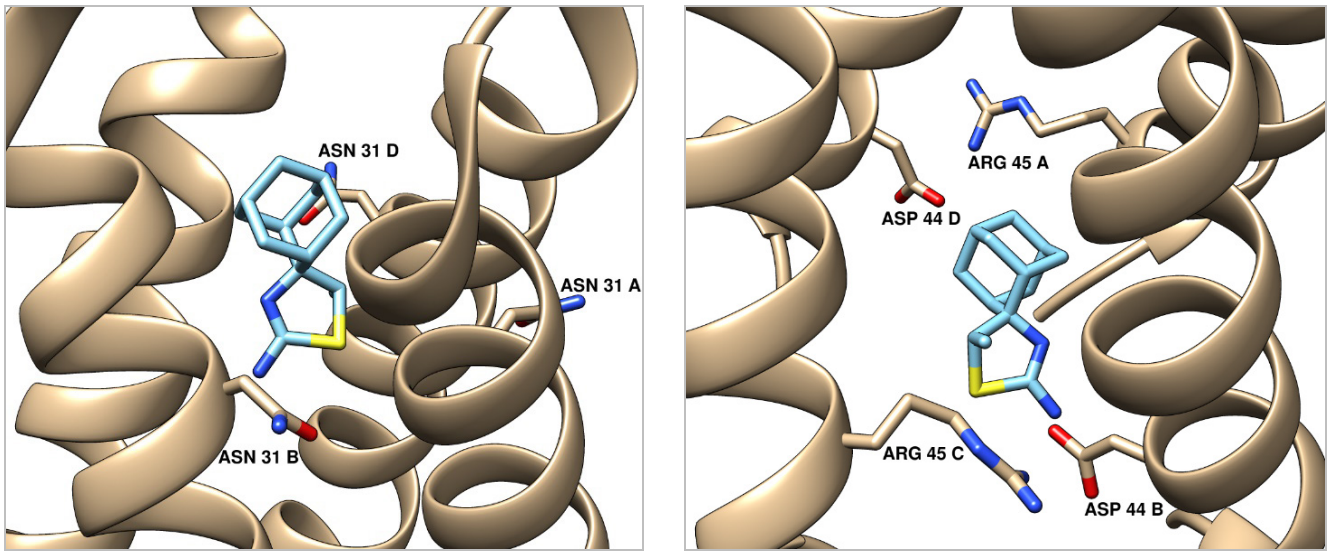
1. Molecular modeling

Molecular docking was carried out using a spatial model of the structure of the fragment (19–49) of the M2 channel with the S31N mutation of the influenza A virus strain A/Chiba/5/71(H3N2) (PDB ID 2LY0,[S1] conformer with minimal energy) into two regions of amino acid residues 1) 20 – 35 (main site) and 2) 35 – 49 (peripheral site) in accordance with the data.[S2] The docking procedure was carried out according to the protocols described in works[S3–S6] using the AutoDock Vina 1.1.2[S7] program (all docking parameters were as in Ref.[S6]). The resulting complexes were visualized using UCSF Chimera 1.15 software.[S8]

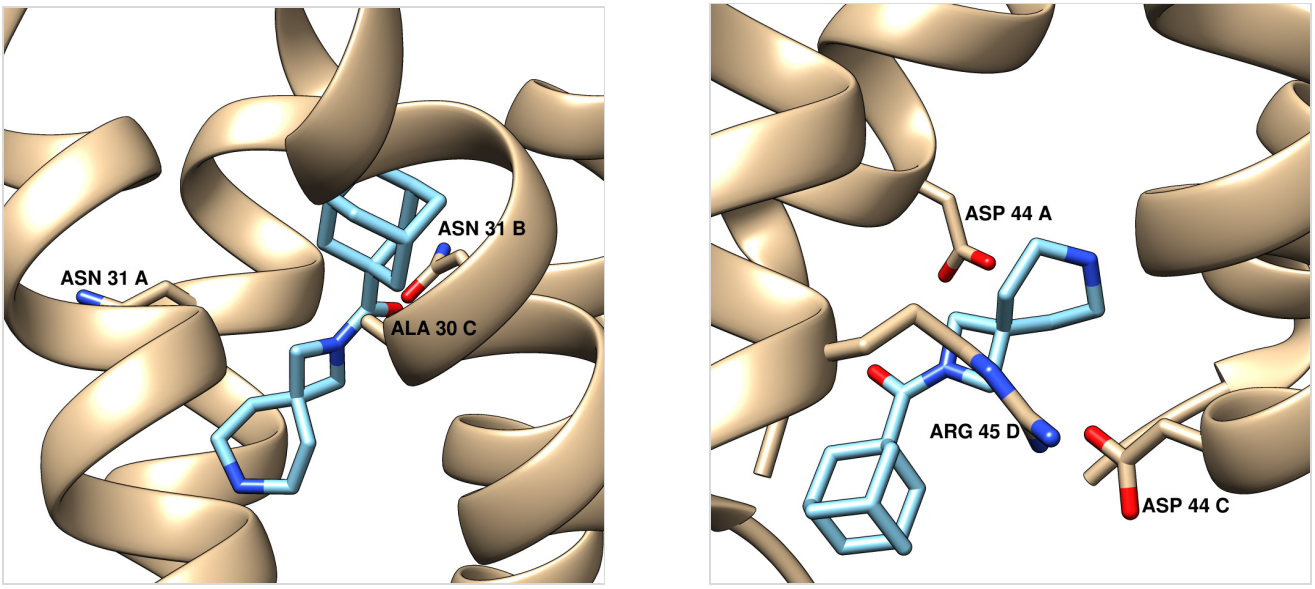
5'(*S*)-Methyl-5'*H*-spiro[adamantane-2,4'-thiazol]-2'-amine (**5**) was predicted to interact effectively with both rimantadine binding sites of the S31N mutant M2 channel of influenza A virus (the locations of the ligand see at Figure S1, parts A, B).



A **B**

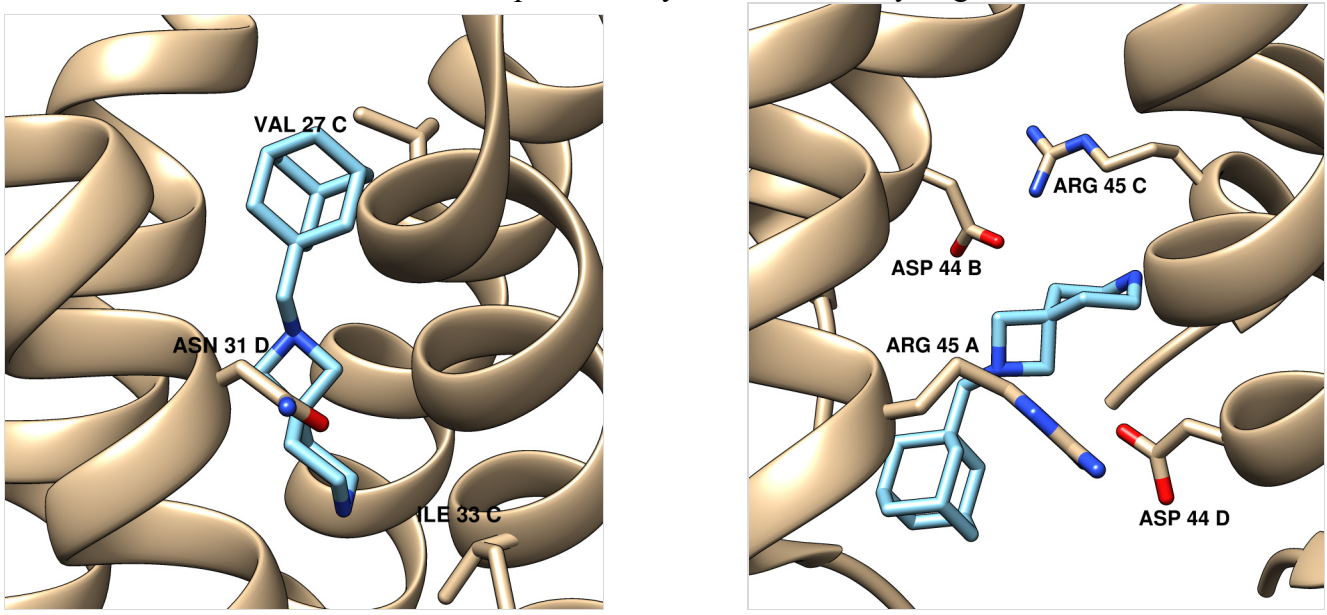
Figure S1 Positions of 5'(*S*)-methyl-5'*H*-spiro[adamantane-2,4'-thiazol]-2'-amine (**5**, represented by ball-and-stick model, in blue) in S31N mutant M2 channel of influenza A virus (PDB ID: 2LY0) as predicted by molecular docking: A) main rimantadine binding site; B) peripheral rimantadine binding site. Selected amino acid residues are represented by colored sticks, hydrogen atoms are omitted for clarity. Protein secondary structure is shown by ribbons.

The positions of (adamantan-1-yl)(2,7-diazaspiro[3.5]nonan-2-yl)methanone (**9a**) and 2-(adamantan-1-ylmethyl)-2,7-diazaspiro[3.5]nonane (**9b**) and are close (regardless of the basicity of the central nitrogen atoms) and favorable for the interaction with both the main and peripheral rimantadine binding sites of the S31N mutant M2 channel of influenza A virus (the locations of the ligands see at Figures S2, and S3, parts A, B).



A **B**

Figure S2 Positions of (adamantan-1-yl)(2,7-diazaspiro[3.5]nonan-2-yl)methanone (**19**, represented by ball-and-stick model, in blue) in S31N mutant M2 channel of influenza A virus (PDB ID: 2LY0) as predicted by molecular docking: A) main rimantadine binding site; B) peripheral rimantadine binding site. Selected amino acid residues are represented by colored sticks, hydrogen atoms are omitted.



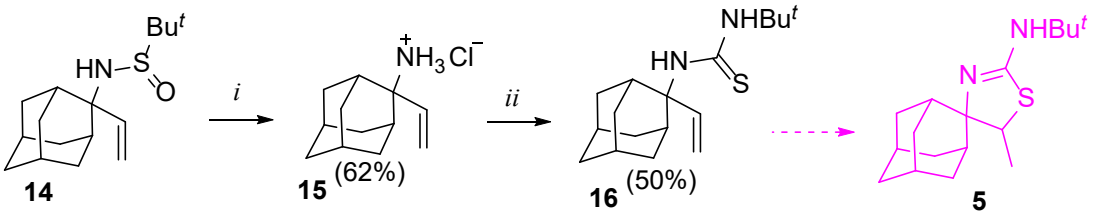
A **B**

Figure S3 Positions of 2-(adamantan-1-ylmethyl)-2,7-diazaspiro[3.5]nonane (**9**, represented by ball-and-stick model, in blue) in S31N mutant M2 channel of influenza A virus (PDB ID: 2LY0) as predicted by molecular docking: A) main rimantadine binding site; B) peripheral rimantadine binding site. Selected amino acid residues are represented by colored sticks, hydrogen atoms are omitted.

2. Chemistry

All starting materials and reagents were purchased as high-grade commercial products and used without further purification; the solvents were technical grade and distilled from standard drying agents. *N*,*N*′-Dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), EDCI (1-(3-dimethylaminipropyl)-3-ethylcarbodiimide hydrochloride), HBTU (benzotriazolyl tetramethyl uronium hexafluorophosphate), DIPEA (diisopropylethylamine), *N*-methylmorpholine, adamantanone, adamantane carboxylic acid, 1-adamantylmethanol, rimantadine (**2**) (1-(1-adamantyl)ethanamine), pyrazine-2-carboxylic acid, 5-methylpyrazine-2-carboxylic acid, 4-imidazolecarboxylic acid, thiourea and methyl 2-oxopropanoate were used as commercial products. If not specially indicated liquid column chromatography was performed using silica gel 'Macherey–Nagel' (0.063–0.2 mm). Thin-layer chromatography (TLC) was performed on ALUGRAM Xtra G/UV254 silica gel sheets. ^{1}H and ^{13}C NMR spectra were recorded on Agilent 400-MR spectrometer (400.0 MHz for ^{1}H; 100.6 MHz for ^{13}C) at 28°C. Chemical shifts (δ) are reported in ppm referenced to residual solvent peak ($CDCl_3$, δ_H=7.27 ppm, δ_C=77.0 ppm; methanol-d_4, δ_H=4.78 ppm, δ_C=49.0 pp, DMSO-d_6, δ_H=2.50 ppm, δ_C=39.5 pp); spin-spin coupling constants (*J*) are reported in Hz. Liquid chromatography (LC) and ElectroSpray ionization mass spectrometry (ESI-MS) data were obtained on an Agilent 1100 LC/MSD with an Agilent 1100 SL quadrupole mass spectrometer (electrospray ionization) with Sedex 75 ELSD detector (positive-ion monitoring mode). CHN elemental analysis was performed using a Carlo-Erba ER-20 analyzer. IR-spectra were registered on FT-IR Termo Nicolet IR200 Spectrometer with 4 cm^{-1} resolution, absorption bands are given in cm^{-1}, samples were prepared as fin films. Melting points were determined using a capillary melting point apparatus and were uncorrected.

Synthetic scheme carried out in an attempt to obtain 5'-methyl-5'*H*-spiro[adamantane-2,4'-thiazol]-2'-amine (5)



Scheme S1 *Reagents and conditions. i,* HCl•dioxane, 0–20°C, 10 min, *ii,* 1. $CSCl_2$, $NaHCO_3$, H_2O, EtOAc, 3–20°C, 30 min, 2. Bu^tNH_2, EtOAc, 20°C, 12 h.

2-Methyl-*N*-(2-vinyladamantan-2-yl)propan-2-sulfinamide (14) was obtained from adamantanone according to the method described in Ref.[S9]

2-Vinyladamantan-2-amine hydrochloride (15). To a solution of compound **14** (0.500 g, 1.78 mmol) in dioxane (10 ml) at 0°C was added a solution of 4N HCl in dioxane (2 ml, 8 mmol), then warmed to room temperature and stirred 10 min. The reaction mixture was concentrated under reduced pressure and chromatographed (eluent: methylene chloride – methanol, gradient 100:1 – 100:15) to give **15** as white solid (0.235 g, yield 62%).

^{1}H NMR (δ, $CDCl_3$): 8.24 – 7.92 (brs, 3H, NH_3^+), 6.02 (dd *J* = 17.9, 11.1 Hz, 1H, CH=), 5.69 (d, *J* = 17.9 Hz, 1H, CH_2=), 5.45 (d, *J* = 11.1 Hz, 1H, CH_2=), 2.45 – 2.41 (m, 2H), 2.27 – 2.23 (m, 2H), 1.97 – 1.82 (m, 4H), 1.74 – 1.67 (m, 6H).

^{13}C NMR (δ, $CDCl_3$): 138.9 (CH=), 119.5 (CH_2=), 61.2 (C^3), 38.1, 34.1, 33.5, 31.6, 26.9, 26.6.

MS (ESI), m/z: 161.1 $[M-NH_2]^+$, 178.3 $[M+H]^+$. Calculated for $C_{19}H_{20}N$: 178.3

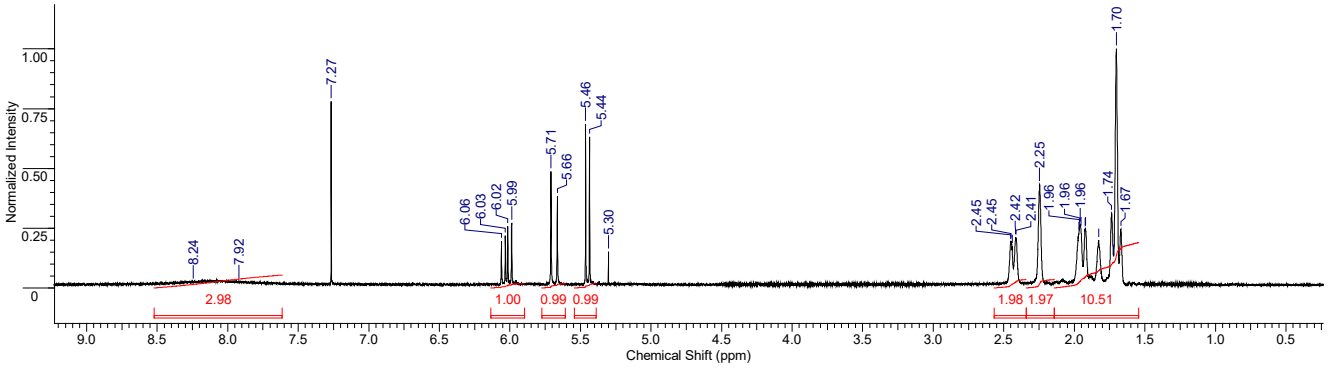


Figure S4 ^{1}H NMR spectrum of compound **15**.

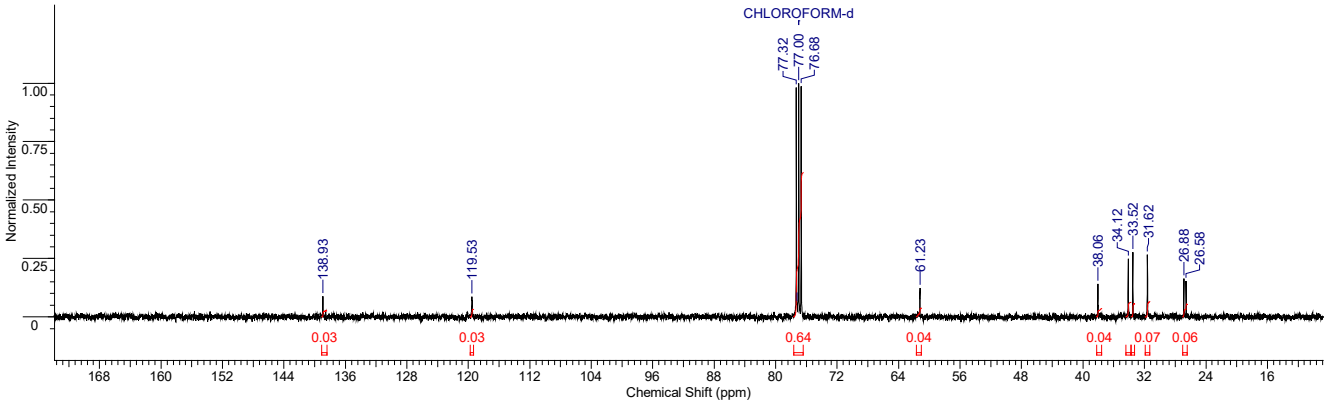


Figure S5 ^{13}C NMR spectrum of compound **15**.

1-(*tert*-Butyl)-3-(2-vinyladamantan-2-yl)thiourea (16). To a solution of compound **15** (0.190 g, 0.89 mmol) in ethyl acetate (10 ml) at 3–5°C was added aqueous solution of $NaHCO_3$ (0.3 g in 10 ml) and thiophosgene (0.076 ml, 1.0 mmol), and the mixture was stirred at room temperature 30 min. The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and after addition of the *tert*-butylamine (0.105 ml, 1 mmol) the

mixture was stirred at room temperature 12 h, then concentrated under reduced pressure and chromatographed (eluent: ethyl acetate – petroleum ether 40–70°C, 1:3) to give **16** as ivory solid (0.130 g, yield 50%).

^{1}H NMR (δ, $CDCl_3$): 6.12 (dd, *J* = 17.7, 10.9 Hz, 1H, CH=), 5.94 (brs, 1H, NH), 5.85 (brs, 1H, NH), 5.43 (d, *J* = 10.9 Hz, 1H, CH_2=), 5.38 (d, *J* = 17.7 Hz, 1H, CH_2=), 2.11 – 2.04 (m, 3H), 1.98 – 1.94 (m, 2H), 1.88 – 1.84 (m, 2H), 1.73 – 1.65 (m, 7H), 1.47 (s, 9H, t-Bu).

^{13}C NMR (δ, $CDCl_3$): 179.3 (CS), 140.1 (CH=), 117.0 (CH_2=), 62.6 (C^3), 53.9 (CMe_3), 37.8, 35.3, 33.1, 32.7, 29.1 (Me_3), 27.1, 26.3.

MS (ESI), m/z: 293.3 $[M+H]^+$. Calculated for $C_{17}H_{29}N_2S$: 293.5

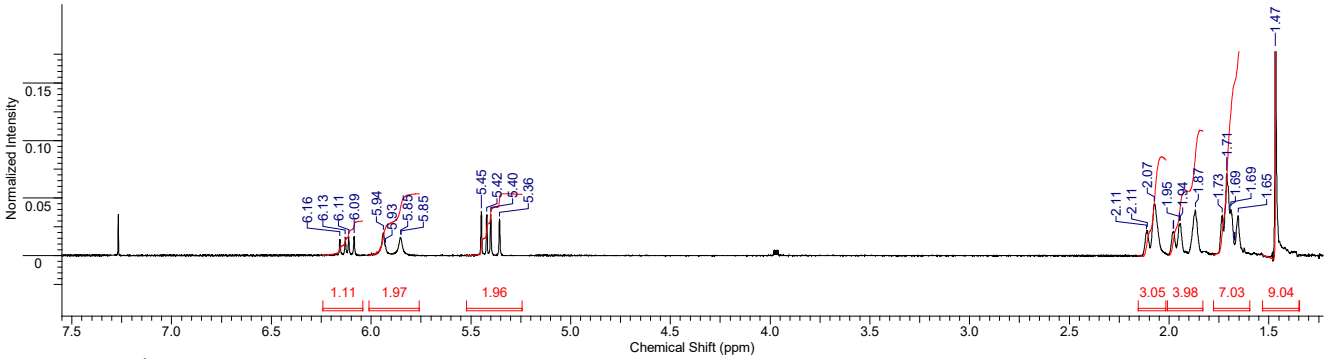


Figure S6 ^{1}H NMR spectrum of compound **16**.

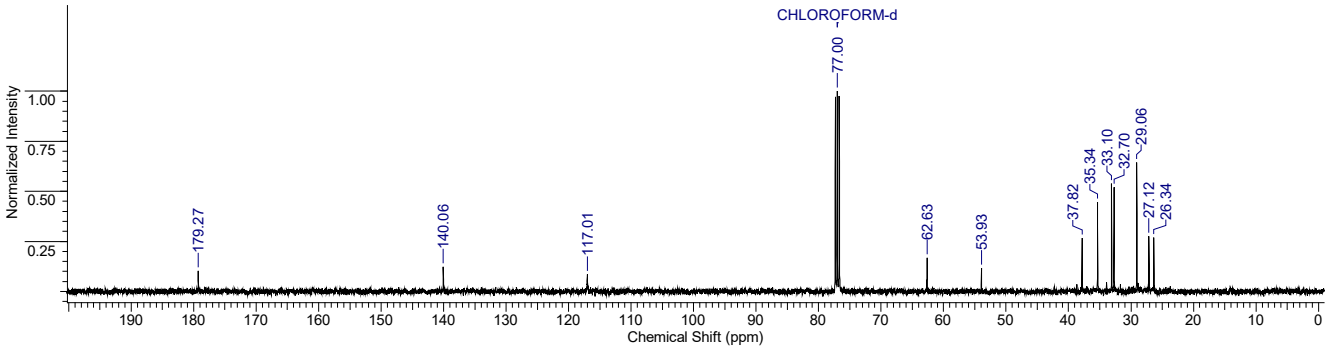
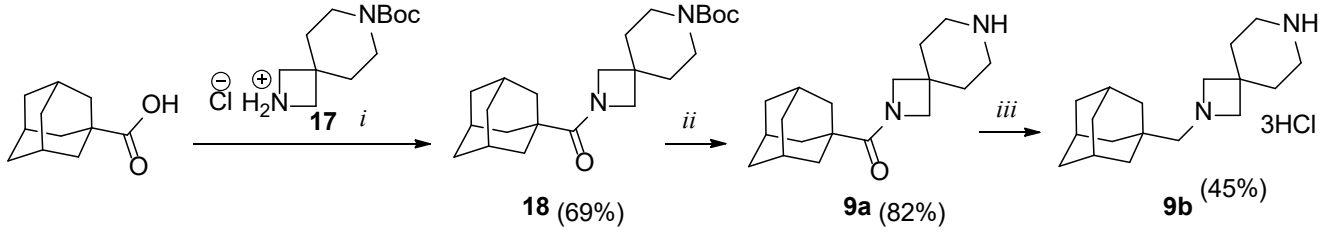


Figure S7 ^{13}C NMR spectrum of compound **16**.

Attempts of intramolecular cyclization of thiourea 16: A) A mixture of acetyl bromide (0.026 ml, 0.350 mmol) and methanol (0.015 ml, 0.370 mmol) in dichloromethane (5 ml) was stirred at room temperature 30 min, then a solution of compound **16** (0.050 g, 0.17 mmol) in dichloromethane (10 ml) was added and stirring continued for 12 to 24 h. No substrate conversion was detected.

B) To a solution of compound **16** (0.062 g, 0.188 mmol) in dichloromethane (10 ml) was added bromine (0.010 ml, 0.193 mmol), and this was stirred in the darkness at room temperature 12 h. A very complex mixture of products, inseparable by column chromatography, was obtained.

Procedures to synthesize (adamantan-1-yl)(2,7-diazaspiro[3.5]nonan-2-yl)methanone (9a) and 2-(adamantan-1-ylmethyl)-2,7-diazaspiro[3.5]nonane (9b)



Scheme S2 *Reagents and conditions. i*, EDCI, DIPEA, DMAP (cat.), 20ºC, 16 h, *ii*, 1. CF_3COOH, CH_2Cl_2, 20ºC, 16 h, 2. $NaHCO_3$ (sat.), H_2O, *iii*, 1. $LiAlH_4$, THF, 20ºC, 16 h, 2. NaOH (15%), H_2O. 3. 5% HCl in EtOH, Et_2O.

***tert*-Butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate hydrochloride** (**17**) was purchased from Sigma (USA).

***tert*-Butyl 2-(1-adamantylcarbonyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate (18).** To a solution of adamantane-1-carboxylic acid (0. 076 g, 0.419 mmol) and compound **17** (0.100 g, 0.381 mmol) in dichloromethane (5 ml) was added EDCI (0.118 g, 0.762 mmol), DIPEA (0.132 ml, 0.762 mmol) and DMAP (catalytic amount ~10 mol%: 0.005 g,), and this was stirred at room temperature for 16 h. The mixture was washed with distilled water (10 ml) and extracted with CH_2Cl_2 (4×10 ml). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and chromatographed (eluent: methylene chloride, then 1% methanol in methylene chloride) to give **18** as white crystals (0.111 g, yield 69%). M.p. 184 – 186ºC.

^{1}H NMR (δ, $CDCl_3$): 4.05 (s, 2H, C$\underline{H_2}$NH), 3.65 (s, 2H, C$\underline{H_2}$NH), 3.45 – 3.20 (m, 4H, C$\underline{H_2}$NH), 2.02 – 1.96 (m, 3H, Ad), 1.92 – 1.83 (m, 6H), 1.75 – 1.58 (m, 10H, Ad), 1.40 (s, 9H, $3Me^{Boc}$).

^{13}C NMR (δ, $CDCl_3$): 177.2 (CON), 154.6 (CO_2N), 79.5 (Me_3C-O), 62.9 (C^1), 58.3 (C^3), 41.1 (C^4), 38.3, 36.4, 35.0, 33.9, 28.2 (Me^{Boc}), 28.0.

MS (ESI), m/z: 289.1 $[M\text{-Boc}+H]^+$, 389.5 $[M+H]^+$. Calculated for $C_{23}H_{37}N_2O_3$: 389.6

Anal. Calcd for $C_{23}H_{36}N_2O_3$: C, 71.10; H, 9.34; N, 7.21. Found: C, 71.08, H, 9.38, N, 7.20.

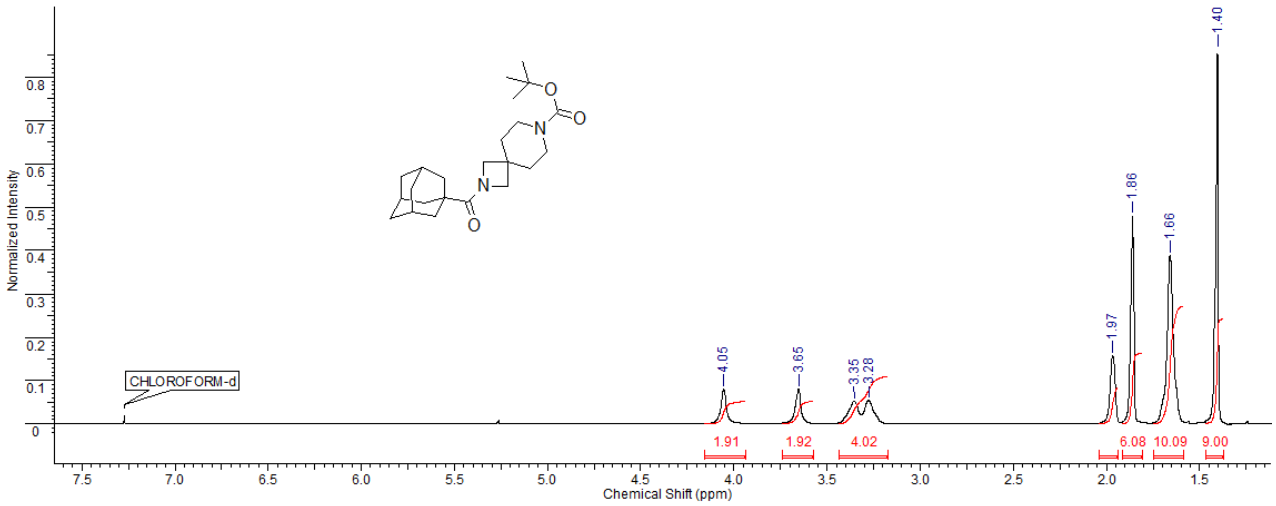


Figure S8 ^{1}H NMR spectrum of compound **18**.

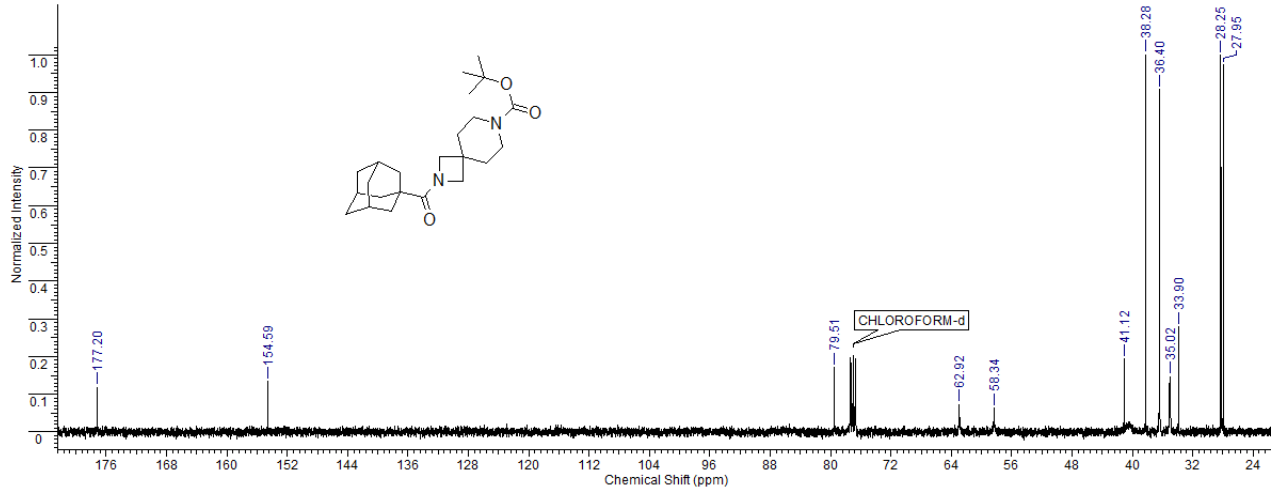


Figure S9 ^{13}C NMR spectrum of compound **18**.

(Adamantan-1-yl)(2,7-diazaspiro[3.5]nonan-2-yl)methanone (9a). Compound **18** (0.076 g 0.196 mmol) was dissolved in a mixture of trifluoroacetic acid and dichloromethane (4:1, 5 ml), stirred at room temperature 16 h, washed with saturated aqueous solution of $NaHCO_3$ (5 ml), dried over Na_2SO_4, then concentrated under reduced pressure and chromatographed (eluent: methylene chloride). The collected fractions were concentrated under reduced pressure to afford **9a** as white solid (0.046 g, yield 82%). M.p. 158 – 159ºC.

^{1}H NMR (δ, $CDCl_3$): δ 4.04 (s, 2H, CH_2NH), 3.64 (s, 2H, CH_2NH), 2.80 – 2.70 (m, 4H, CH_2NH), 2.02 – 1.96 (m, 3H, Ad), 1.88 (s, 7H), 1.73 – 1.60 (m, 9H, Ad).

^{13}C NMR (δ, $CDCl_3$): 177.2 (CON), 63.6 (C^1), 59.1 (C^3), 43.2, 41.1 (C^4), 38.3, 36.5, 36.3, 34.2, 28.0.

MS (ESI), m/z: 289.3 $[M+H]^+$. Calculated for $C_{18}H_{29}N_2O$: 289.4

Anal. Calcd for $C_{18}H_{28}N_2O$: C, 74.96; H, 9.78; N, 9.71. Found: C, 74.99, H, 9.69, N, 9.62.

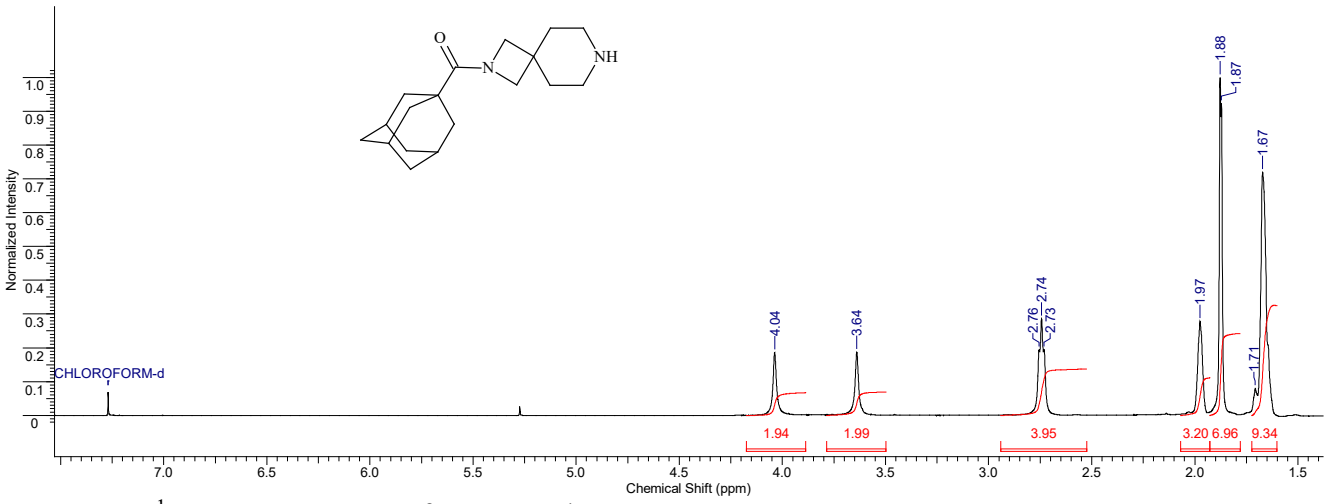


Figure S10 ^{1}H NMR spectrum of compound **9a**.

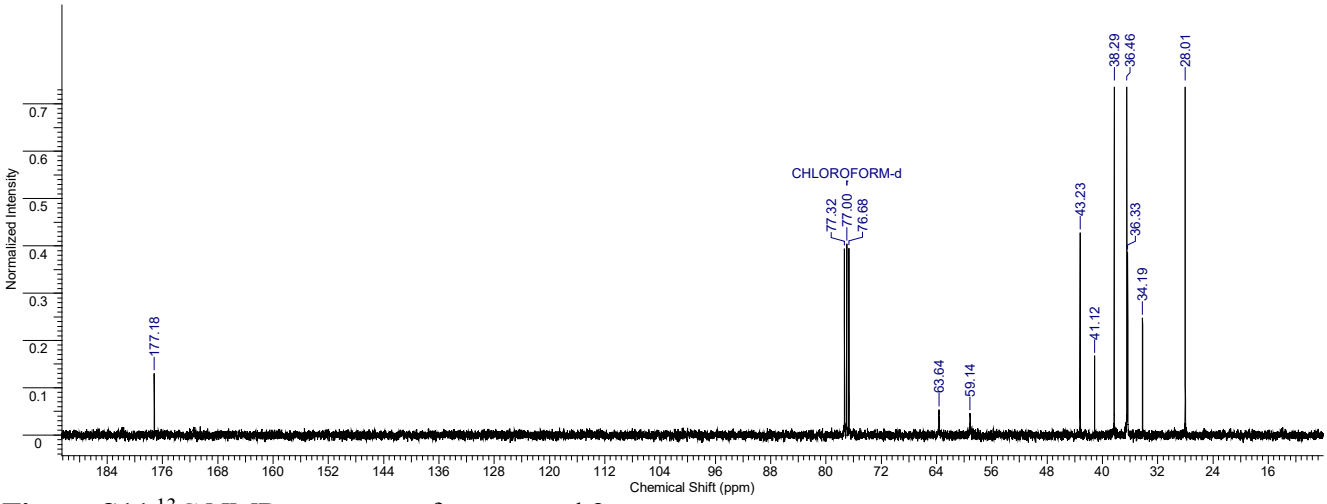


Figure S11 ^{13}C NMR spectrum of compound **9a**.

2-(Adamantan-1-ylmethyl)-2,7-diazaspiro[3.5]nonane hydrochloride (9b). Compound **9a** (0.070 g, 0.242 mmol) dissolved in absolute THF (5 ml) was added dropwise at 10–15°C to a solution of $LiAlH_4$ (0.035 g, 0.946 mmol) in absolute THF (5 ml), and this was stirred at room temperature 16 h. The mixture was washed with 0.5 ml 10% NaOH, the organic layer was decanted and the inorganic residue was washed with THF (2×10 ml). The combined organic layers were concentrated under reduced pressure, chromatographed on Al_2O_3 (neutral, 70-230 mesh) (eluent: 2% methanol in methylene chloride). The main chromatographic fractions were concentrated, re-evaporated with 5% HCl in ethanol (30 ml), precipitated from diethyl ether (20 ml) and filtered to give **9b** as white crystals (0.042 g, yield 45%). M.p. > 230°C (sublimation).

^{1}H NMR (δ, methanol-d4): δ 4.27 (d, *J* = 11.5 Hz, 2H, CH_2NH), 3.96 (d, *J* = 11.5 Hz, 2H, CH_2NH), 3.15 – 3.06 (m, 4H, CH_2NH), 3.0 (s, 2H, AdCH_2N), 2.21 – 2.19 (m, 2H, CH_2N), 2.07 – 2.04 (m, 2H, CH_2N), 1.94 – 1.91 (m, 3H, Ad), 1.70 – 1.61 (m, 9H, Ad), 1.56 – 1.57 (m, 3H).

^{13}C NMR (δ, methanol-d4): 70.3 (Ad$\underline{C}$H$_2$N), 68.4 (C^{6,8}H$_2$N), 41.9 (C^{1}H$_2$N), 41.8 (C^{3}H$_2$N), 40.8, 37.3, 34.5, 34.0, 32.9, 31.1, 29.3.

MS (ESI), m/z: 275.4 $[M+H]^+$. Calculated for $C_{18}H_{31}N_2$: 275.4.

Anal. Calcd for $C_{18}H_{33}N_2Cl_3$: C, 56.33; H, 8.67; N, 7.30. Found: C, 56.28, H, 8.60, N, 7.25.

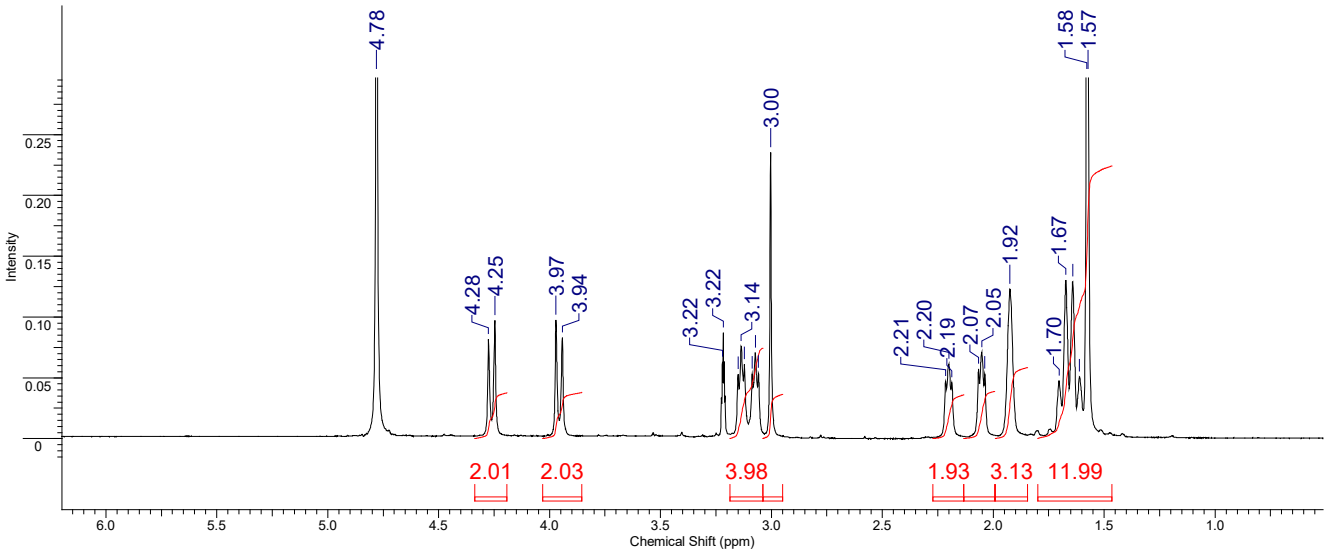


Figure S12 ^{1}H NMR spectrum of compound **9b** (in methanol-d4).

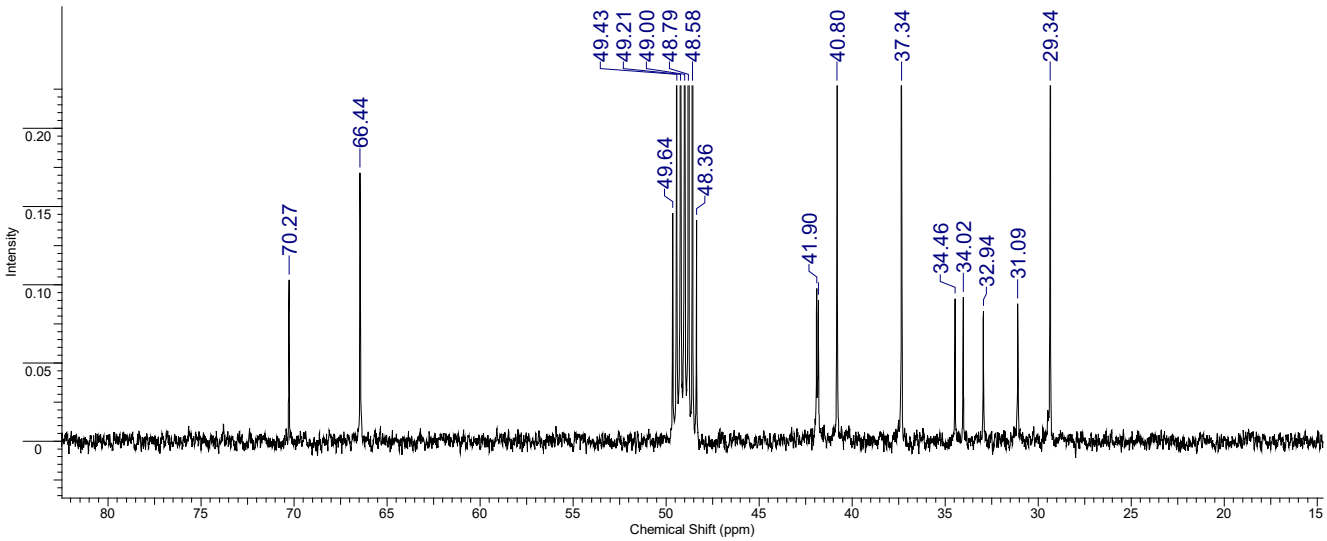
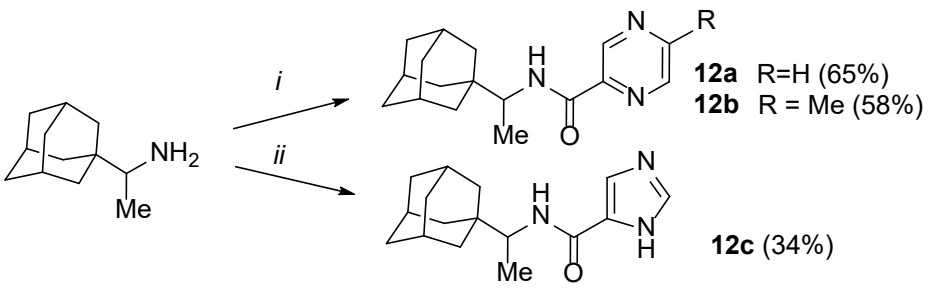


Figure S13 ^{13}C NMR spectrum of compound **9b** (in methanol-d4).

Synthetic procedures for obtaining compounds 12a-d, 13a-d and 20,21



Scheme S3 *Reagents and conditions. i*, pyrazine-2-carboxylic acid or 5-methylpyrazine-2carboxylic acid, DCC, DIPEA, DMAP (cat.), CH_2Cl_2, 20ºC, 24 h; *ii*, 4-imidazolecarboxylic acid, HBTU, NMM, DMF, 20ºC, 24 h.

***N*-[1-(Adamantan-1-yl)ethyl]pyrazine-2-carboxamide (12a).** To a solution of pyrazine-2-carboxylic acid (0.029 g, 0.232 mmol) in dichloromethane (5 ml) was added DCC (0.062 g, 0.300 mmol), DIPEA (0.042 ml, 0.232 mmol), rimantadine (**2**) (0.041 g, 0.229 mmol) and DMAP (0.003 g). After stirring at room temperature for 24 h, the mixture was concentrated under reduced pressure and chromatographed (eluent: ethyl acetate – petroleum ether 40–70ºC, 1:4) to give **12a** as white solid (0.045 g, yield 65%). M.p. 145 – 147°C.

^{1}H NMR (δ, $CDCl_3$): 9.40 (d, *J* = 1.5 Hz, 1H, H^3), 8.73 (d, *J* = 2.5 Hz, 1H, H^6), 8.52 (dd, *J* = 2.5, 1.5 Hz, 1H, H^5), 7.75 (d, *J* = 10.2 Hz, 1H, NH), 3.90 (dq, *J* = 10.1, 6.9 Hz, 1H, CH), 2.05 – 1.95 (m, 3H), 1.73 – 1.54 (m, 12H), 1.15 (d, *J* = 6.9 Hz, 3H, Me).

^{13}C NMR (δ, $CDCl_3$): 162.2 (CONH), 147.0 (C^5), 144.7 (C^2), 144.5 (C^3), 142.4 (C^6), 53.2 (CH), 38.4, 36.9, 36.1, 28.2, 14.4 (Me).

MS (ESI), m/z: 286.4 $[M+H]^+$. Calculated for $C_{17}H_{24}N_3O$: 286.4.

Anal. Calcd for $C_{17}H_{23}N_3O$: C, 71.55; H, 8.12; N, 14.72. Found: C, 71.48, H, 8.04, N, 14.62.

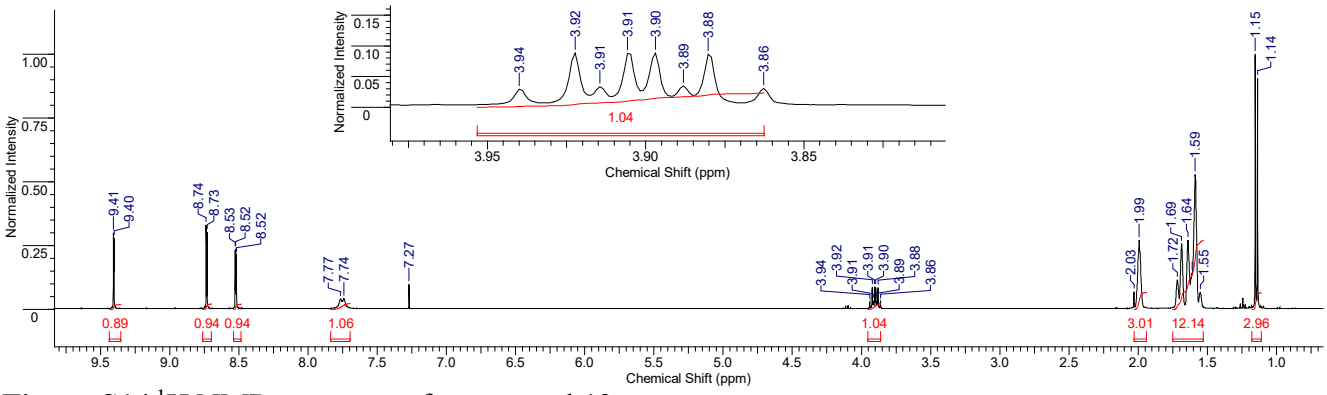


Figure S14 ^{1}H NMR spectrum of compound **12a**.

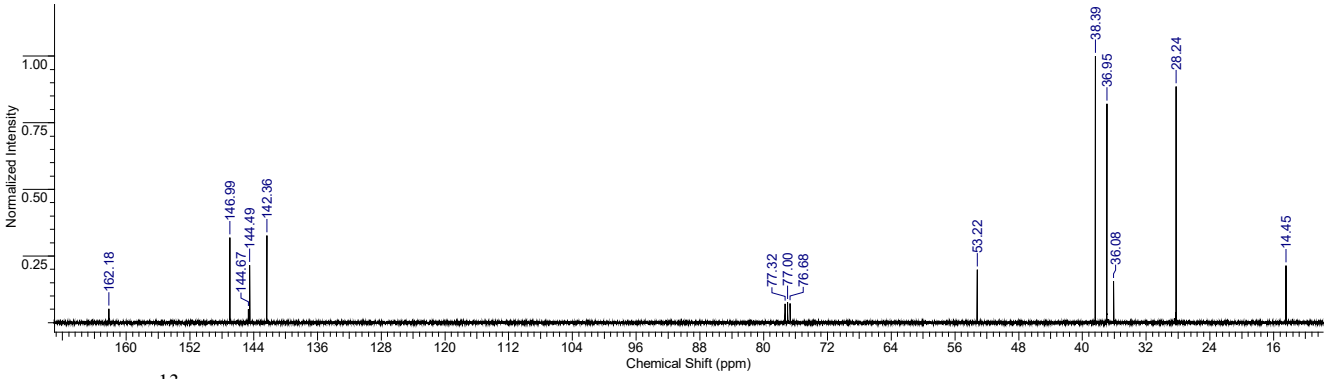


Figure S15 ^{13}C NMR spectrum of compound **12a**.

***N*-[1-(Adamantan-1-yl)ethyl]-5-methylpyrazine-2-carboxamide (12b)** was obtained in the same way as compound **12a** from 5-methylpyrazine-2-carboxylic acid (0.032 g, 0.232 mmol), rimantadine (**2**) (0.041 g, 0.229 mmol), DCC (0.062 g, 0.300 mmol), DIPEA (0.042 ml, 0.232 mmol) and DMAP (0.003 g). Yield of **12b** was 0.040 g (58%), white crystals, m.p. 105 – 107 °C.

^{1}H NMR (δ, $CDCl_3$): 9.28 (d, J = 1.4 Hz, 1H, H^3), 8.39 (m, 1H, H^6), 7.71 (d, J = 10.2 Hz, 1H, NH), 3.91 (dq, J = 10.2, 6.9 Hz, 1H, CH), 2.66 (s, 3H, Me^{Ar}), 2.03 – 1.97 (m, 3H), 1.75 – 1.55 (d, 12H), 1.15 (d, J = 6.9 Hz, 3H, Me).

^{13}C NMR (δ, $CDCl_3$): 162.5 (CONH), 156.7 (C^2), 143.4 (C^3), 142.2 (C^6), 142.0 (C^5), 53.1 (CH), 38.4, 37.0, 36.1, 28.3, 21.8 (Me^{Ar}), 14.5 (Me).

MS (ESI), m/z: 300.3 $[M+H]^+$. Calculated for $C_{18}H_{26}N_3O$: 300.4.

Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.21; H, 8.42; N, 14.03. Found: C, 72.29, H, 8.48, N, 14.22.

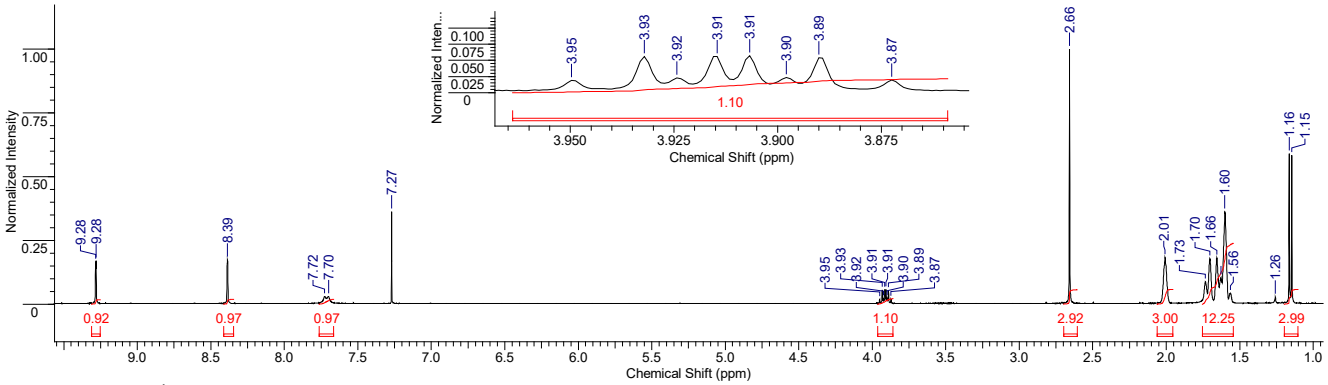


Figure S16 ^{1}H NMR spectrum of compound **12b**.

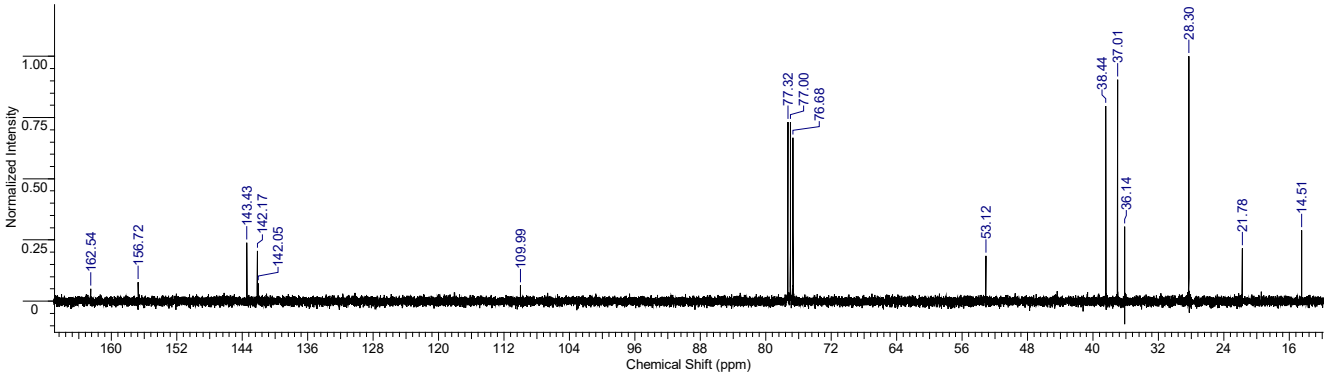


Figure S17 ^{13}C NMR spectrum of compound **12b**.

***N*-[1-(Adamantan-1-yl)ethyl]-4-imidazolecarboxamide (12c).** To a solution of imidazole-4-carboxylic acid (0.070 g, 0.625 mmol), rimantadine (**2**) (0.100 g, 0.559 mmol) in DMF (3 ml) was added *N*-methylmorpholine (NMM) (0.100 ml, 0.909 mmol), HBTU (0.414 g, 1.091 mmol), and this was stirred at room temperature 24 h. The mixture was washed with distilled water (10 ml) and extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were washed with brine (3×10 ml), dried over Na_2SO_4, concentrated under reduced pressure and chromatographed (eluent: methylene chloride, then 1.5% methanol in dichloromethane) to give **12c** as white crystals (0.052 g, yield 34%). M.p. 193 – 195°C.

^{1}H NMR (δ, $CDCl_3$): 9.98 (brs, 1H, NH^1), 7.66 (s, 1H, H^2), 7.53 (s, 1H, H^4), 7.29 (d, J = 10.1 Hz, 1H, NH), 3.87 (dq, J = 10.1, 6.8 Hz, 1H, CHNH), 2.01 – 1.95 (m, 3H), 1.70 – 1.54 (m, 12H), 1.13 (d, J = 6.8 Hz, 3H, Me).

^{13}C NMR (δ, $CDCl_3$): 162.7 (CONH), 135.6 (C^2), 135.5 (C^5), 119.3 (C^4), 53.0 (CH-NH), 38.4, 36.9, 36.1, 28.2, 14.5 (Me).

MS (ESI), m/z: 274.4 $[M+H]^+$. Calculated for $C_{16}H_{24}N_3O$: 274.4

IR (cm^{-1}): 3383 (N-H), 2899 (C-H), 2846 (C-H), 1657 (C=O), 1627 (C=N), 1570 (N-H), 1512 (C=C), 1442 (C-H), 1362, 1076, 970.

Anal. Calcd for $C_{16}H_{23}N_3O$: C, 70.30; H, 8.48; N, 15.37. Found: C, 70.35, H, 8.39, N, 15.34.

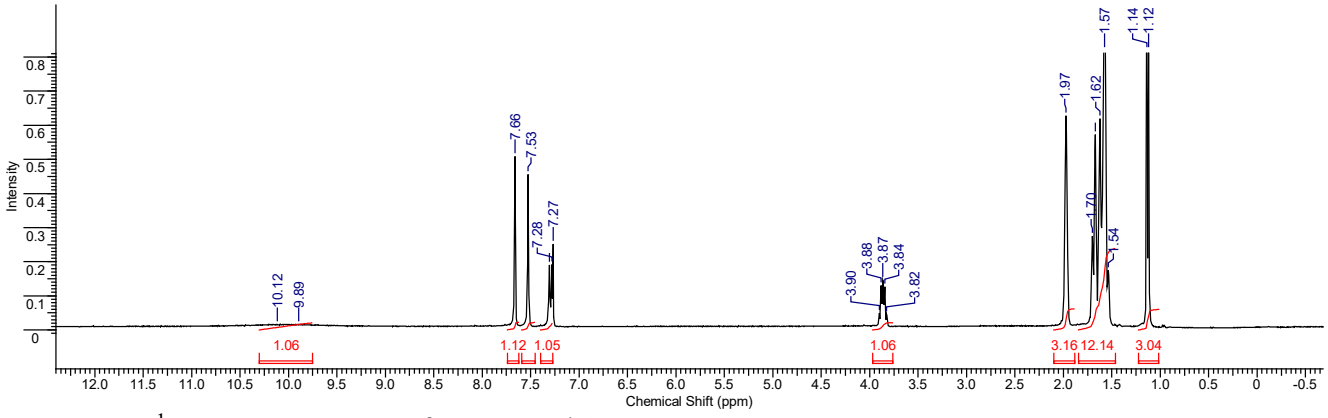


Figure S18 ^{1}H NMR spectrum of compound **12c**.

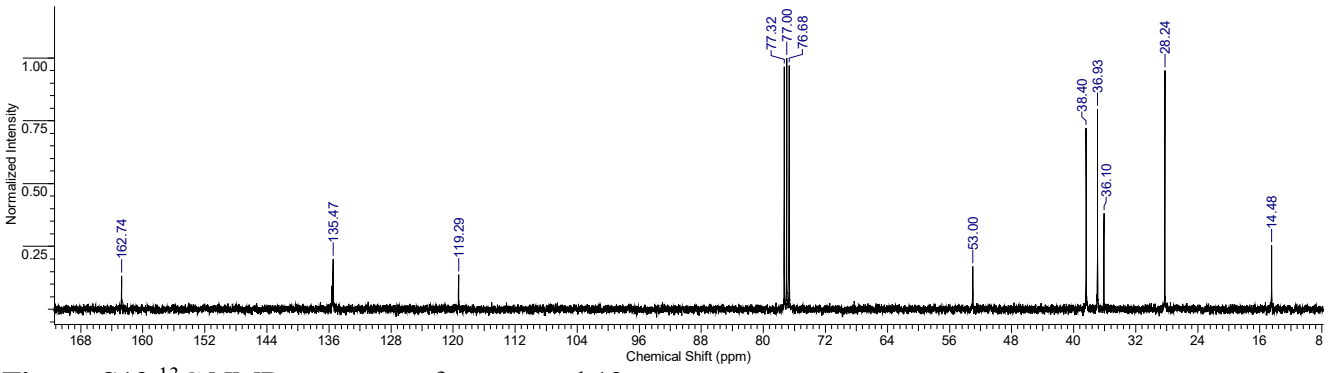


Figure S19 ^{13}C NMR spectrum of compound **12c**.

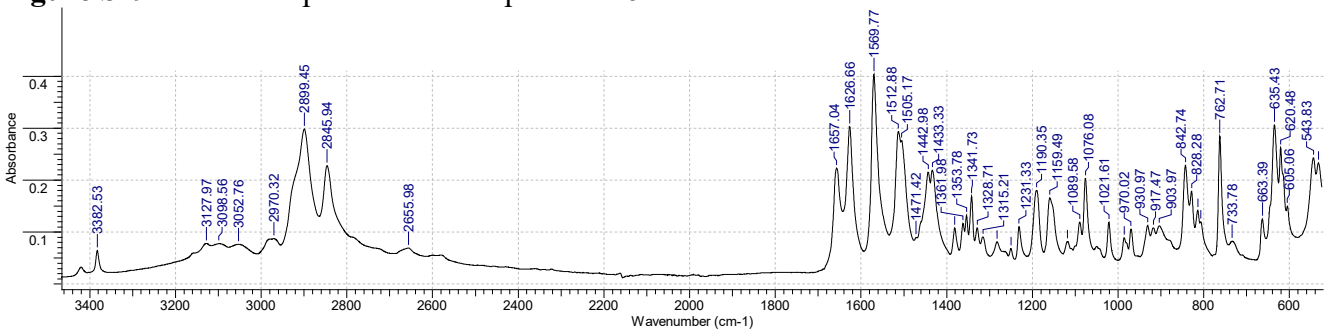
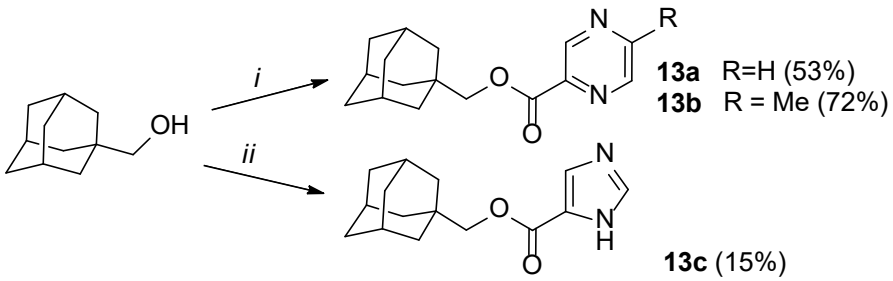


Figure S20 Infrared spectrum of compound **12c** (thin film).



Scheme S4 *Reagents and conditions.* i, pyrazine-2-carboxylic acid or 5-methylpyrazine-2-carboxylic acid, EDCI, DMAP (cat.), CH_2Cl_2, 20ºC, 16 h; ii, 4-imidazolecarboxylic acid, HBTU, NMM, DMF, 20ºC, 24 h.

1-Adamantylmethyl pyrazine-2-carboxylate (13a) was obtained using a procedure similar to the one for compound (**18**) from pyrazine-2-carboxylic acid (0.100 g, 0.806 mmol), 1-adamantylmethanol (0.134 g, 0.806 mmol), EDCI (0.231 g, 1.209 mmol) and DMAP (0.009 g). Eluent for column chromatography: ethyl acetate – petroleum ether 40–70ºC, 1:5. Yield of **13a** 0.118 g (53%), white crystals, m.p. 80 – 81°C.

^{1}H NMR (δ, $CDCl_3$): 9.30 (s, 1H, H^3), 8.76 (s, 2H, $H^{5,6}$), 4.06 (s, 2H, CH_2O), 2.05 – 1.99 (m, 3H), 1.78 – 1.62 (m, 12H).

^{13}C NMR (δ, $CDCl_3$): 163.9 (COO), 147.3 (C^5), 146.0 (C^2), 144.7 (C^3), 143.8 (C^6), 75.5 (CH_2O), 39.3, 36.8, 33.6, 27.9.

MS (ESI), m/z: 273.3 $[M+H]^+$. Calculated for $C_{16}H_{21}N_2O_2$: 274.3

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.58, H, 7.42, N, 10.18.

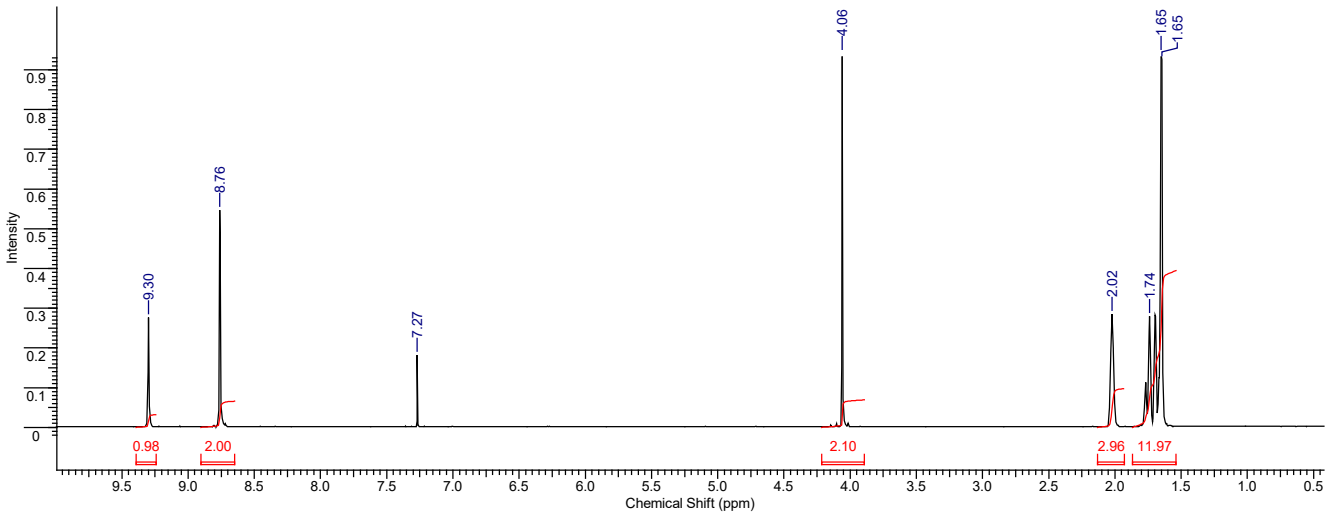


Figure S21 ^{1}H NMR spectrum of compound **13a**.

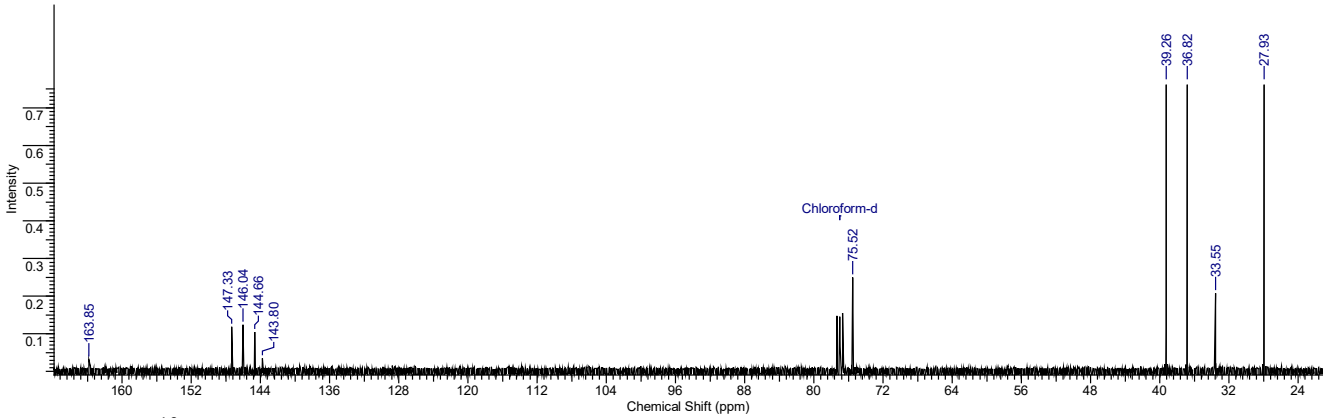


Figure S22 ^{13}C NMR spectrum of compound **13a**.

1-Adamantylmethyl 5-methylpyrazine-2-carboxylate (13b) was obtained using a procedure similar to the one for compound (**13a**) from 5-methylpyrazine-2-carboxylic acid (0.100 g, 0.725 mmol), 1-adamantylmethanol (0.121 g, 0.725 mmol), EDCI (0.209 g, 1.088 mmol) and DMAP (0.008 g). Eluent for column chromatography: ethyl acetate – petroleum ether 40–70ºC, 1:6. Yield of **13b** 0.149 g (72%), white crystals, m.p. 85 – 86°C.

^{1}H NMR (δ, $CDCl_3$): 9.15 (s, 1H, H^3), 8.60 (s, 1H, H^6), 4.03 (s, 2H, CH_2O), 2.66 (s, 3H, Me), 2.03 – 1.97 (m, 3H), 1.75 – 1.61 (m, 12H).

^{13}C NMR (δ, $CDCl_3$): 164.1 (COO), 157.3 (C^2), 145.0 (C^3), 144.5 (C^6), 140.9 (C^5), 75.2 (CH_2O), 39.2, 36.8, 33.5, 27.9, 21.8 (Me^{Ar}).

MS (ESI), m/z: 287.3 $[M+H]^+$. Calculated for $C_{17}H_{23}N_2O_2$: 287.4

IR (cm^{-1}): 2896 (C-H), 2849 (C-H), 1739 (C=O), 1447, 1275, 1132, 970.

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.28, H, 7.76, N, 11.16.

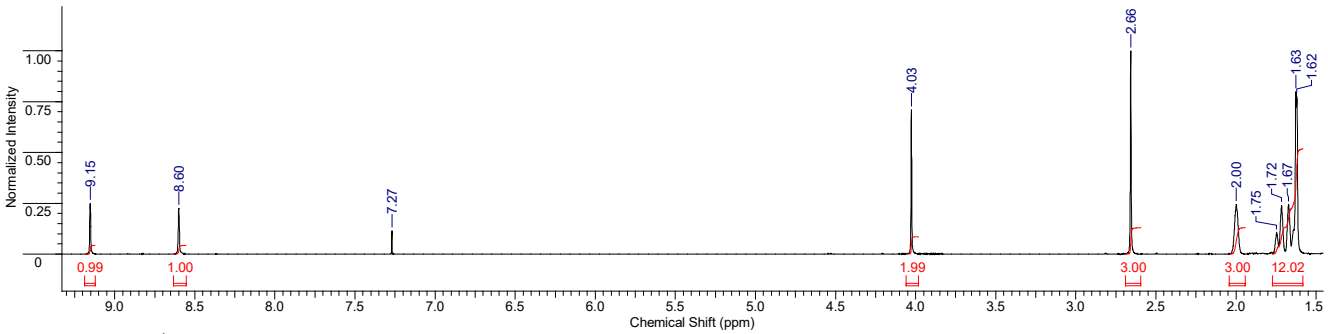


Figure S23 ^{1}H NMR spectrum of compound **13b**.

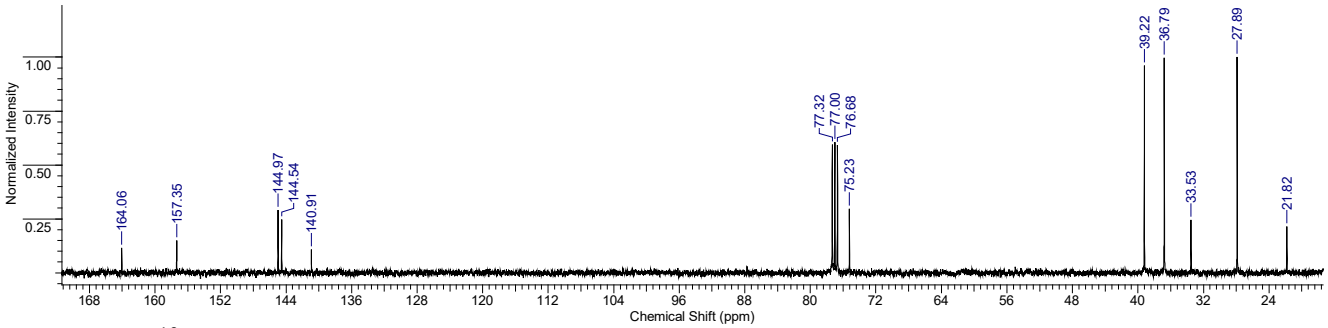


Figure S24 ^{13}C NMR spectrum of compound **13b**.

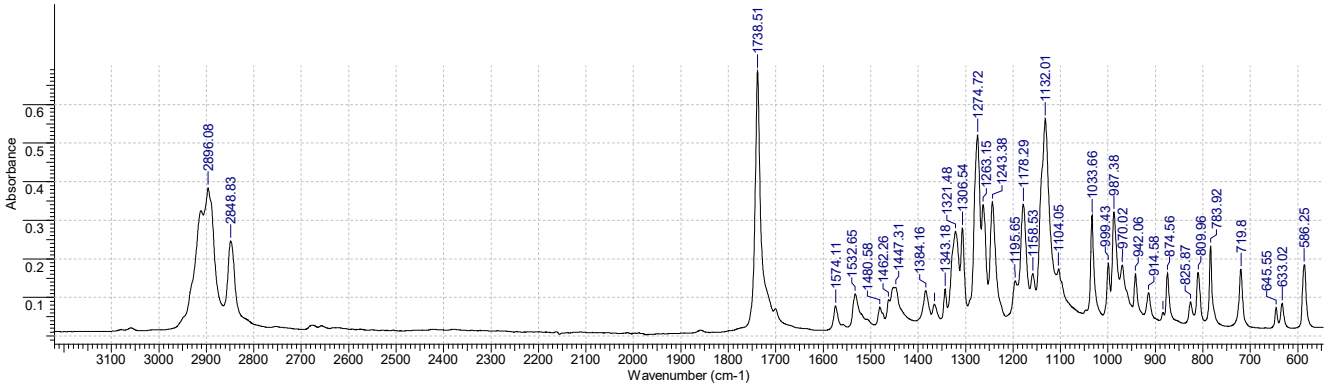


Figure S25 Infrared spectrum of compound **13b** (thin film).

1-Adamantylmethyl 1*H*-imidazole-4-carboxylate (13c). To a solution of imidazole-4-carboxylic acid (0.070 g, 0.625 mmol), 1-adamantylmethanol (0.100 g, 0.558 mmol) in DMF (3 ml) was added *N*-methylmorpholine (0.198 ml, 1.808 mmol), HBTU (0.536 g, 1.414 mmol), and this was stirred at room temperature for 24 h. The mixture was washed with distilled water (15 ml) and extracted with ethyl acetate (3×10 ml). The combined organic layers were washed with brine (3×10 ml), dried over Na_2SO_4, concentrated under reduced pressure and chromatographed (eluent: dichloromethane, then gradient 0–3% methanol in dichloromethane). The collected fractions were concentrated under reduced pressure, the residue was dissolved saturated aqueous solution of Na_2CO_3, extracted with ethyl acetate (3×10 ml) and combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give **13c** as pale-ivory solid (0.040 g, yield 15%). M.p. 210 – 212°C.

^{1}H NMR (δ, $CDCl_3$): 7.91 (dd, J = 6.3, 3.1 Hz, 1H, H^2), 7.44 (dd, J = 6.3, 3.1 Hz, 1H, H^4), 6.18 (brs,

1H, NH), 3.20 (s, 2H, CH_2O), 2.01 – 1.95 (m, 3H), 1.75 – 1.49 (m, 12H).

^{13}C NMR (δ, $CDCl_3$): 165.8 (CO_2), 133.7 (C^5), 125.9 (C^2), 114.9 (C^4), 73.7 (CH_2O), 39.0, 37.1, 34.4, 28.1.

^{1}H NMR (δ, DMSO-d_6): 7.82 (s, 1H, H^2), 7.79 (s, 1H, H^4), 3.78 (s, 2H, CH_2O), 1.96 – 1.90 (m, 3H), 1.70 – 1.58 (m, 6H), 1.54 (d, J = 2.9 Hz, 6H).

^{13}C NMR (δ, DMSO-d_6): 161.7 (COO), 137.5 (C^5), 126.1 (C^2), 107.0 (C^4), 72.6 (CH_2O), 38.7, 36.4, 33.0, 27.4.

MS (ESI), m/z: 261.2 $[M+H]^+$. Calculated for $C_{15}H_{21}N_2O_2$: 261.3

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.15, H, 7.72, N, 10.62.

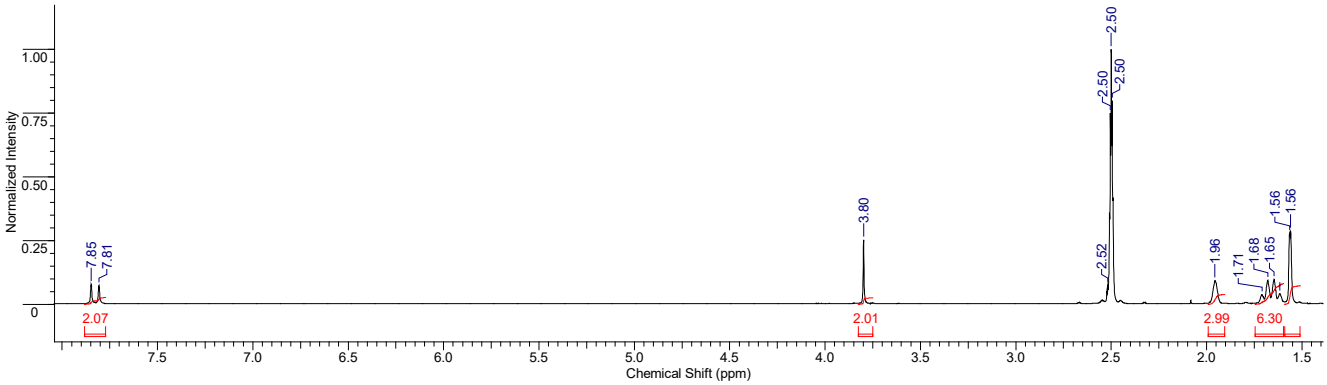


Figure S26 ^{1}H NMR spectrum of compound **13c** in DMSO-d_6.

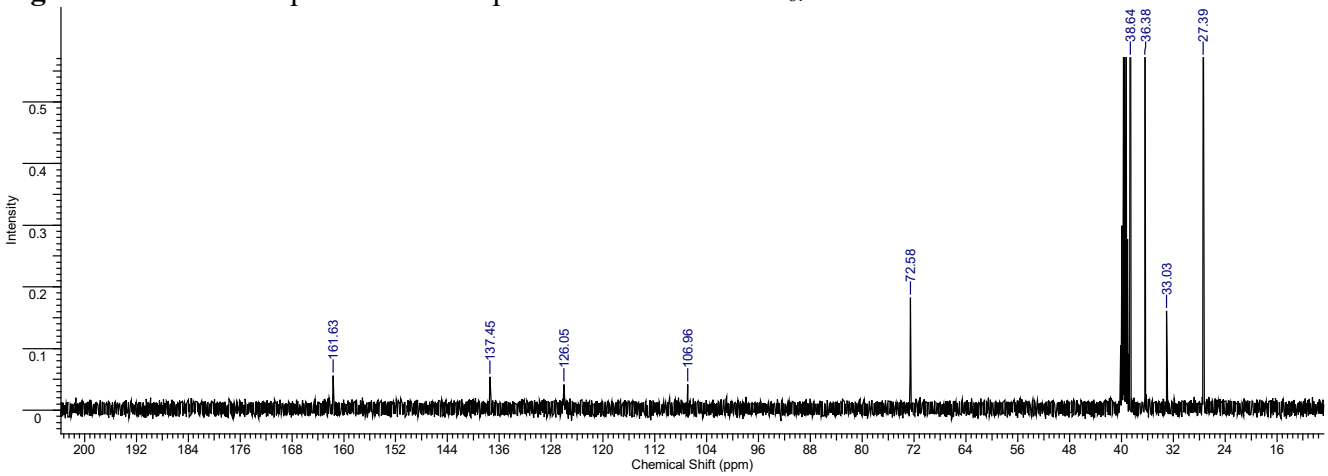
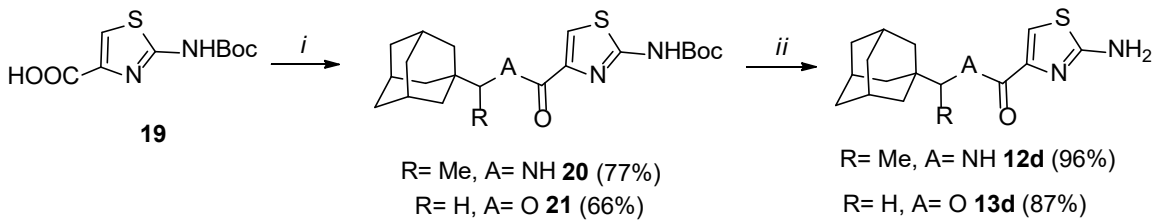


Figure S27 ^{13}C NMR spectrum of compound **13c** in DMSO-d_6.



Scheme S5 *Reagents and conditions. i*, rimantadine, EDCI, DIPEA, DMAP (cat.) (for **20**) or 1-adanatylmethanol, DCC, DMAP (for **21**), CH_2Cl_2, 20°C, 16 h; *ii*, 1) TFA, CH_2Cl_2, 20°C, 16 h, 2) aq $NaHCO_3$.

2-(*tert*-Butoxycarbonylamino)thiazole-4-carboxylic acid (19) was obtained in three steps from thiourea and methyl ester of 2-oxopropanoic acid as described in Ref.[S10]

***tert*-Butyl (4-{*N*-[1-(1-adamantyl)ethyl]carbamoyl}thiazol-2-yl)carbamate (20)** was obtained using a procedure similar to the one for compound (**18**) from acid **19** (0.100 g, 0.410 mmol), rimantadine (**2**) (0.089 g, 0.496 mmol), EDCI (0.117 g, 0.615 mmol), DIPEA (0.072 ml, 0.615 mmol) and DMAP (0.005 g). Eluent for column chromatography: ethyl acetate – petroleum ether 40–70ºC, 1:5. Yield of **20** 0.140 g (77%), ivory amorphous solid, m.p. 215 – 216°C.

^{1}H NMR (δ, $CDCl_3$): 7.98 (s, 1H, NH-Boc), 7.68 (s, 1H, H^5), 7.04 (d J = 10.1 Hz, 1H, NH), 3.83 (dq, J = 10.1, 6.8 Hz, 1H, CH), 2.02 – 1.96 (m, 3H), 1.74 – 1.53 (m, 21H, Ad +3Me^{Boc}), 1.10 (d, J = 6.9 Hz, 3H, Me).

^{13}C NMR (δ, $CDCl_3$): 160.5 (C^2), 158.5 (CONH), 151.8 (C^4), 145.1 (CO_2N), 117.0 (C^5), 84.4 (Me_3C-O), 52.9 (CHN), 38.4, 37.0, 36.0, 28.3, 28.1 (Me^{Boc}), 14.5 (Me).

MS (ESI), m/z: 406.5 $[M+H]^+$. Calculated for $C_{21}H_{32}N_3O_3S$: 406.6.

Anal. Calcd for $C_{21}H_{31}N_3O_3S$: C, 62.19; H, 7.70; N, 10.36. Found: C, 62.10, H, 7.65, N, 10.38.

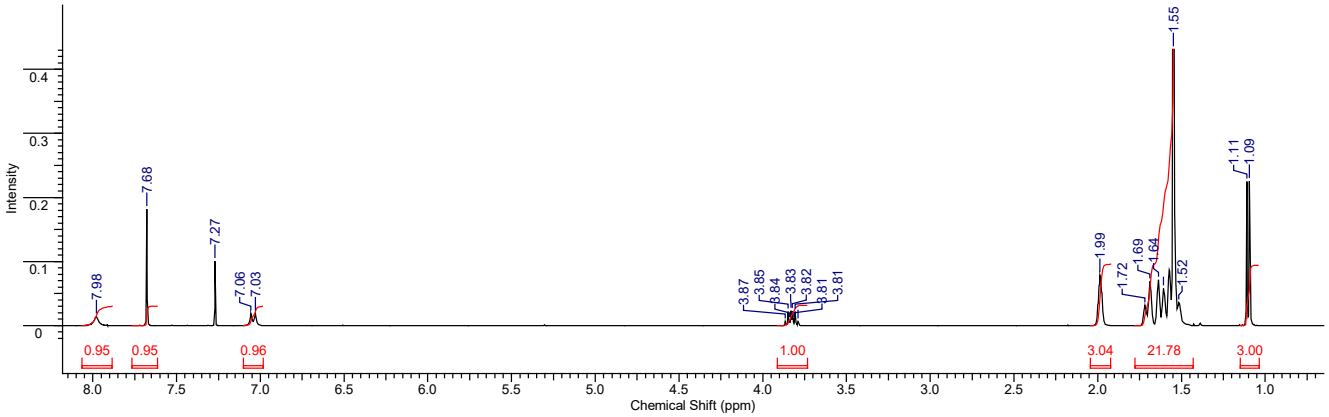


Figure S28 ^{1}H NMR spectrum of compound **20**.

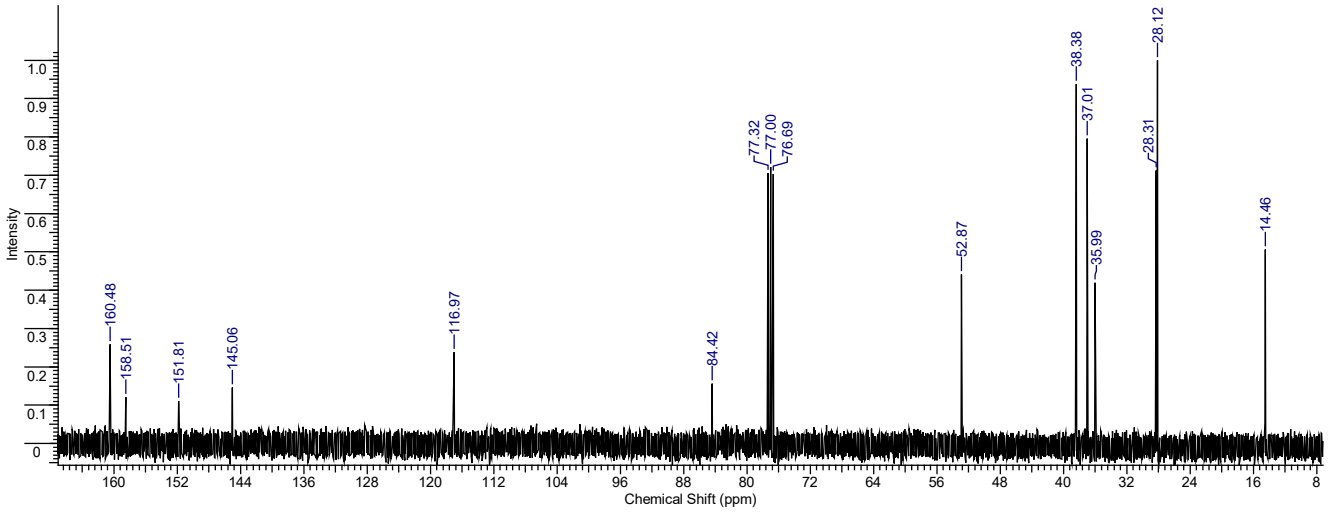


Figure S29 ^{13}C NMR spectrum of compound **20**.

***N*-[1-(1-Adamantyl)ethyl]-2-aminothiazole-4-carboxamide (12d).** Compound **20** (0.110 g 0.272 mmol) was dissolved in a mixture of trifluoroacetic acid and dichloromethane (1:4, 10 ml), stirred at room temperature 16 h, then concentrated under reduced pressure. The residue was redissolved in dichloromethane (30 ml), washed with saturated aqueous solution of $NaHCO_3$ (5 ml), dried over Na_2SO_4, concentrated under reduced pressure and chromatographed (eluent: dichloromethane, then 1% methanol in dichloromethane) to afford **12d** as white solid (0.079 g, yield 96%). M.p. 120 – 122°C.

^{1}H NMR (δ, $CDCl_3$): 7.31 (s, 1H, H^5), 7.07 (d, J = 10.1 Hz, 1H, NH), 5.44 (s, 2H, NH_2), 3.80 (dq, J = 10.0, 6.9 Hz, 1H, CH), 2.00 – 1.94 (m, 3H), 1.72 – 1.50 (m, 12H), 1.09 (d, J = 6.9 Hz, 3H, Me).

^{13}C NMR (δ, $CDCl_3$): 167.0 (C^2), 160.6 (CONH), 145.6 (C^4), 113.3 (C^5), 53.0 (CH), 38.3, 37.0, 36.0, 28.3, 14.5 (Me).

MS (ESI), m/z: 306.4 $[M+H]^+$. Calculated for $C_{16}H_{24}N_3OS$: 306.4.

IR (thin film, cm^{-1}): 3383 (N-C), 3298 (amide N–H), 3188 (N-H), 2902 (C-H), 2847 (C-H), 1650 (C=O), 1548, 1495 (C=C), 1450.

Anal. Calcd for $C_{16}H_{23}N_3OS$: C, 62.92; H, 7.59; N, 13.76. Found: C, 62.98, H, 7.60, N, 13.63.

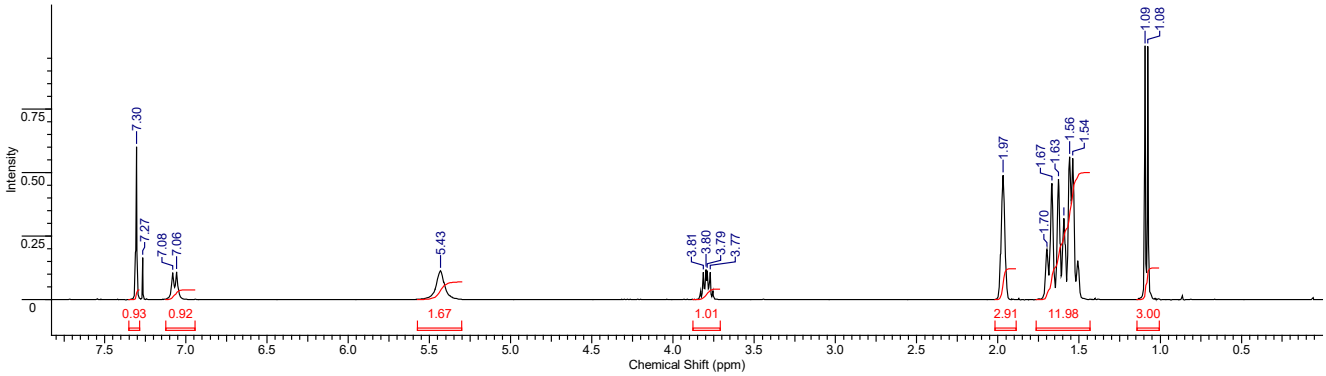


Figure S30 ^{1}H NMR spectrum of compound **12d**.

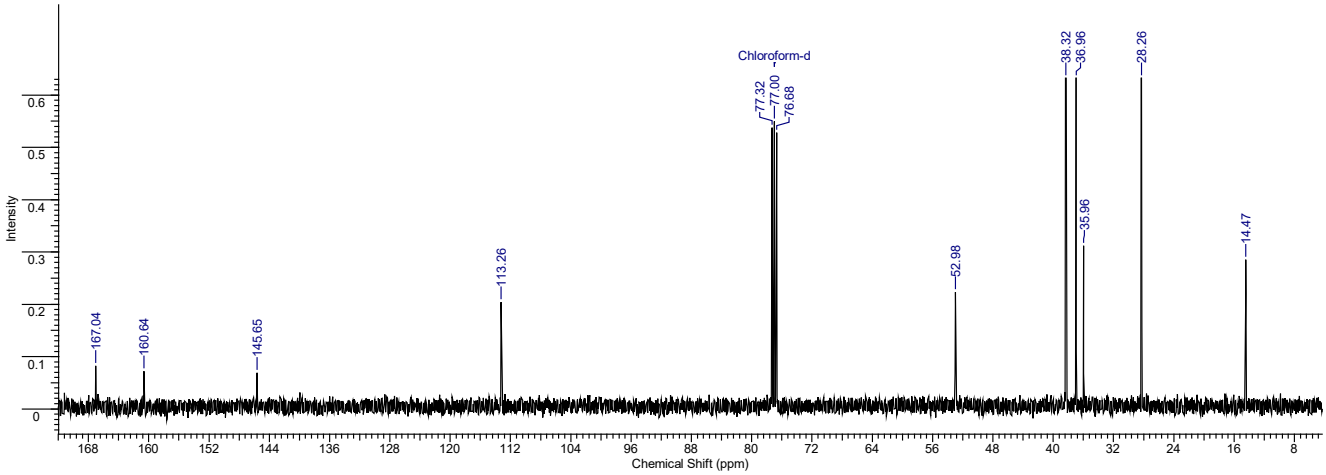


Figure S31 ^{13}C NMR spectrum of compound **12d**.

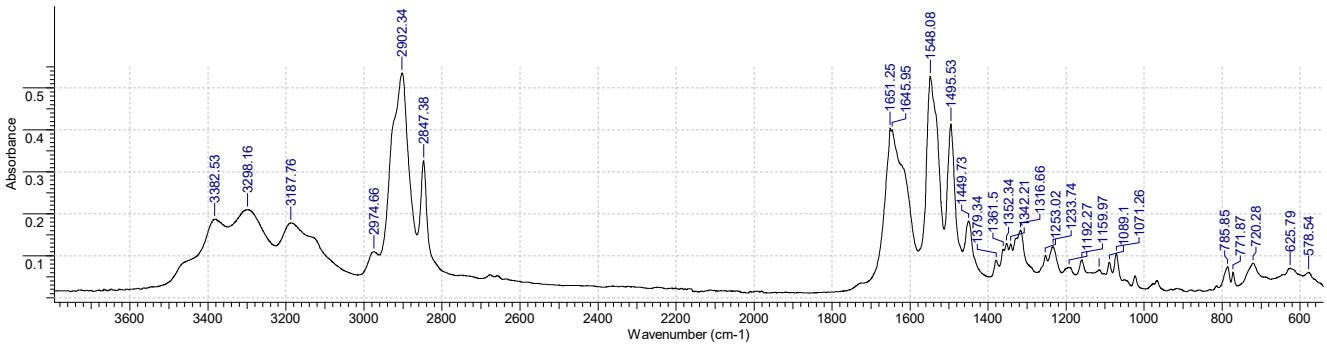


Figure S32 Infrared spectrum of compound **12d** (thin layer).

1-Adamantylmethyl 2-(*tert*-butoxycarbonylamino)thiazole-4-carboxylate (21) was obtained using a procedure similar to the one for compound **12a** without using DIPEA as a base from acid **19** (0.130 g, 0.533 mmol), 1-adamantylmethanol (0.089 g, 0.536 mmol), DCC (0.165 g, 0.8 mmol) and DMAP (0.006 g). Eluent for column chromatography: ethyl acetate – petroleum ether 40–70°C, 1:9. Yield of **21** 0.132 g (66%), white crystals, m.p. 54 – 55°C.

^{1}H NMR (δ, $CDCl_3$): 8.54 (s, 1H, NH), 7.75 (s, 1H, H^5), 3.92 (s, 2H, CH_2O), 2.03 – 1.97 (m, 3H), 1.75 –1.60 (m, 12H), 1.54 (s, 9H, $3Me^{Boc}$).

^{13}C NMR (δ, $CDCl_3$): 161.4 (C^2), 158.2 (COO), 155.6 (CO^tBu), 141.9 (C^4), 114.8 (C^5), 83.6 (CMe_3), 74.6 (CH_2O), 39.3, 36.9, 31.6, 28.0, 27.7 (Me_3).

MS (ESI), m/z: 293.4 $[M\text{-Boc}+H]^+$, 393.4 $[M+H]^+$. Calculated for $C_{20}H_{29}N_2O_4S$: 393.5

Anal. Calcd for $C_{20}H_{28}N_2O_4S$: C, 61.20; H, 7.19; N, 7.14. Found: C, 61.29, H, 7.26, N, 7.12.

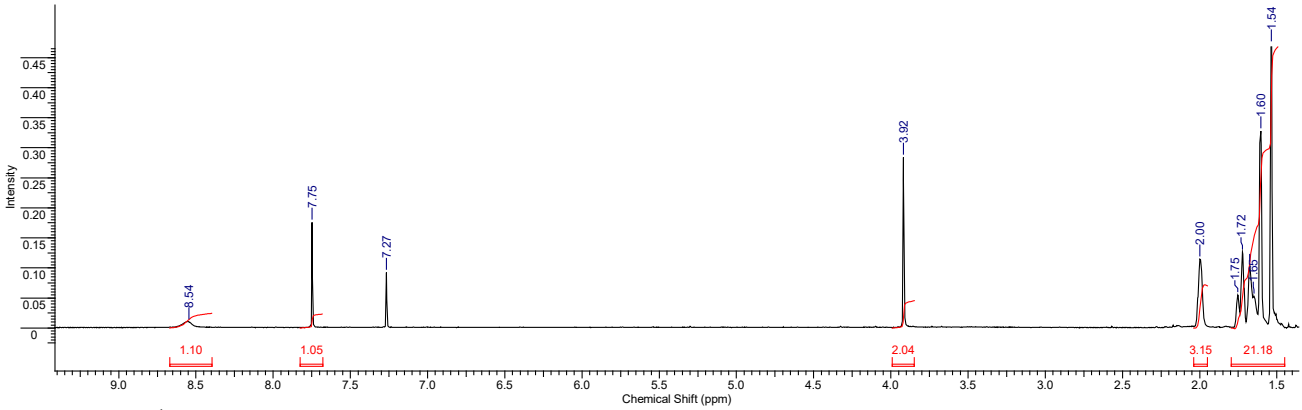


Figure S33 ^{1}H NMR spectrum of compound **21**.

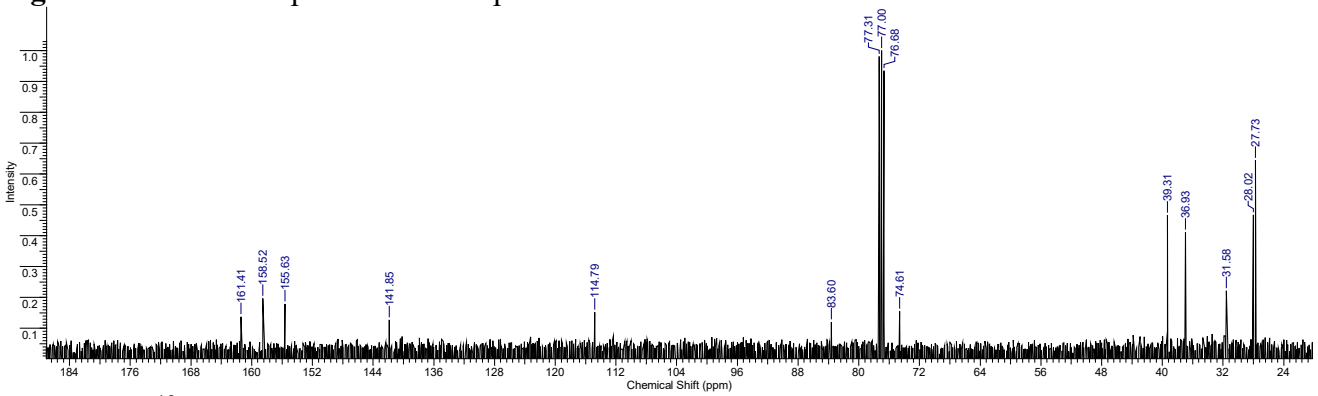


Figure S34 ^{13}C NMR spectrum of compound **21**.

1-Adamantylmethyl 2-aminothiazole-4-carboxylate (13d) was obtained using a procedure similar to the one for compound (**12a**) from ester **21** (0.119 g, 0.303 mmol). Eluent for column chromatography: ethyl acetate – petroleum ether 40–70ºC, 1:3. Yield of **13d** 0.077 g (87%), white crystals, m.p. 196 – 197°C.

^{1}H NMR (δ, $CDCl_3$): 7.38 (s, 1H, H^5), 5.76 (s, 2H, NH_2), 3.90 (s, 2H, CH_2O), 2.03 – 1.97 (m, 3H), 1.78 – 1.58 (m, 12H).

^{13}C NMR (δ, $CDCl_3$): 168.3 (C^2), 161.4 (COO), 142.7 (C^4), 116.9 (C^5), 74.3 (CH_2O), 39.3, 36.9, 33.5, 28.0.

MS (ESI), m/z: 294.4 $[M+2H]^+$. Calculated for $C_{15}H_{22}N_2O_2S$: 294.4

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.61; H, 6.89; N, 9.58. Found: C, 61.60, H, 6.88, N, 9.62.

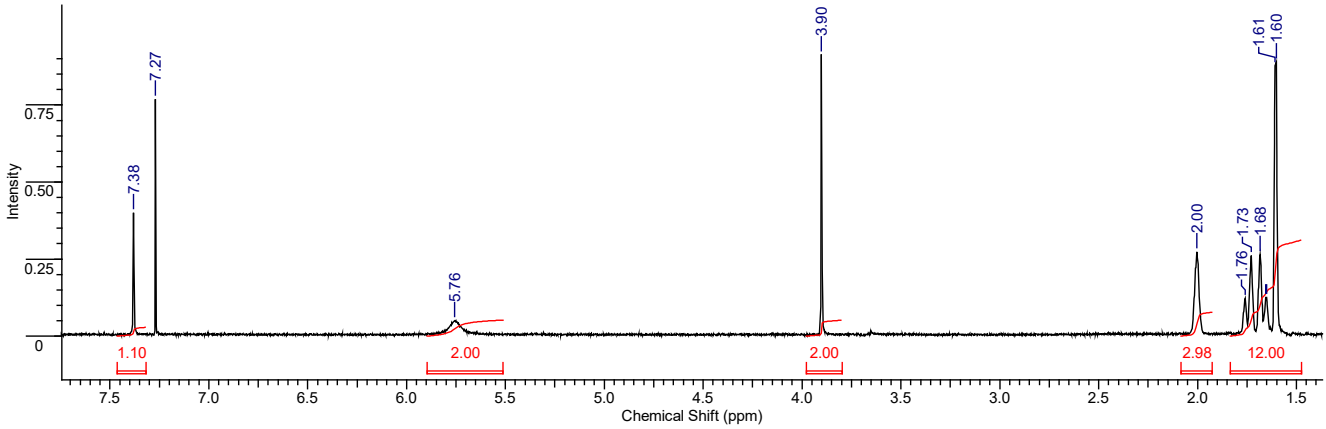


Figure S35 ^{1}H NMR spectrum of compound **13d**.

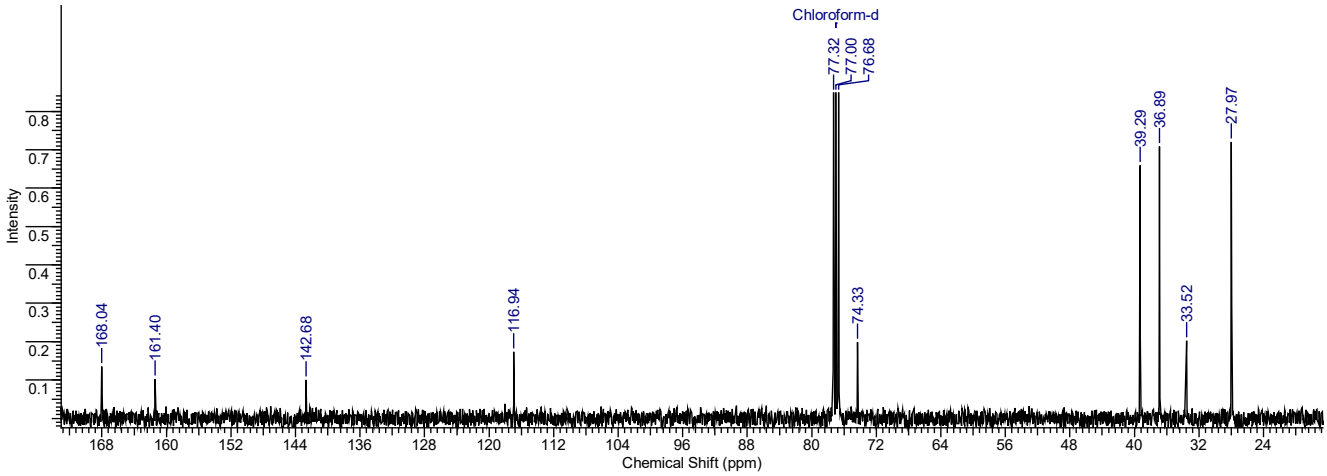


Figure S36 ^{13}C NMR spectrum of compound **13d**.

3. Biological Assays

Virus and cells

Influenza virus A/Puerto Rico/8/34 (H1N1) was obtained from the collection of viruses of the Saint Petersburg Pasteur Research Institute of Epidemiology and Microbiology. Before the experiment, viruses were propagated in Madin-Darby canine kidney (MDCK) cells (ATCC-CCL-34) for 48 h at 36°C. The infectious titers of the virus were determined in MDCK cells grown in 96-well plates in alpha-MEM serum-free medium.

Cytotoxicity Assay

MDCK cells were seeded onto 96-well culture plates (10^4 cells per well) and incubated at 36°C in 5% CO_2 until a continuous monolayer formation. To assess the toxicity of compounds, a series of their 3-fold dilutions at concentrations of 300 to 3.7 μg/mL in Eagle's Minimal Essential Medium (MEM) were prepared. The dilutions were added to the wells of the plates. Cells were incubated for 72 h at 36°C in a CO_2 incubator under 5% CO_2. Further, a microtetrazolium [MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay was performed on 96-well plates. The cells were washed 2 times with saline (0.9% NaCl), and 100 μL/well of MTT solution at a concentration of 0.5 g/mL in MEM was added. The plates were incubated for 1 h at 36°C, the liquid was removed, and DMSO (0.1 mL per well) was added. The optical density (OD) in wells was measured on a Thermo Multiskan FC spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) at a wavelength of 540 nm. For each specimen the half-maximal cytotoxic concentration CC_{50}, i.e., the concentration of the compound that destroys 50% of the cells in the culture, was calculated.

CPE Reduction Assay

The compounds in appropriate concentrations were added to MDCK cells (0.1 mL per well). MDCK cells were further infected with influenza virus (m.o.i 0.01). Plates were incubated for 72 h at 36°C at 5% CO_2. Then the cell viability was assessed by the MTT test as described above. The cytoprotective activity of compounds was considered as their ability to increase the values of the OD compared to the control wells (virus only; no compounds). The half-maximal inhibitory concentration IC_{50} values, i.e., the concentration of a compound that results in 50% cell protection, was calculated for each compound using GraphPad Prism 6.01 software. IC_{50} values in μg/mL were then calculated into μmol/L. For each compound, the value of the selectivity index (SI) was calculated as a ratio of CC_{50} to IC_{50}.

The results are presented in Tables 1 and 2 of the main text. For clarity of the SAR analysis, Tables S1 and S2 with the structures of the substances are herein presented. The mean values of IC_{50} and CC_{50} are given in the tables, standard deviation (SD) did not exceed 10% in each case (for SD values see Tables 1 and 2).

Table S1

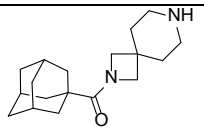
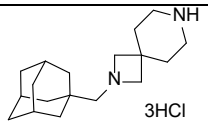
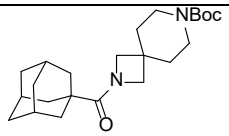
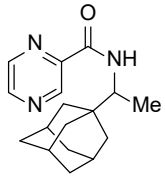
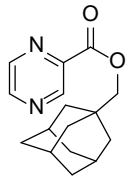
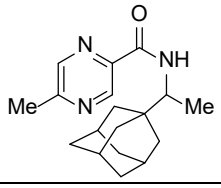
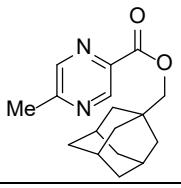
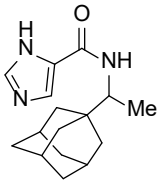
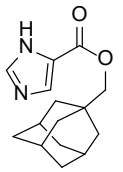
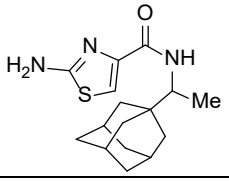
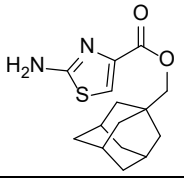
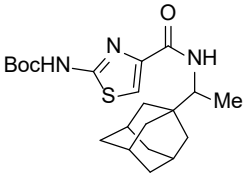
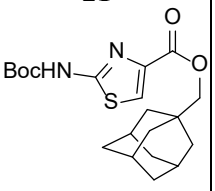
Cpd	Structure	Influenza virus H1N1, IC_{50}, μM	MDCK, CC_{50}, μM	SI
9a		12.8	16.6	1
9b (3HCl)		4.4	4.6	1
18		84.9	150	2
2	Rimantadine	67	400	6

Table S2

Compound	Influenza virus H1N1, IC_{50}, μM	MDCK CC_{50}, μM	SI		Influenza virus H1N1, IC_{50}, μM	MDCK CC_{50}, μM	SI
12a 	38.5	110	3	**13a** 	>400	>400	-
12b 	36.7	73.5	2	**13b** 	12.6	105	8
12c 	>400	>400	-	**13c** 	46.5	400	8
12d 	36.0	64.8	2	**13d** 	3.4	15.7	5
20 	81.4	210	3	**21** 	1.5	8.5	6
10a[S6]	13	83	6	**10c**[S6]	7.7	>1000	>130
10b[S6]	100	>1000	>10	**2**	67	400	6

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