Electronic supplementary information

for the article:

Synthesis of HIV-1 capsid protein assembly inhibitor (CAP-1) and its analogues based on biomass approach

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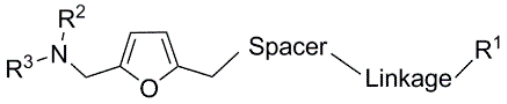
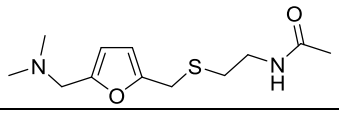
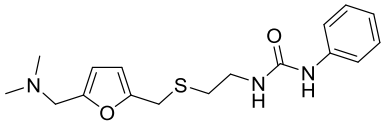
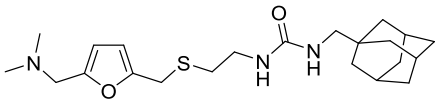
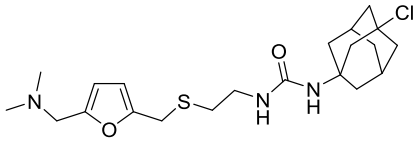
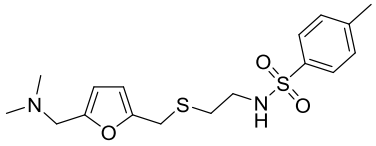
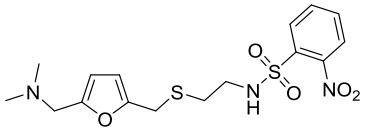
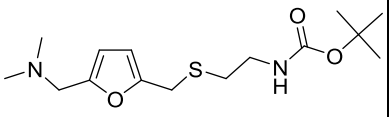
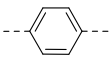
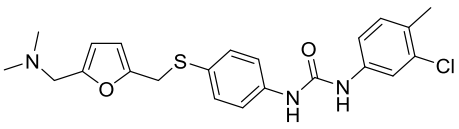
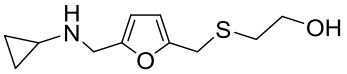
General information

All reactions were performed in oven-dried (150 °C) glassware under an argon atmosphere unless otherwise noted. Chromatographic separations were performed on silica gel (Merck Kieselgel 230–400 mesh) with analytical grade solvents. Analytical TLC was per formed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV light and/or p-anisaldehyde–MeOH–H_2SO_4 and/or basic solution of $KMnO_4$. NMR spectra were recorded on NMR spectrometers Bruker DRX500 and Bruker Avance 400 with residual solvent peak as an internal standard. Elemental analyses were performed by the analytical center of N.D. Zelinsky Institute of Organic Chemistry. Mass spectra were measured on high-resolution time-of-flight Bruker maXis instrument using electrospray ionization (ESI-MS). Measurements were performed in positive ion mode, interface capillary voltage at 4.5 kV, effective scan range at m/z 100 – 1200, external calibration (0.016 M sodium formate in MeCN-water 1:1 mixture or ESI-L Low Concentration Tuning Mix, Agilent Technologies), direct syringe injection at flow rate of 3 μL/min, nitrogen as dry gas at 4 L/min, interface temperature at 180°C. The spectra were processed using Bruker Data Analysis 4.0 software package.

All reagents from commercial sources were used as received. Petroleum ether, EtOAc, EtOH were distilled without drying agents. The following solvents were distilled from the indicated drying agents: CH_2Cl_2, DCE (CaH_2), $CHCl_3$ (P_2O_5), benzene, Et_2O (Na), toluene, THF (Na/benzophenone ketyl), MeOH (Mg).

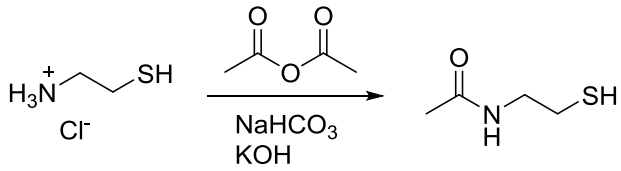
Compounds numbering



Entry	*Number*	*R^1*	*R^2*	*R^3*	*Linkage*	*Spacer*	*Yield, %*	*Stucture*
1	**2**	Me	Me	Me	amide	-SCH_2CH_2-	79	
2	**5a**	Ph	Me	Me	urea	-SCH_2CH_2-	70	
3	**5b**	1-adamantan-methyl[17]	Me	Me	urea	-SCH_2CH_2-	72	
4	**5c**	1-chloro-3-adamantyl	Me	Me	urea	-SCH_2CH_2-	66	
5	**6a**	*p*-tolyl	Me	Me	sulfonamide	-SCH_2CH_2-	75	
6	**6b**	2-nitrophenyl	Me	Me	sulfonamide	-SCH_2CH_2-	65	
7	**7**	*t*-Bu	Me	Me	carbamate	-SCH_2CH_2-	73	
8	**11**	4-methyl-3-chlorophenyl	Me	Me	urea		46	
9	**13**	H	H	cyclopropyl	alcohol	-SCH_2CH_2-	55	

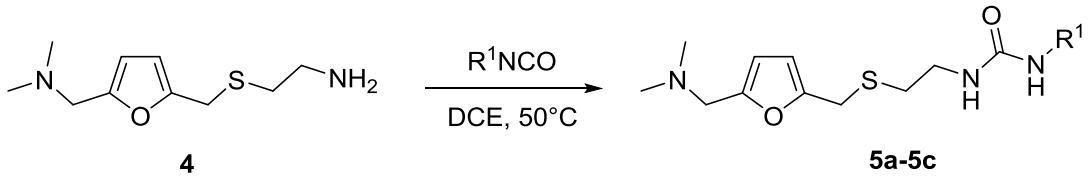
Experimental procedures

Synthesis of N-acetylcysteamine



A 100 ml round bottom flask was loaded with KOH (0.56 g, 10 mmol), $NaHCO_3$ (2.52 g, 30 mmol), cysteamine hydrochloride (1.14 g, 10 mmol), and degassed water (50 mL). Acetic anhydride (0.95 mL, 10 mmol) was added dropwise to the mixture under stirring. The reaction mixture was stirred at room temperature for 2.5 hours. The mixture was neutralized by conc. HCl to pH ~ 4-5, and then was extracted with ethyl acetate (3 x 50 mL). Organic layer was separated, dried over anhydrous $MgSO_4$. Solvent was removed under reduced pressure and the product was dried *in vacuo* to give N-acetylcysteamine (110 mg, 92%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.24 (brs, 1H), 3.39 (q, 2H, J = 6.4 Hz), 2.64 (dt, 2H, J = 8.4, 6.4 Hz), 1.97 (s, 3H), 1.36 (t, 1H, J = 8.4 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ = 170.5, 42.6, 24.6, 23.3; Anal. Calcd. for C_4H_9NOS: C, 40.31; H, 7.61; N, 11.75; Found: C, 40.26; H, 7.69, N, 11.67.

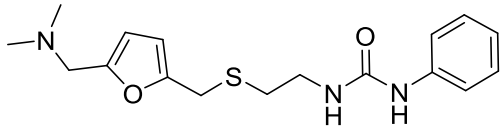
Synthesis of compounds 5a-5c



4 **5a-5c**

General procedure. Amine **4** (42.8 mg, 0.2 mmol) was dissolved in DCE (5 mL), and corresponding isocyanate (0.2 mmol, 1.0 eq.) was added. Mixture was stirred at 50 °C for 5 hours, then solvent was removed under reduced pressure and residue was purified by column chromatography (eluent $CHCl_3$:MeOH = 8:1 (v/v)) and dried *in vacuo* to give ureas **5a-5c**.

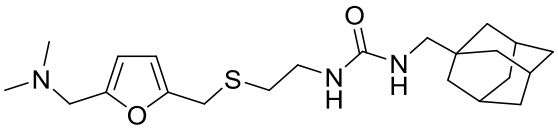
1-(2-(((5-((Dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)-3-phenylurea (5a).



Yield 91%. ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 8.55 (s, 1H), 7.38 (d, 2H, J = 7.7 Hz), 7.21 (t, 2H, J = 7.4 Hz), 6.88 (t, 1H, J = 7.4 Hz), 6.27 (t, 1H, J = 5.8 Hz), 6.17 (d, 1H, J = 3.0 Hz), 6.11 (d, 1H, J = 3.0 Hz), 3.78 (s, 2H), 3.36 (s, 2H), 3.25 (q, 2H, J = 6.6 Hz), 2.56 (t, 2H, 6.6

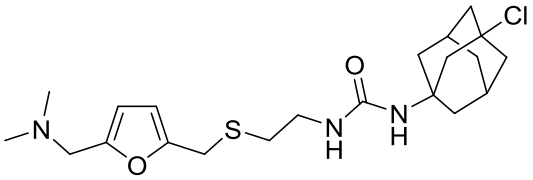
Hz), 2.12 (s, 6H). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6, 126 MHz) δ = 155.0, 151.8, 150.7, 140.5, 128.6, 121.0, 117.6, 109.2, 108.2, 55.1, 44.5, 38.5, 31.3, 27.1. Anal. Calcd. for $C_{17}H_{23}N_3O_2S$: C, 61.23; H, 6.95; N, 12.60; Found: C, 61.01; H, 6.99, N, 12.74. HRMS (ESI): calcd. $[M+H]^+$ 334.1584, Found: 334.1576.

1-((Adamantan-1-yl)methyl)-3-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio) ethyl)urea (5b)



Yield 94%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 6.07 (d, 1H, *J* = 3.0 Hz), 6.06 (d, 1H, *J* = 3.0 Hz), 5.56 (brs, 1H), 5.23 (brs, 1H), 3.66 (s, 2H), 3.37 (s, 2H), 3.28 (dd, 2H, *J* = 6.3, 6.0 Hz), 2.79 (d, 2H, *J* = 6.0 Hz), 2.59 (t, 2H, *J* = 6.3 Hz), 2.20 (s, 6H), 1.90 (brs, 3H), 1.65 (brd, 3H), 1.56 (brd, 3H), 1.42 (brs, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz) δ =159.0, 151.7, 151.2, 109.6, 108.2, 55.9, 52.1, 45.0, 40.2, 39.4, 37.0, 33.9, 32.7, 28.3. HRMS (ESI): calcd. $[M+H]^+$ 406.2523, Found: 406.2515.

1-(-3-Chloroadamantan-1-yl)-3-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio) ethyl)urea (5c)



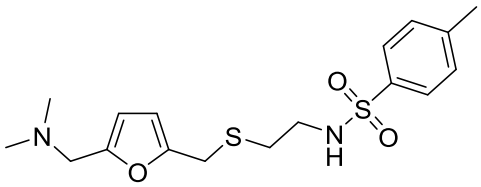
Yield 86%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 6.13 (d, 2H, *J* = 3.0 Hz), 6.11 (d, 2H, *J* = 3.0 Hz), 5.28 (brs, 1H), 4.77 (brs, 1H), 3.68 (s, 2H), 3.49 (s, 2H), 3.19 (t, 2H, *J* = 6.2 Hz), 2.61(t, 2H, *J* = 6.2 Hz), 2.34 (brs, 2H), 2.28 (s, 6H), 2.21 (brs, 2H), 2.10 (brs, 1H), 2.04 (brs, 4H), 1.95 (brd, 2H), 1.86 (brs, 2H), 1.83 (brs, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz) δ = 157.1, 151.8, 150.7, 110.5, 108.3, 67.6, 55.4, 53.5, 52.0, 47.0, 46.7, 44.5, 40.8, 38.8, 37.9, 34.6, 32.9, 31.8, 31.5, 28.4. HRMS (ESI): calcd. $[M+H]^+$ 426.1977, Found: 426.1962.

Synthesis of compounds 6a, 6b

4 **6a, 6b**

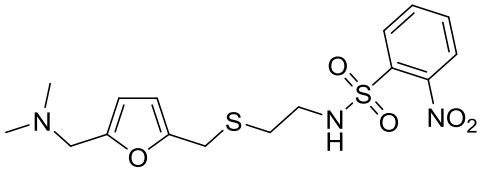
General procedure. Amine **4** (42.8 mg, 0.2 mmol) and triethylamine (62 μL, 0.44 mmol) were dissolved in DCE (3 mL). Then, solution of corresponding sulfonylchloride (0.2 mmol) in DCE (2 mL) was added. Mixture was stirred at room temperature for 3 hours, then mixture was diluted with DCM (20 mL). Organic phase was subsequently washed with water (2 x 15 mL), saturated aqueous $NaHCO_3$ (1 x 15 mL), and saturated aqueous NaCl (1 x 15). Organic phase was dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure. Residue was purified by column chromatography (eluent $CHCl_3$:MeOH = 7:1 (v/v)) and dried *in vacuo* to give sulfonamides **6a, 6b**.

N-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)-4-methylbenzene-sulfonamide (6a)



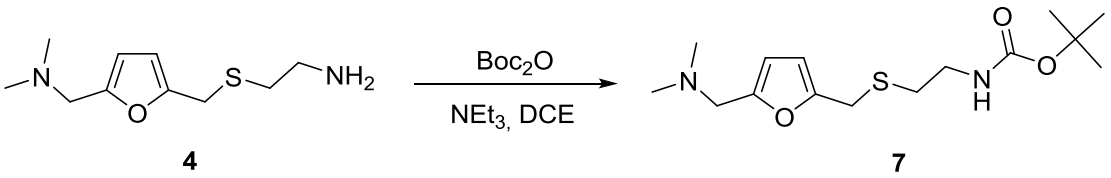
Yield 98%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.63 (d, 2H, J = 8.2 Hz), 7.19 (d, 2H, J = 8.2 Hz), 6.20-6.70 (brs, 1H), 6.01 (d, 1H, J = 3.0 Hz), 5.98 (d, 1H, J = 3.0 Hz), 3.52 (s, 2H), 3.29 (s, 2H), 2.92 (t, 2H, J = 7.1 Hz), 2.41 (t, 2H, J = 7.1 Hz), 2.31 (s, 3H), 2.15 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ = 151.3, 143.2, 137.8, 129.7, 126.9, 110.0, 108.1, 70.5, 55.8, 44.8, 44.8, 42.1, 31.6, 27.5, 21.5. HRMS (ESI): calcd. $[M+H]^+$ 369.1301, Found: 369.1289.

N-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)-2-nitrobenzene sulfonamide (6b).



Yield 85%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.07 (m, 1H), 7.79 (m, 1H), 7.70 (m, 2H), 6.08 (m, 2H), 3.61 (s, 2H), 3.87 (s, 2H), 3.14 (t, 2H, J = 7.1 Hz), 2.58 (t, 2H, J = 7.1 Hz), 2.21 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ = 151.8, 151.0, 148.0, 134.1, 133.6, 132.7, 130.7, 125.2, 109.8, 108.2, 55.8, 44.9, 42.7, 31.5, 27.8. HRMS (ESI): calcd. $[M+H]^+$ 400.0995, Found: 400.0983.

Synthesis of compound 7.

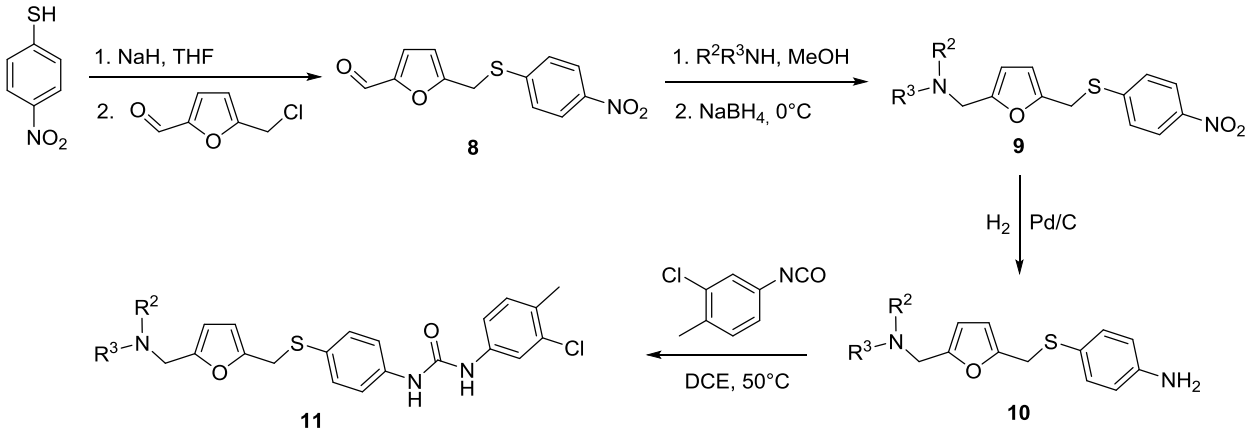


4 **7**

Amine **4** (94.3 mg, 0.44 mmol) and triethylamine (20 μL, 0.14 mmol) were dissolved in DCM (5 mL). Then, solution of Boc_2O (96 mg, 0.44 mmol) in DCM (2 mL) was added. Mixture was stirred at room temperature for 5 hours, then mixture was diluted with DCM (50 mL). Organic phase was subsequently washed with water (2 x 20 mL) and saturated aqueous NaCl (2 x 20). Organic phase was dried over anhydrous $MgSO_4$, and solvent was removed under reduced pressure. Residue was purified by column chromatography (eluent $CHCl_3$:MeOH = 10:1 (v/v)) and dried *in vacuo* to give *tert*-butyl (2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)carbamate **7** (131 mg, 95%) as colorless oil.

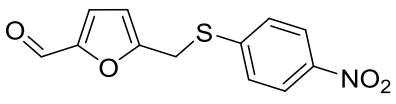
^{1}H NMR ($CDCl_3$, 500 MHz) δ = 6.07 (m, 2H), 5.39 (brs, 1H), 3.66 (s, 2H), 3.36 (s, 2H), 3.17 (m, 2H), 2.56 (t, 2H, J = 6.7 Hz), 2.20 (s, 6H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ = 155.9, 151.9, 151.2, 109.5, 108.0, 79.2, 55.9, 44.9, 39.5, 31.9, 28.5, 27.9. Anal. Calcd for $C_{15}H_{26}N_2O_3S$: C, 57.30; H, 8.33; N, 8.91; Found: C, 57.20; H, 8.41; N, 8.89.

Synthesis of compound 11



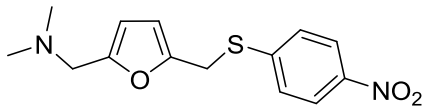
8 **9** **10** **11**

5-(((4-Nitrophenyl)thio)methyl)furan-2-carbaldehyde (8)



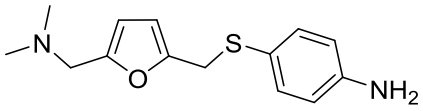
Under argon atmosphere sodium hydride (88 mg, 2.2 mmol, 60% dispersion in mineral oil) was added portionwise to a stirred solution of 4-nitrothiophenol (310 mg, 2 mmol) in absolute THF (15 mL). Mixture was stirred at room temperature for 30 minutes. Then solution of 5-(chloromethyl)furfural (289 mg, 2 mmol) in absolute THF (5 mL) was added dropwise. Mixture was stirred overnight at room temperature. Then mixture was filtered through 5 mm pad of Celite® and evaporated to dryness. Residue was dissolved in CH_2Cl_2 (100 mL). Obtained solution was washed with saturated aqueous NaCl (2 x 50 mL), dried over anhydrous sodium sulfate. Charcoal (80 mg) was added; the mixture was stirred for 20 minutes and filtered through 15 mm Celite® pad. The solvent was removed under reduced pressure to give the product (379 mg, 72%) as yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 9.58 (s, 1H), 8.14 (d, 2H, *J* = 8.8 Hz), 7.39 (d, 2H, *J* = 8.8 Hz), 7.16 (d, 1H, *J* = 3.6 Hz), 6.46 (d, 1H, *J* = 3.6 Hz), 4.29 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) *δ* = 177.3, 156.6, 152.6, 145.9, 144.9, 127.6, 124.5, 124.1, 111.3, 29.5. Anal. Calcd. for $C_{12}H_9NO_4S$: C, 54.75; H, 3.45; N, 5.32; Found: C, 54.47; H, 3.47; N, 5.26. HRMS (ESI): calcd. 286.0144 $[M+Na]^+$, Found: 286.0145.

N,N-dimethyl-1-(5-(((4-nitrophenyl)thio)methyl)furan-2-yl)methanamine (9)



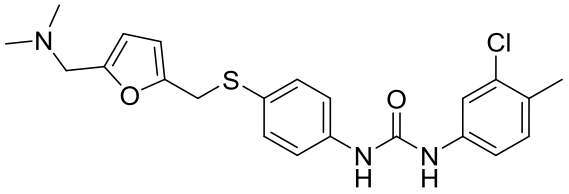
The liquid dimethylamine (0.4 mL, prepared from dimethylamine hydrochloride and solid NaOH) was added to the solution of 5-(((4-nitrophenyl)thio)methyl)furan-2-carbaldehyde (100 mg, 0.380 mmol) in 9 mL of absolute methanol and the resulting mixture was stirred at room temperature for 40 minutes. Reaction mixture was cooled to 0 °C and sodium borohydride (26.3 mg, 0.692 mmol) was added portionwise. The mixture was stirred at 0°C for 20 minutes and then warmed up to room temperature. The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2, filtered from inorganic impurities, and evaporated to dryness to give the product (110 mg, 99%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.11 (d, 2H, *J* = 9.1 Hz), 7.38 (d, 2H, *J* = 9.1 Hz), 6.16 (d, 1H, *J* = 2.9 Hz), 6.11 (d, 1H, *J* = 2.9 Hz), 4.22 (s, 2H), 3.41 (s, 2H), 2.24 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) *δ* = 152.8, 149.1, 146.5, 145.6, 127.3, 124.0, 109.7, 109.2, 56.0, 45.2, 29.8. Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; Found: C, 57.41; H, 5.47; N, 9.55. HRMS (ESI): calcd. 293.0954 $[M+H]^+$, Found: 293.0957.

4-(((5-((Dimethylamino)methyl)furan-2-yl)methyl)thio)aniline (10)



Into a 10 ml Schlenk tube containing solution of N,N-dimethyl-1-(5-(((4-nitrophenyl)thio) methyl)furan-2-yl)methanamine (70 mg, 0.240 mmol) in dry methanol (4 mL) 10% Pd on activated carbon (12.8 mg, 5 mol. %) was added. Reaction vessel was flushed with hydrogen and then connected to a balloon with hydrogen. Reaction mixture was stirred for 6 hours under hydrogen atmosphere at room temperature and then filtered through 10 mm pad of Celite®. Solvent was removed under reduced pressure and the residue was dried *in vacuo* to give 4-(((5-((dimethylamino) methyl)furan-2-yl)methyl)thio)aniline (61 mg, 97%) as an orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.13 (d, 2H, *J* = 8.5 Hz), 6.53 (d, 2H, *J* = 8.5 Hz), 6.02 (d, 1H, *J* = 2.7 Hz), 5.88 (d, 1H, *J* = 2.7 Hz), 3.88 (s, 2H), 3.70 – 3.80 (brs, 2H), 3.39 (s, 2H), 2.22 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) *δ* = 151.8, 151.2, 146.6, 135.2, 122.3, 115.4, 109.3, 108.3, 55.9, 45.0, 34.2. HRMS (ESI): calcd. $[M+H]^+$ 263.1213, Found: 263.1211.

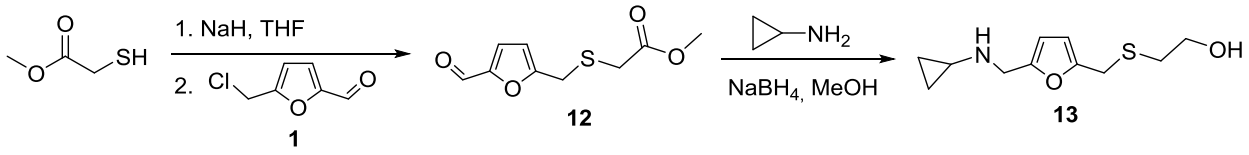
1-(3-Chloro-4-methylphenyl)-3-(4-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)phenyl)urea (11)



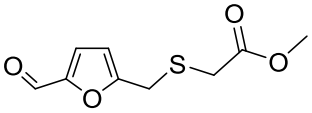
Into a flask containing 4-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)aniline (66 mg, 0.226 mmol) solution of 3-chloro-4-methylphenylisocyanate (38 mg, 0.226 mmol) in DCE (4 mL) was added. Mixture was heated at 50 °C overnight. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (eluent Et_2O:EtOH = 6:1 (v/v)) and dried *in vacuo* to obtain the product (67 mg, 72%) as a yellowish oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.81 (br, 2H), 7.69 (d, 1H, *J* = 1.9 Hz), 7.40 (d, 2H, *J* = 8.6 Hz), 7.27 (d, 2H, *J* = 8.6 Hz), 7.22 (d, 1H, *J* = 8.3 Hz), 7.18 (dd, 1H, J = 8.3, 1.9 Hz), 6.11 (d, 1H, *J* = 2.9 Hz), 6.06 (d, 1H, *J* = 2.9 Hz), 4.10 (s, 2H), 3.35 (s, 2H), 2.25 (s, 3H), 2.12 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) *δ* = 152.3, 151.7, 150.2, 138.8, 138.7, 133.1, 131.8, 131.1, 128.3, 126.8, 118.7, 118.2, 117.0, 109.3, 108.5, 55.0, 44.4, 31.4, 18.8.

Anal. Calcd. for $C_{22}H_{24}ClN_3O_2S$: C, 61.46; H, 5.63; Cl, 8.24; N, 9.77; Found: C, 61.23; H, 5.61; Cl, 8.17; N, 9.65. HRMS (ESI): calcd. $[M+Na]^+$ 286.0144, Found: 286.0145.

Synthesis of compound 13

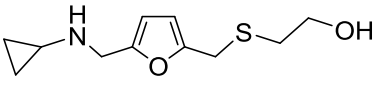


Methyl 2-(((5-formylfuran-2-yl)methyl)thio)acetate (12)



Sodium hydride (1.60 g, 40 mmol, 60% dispersion in mineral oil) was washed 3 times with dry THF (3 x 20 mL), then absolute THF (100 mL) was added. Methyl mercaptoacetate (3 mL, 33.55 mmol) was added dropwise and mixture was stirred at room temperature for 30 minutes. Then mixture was cooled to 0°C and solution of **1** (4.85 g, 33.55 mmol) in THF (10 mL) was added dropwise. Mixture was stirred at this temperature for 2 hours then warmed to room temperature and stirred for additional 3 hours. Obtained red-orange mixture was filtered through a 20 mm pad of Celite®, filtrate was dried under reduced pressure. Residue was dissolved in DCM (100 mL). Obtained solution was washed with saturated aqueous NaCl (2 x 50 mL), dried over anhydrous $MgSO_4$. Solvent was removed under reduced pressure. Residue was purified using column chromatography (eluent petroleum ether: ethyl acetate = 3:1 (v/v)) and dried *in vacuo* to give the product (6.19 g, 86%) as yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 9.58 (s, 1H), 7.18 (d, 1H, *J* = 3.3 Hz), 6.48 (d, 1H, *J* = 3.3 Hz), 3.91 (s, 2H), 3.73 (s, 3H), 3.23 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ = 177.5, 170.4, 157.9, 152.8, 122.3, 111.2, 52.7, 32.9, 28.6. HRMS (ESI): calcd. $[M+Na]^+$ 237.0192, Found: 237.0195.

2-(((5-((Cyclopropylamino)methyl)furan-2-yl)methyl)thio)ethan-1-ol (13)



Into solution of **12** (203 mg, 0.948 mmol) in methanol (5 mL) cyclopropylamine (78 μL, 1.137 mmol) was added and mixture was stirred at room temperature for 2 hours. Then mixture was cooled to 0 °C

and $NaBH_4$ (107 mg, 2.84 mmol) was added. Obtained mixture was stirred overnight at room temperature. Then solvent was removed under reduced pressure, and the residue was dissolved in DCM (20 mL), washed with water (1 x 15 mL), saturated aqueous NaCl (2 x 15 mL), and dried over Na_2SO_4. Solvent was removed under reduced pressure, and the residue was purified by column chromatography (eluent $CHCl_3$:MeOH = 10:1(v/v) and dried *in vacuo* to give a product (148.7 mg, 69%) as orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 6.06 (s, 2H), 3.74 (s, 2H), 3.66 (s, 2H), 3.58 (t, 2H, J = 6.3 Hz), 2.78 (brs, 2H), 2.83 (t, 2H, J = 6.3 Hz), 2.11 (m, 1H), 0.32-0.44 (m, 4H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ = 153.4, 150.8, 108.2, 108.0, 60.5, 45.9, 34.5, 29.8, 28.2, 6.1. HRMS (ESI): calcd. $[M+H]^+$ 228.1053, Found: 228.1062.

NMR spectra of synthesized compounds

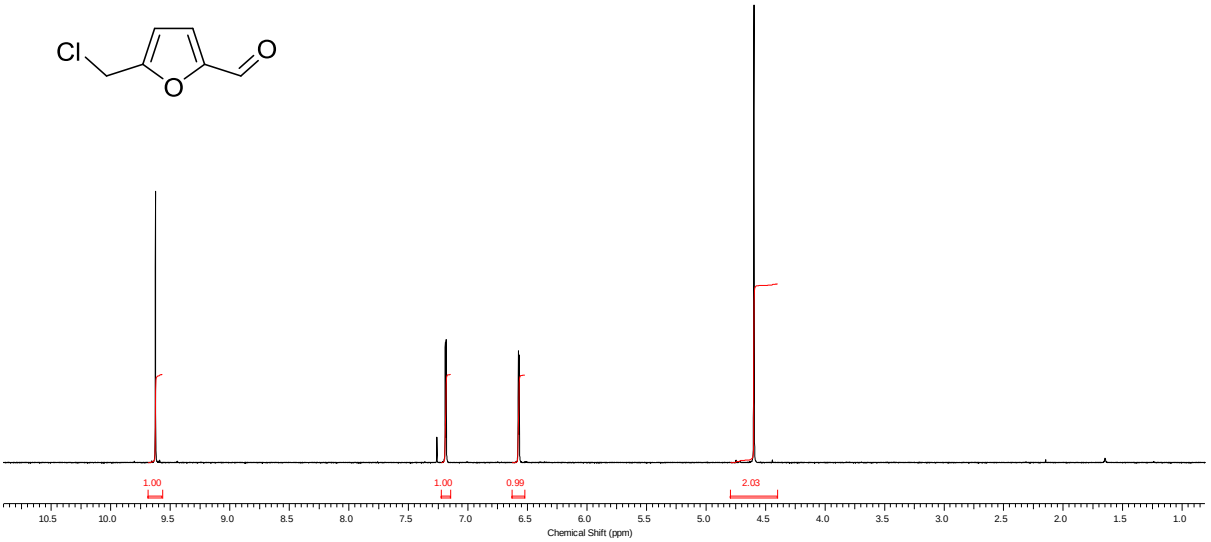


Figure S1. ^{1}H NMR spectrum of 5-(chloromethyl)furfural **1**.

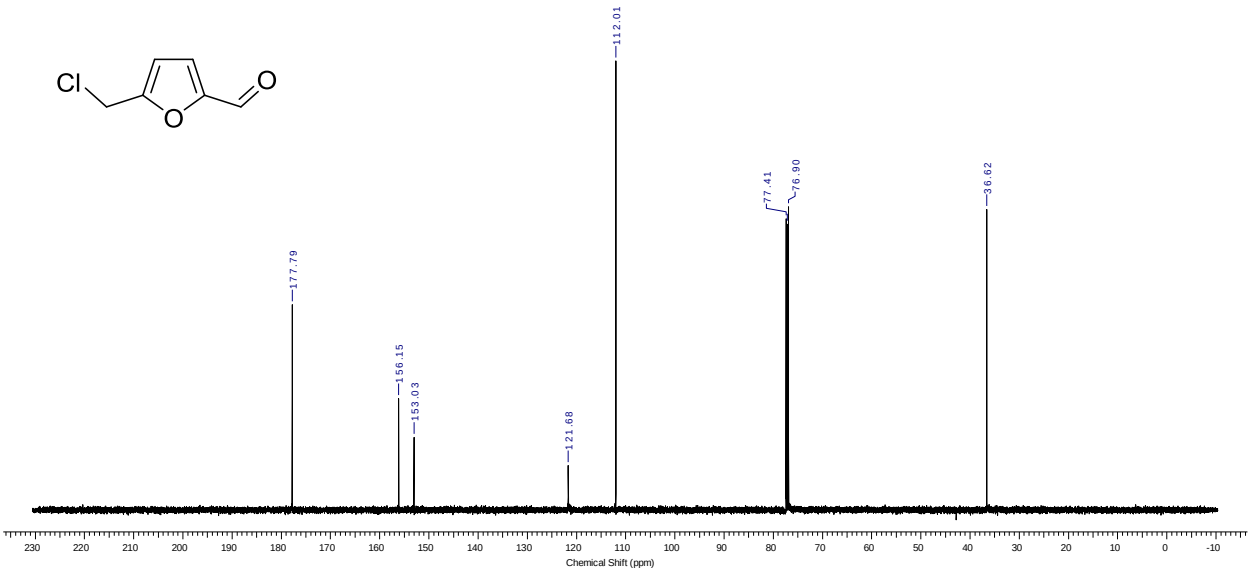


Figure S2. ^{13}C{^{1}H} NMR spectrum of 5-(chloromethyl)furfural **1**.

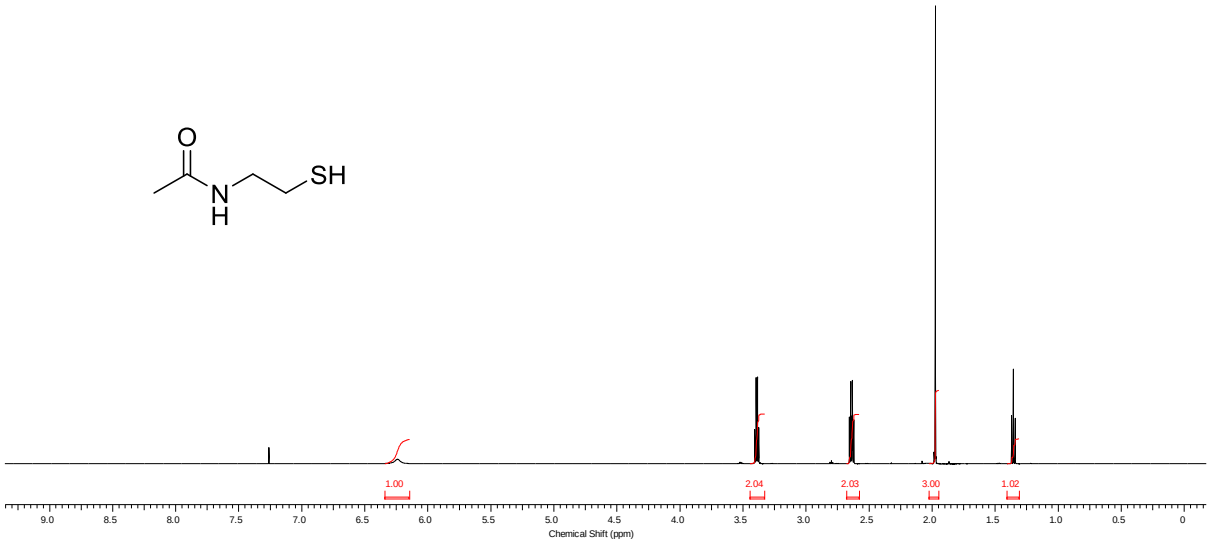


Figure S3. ^{1}H NMR spectrum of N-acetylcysteamine.

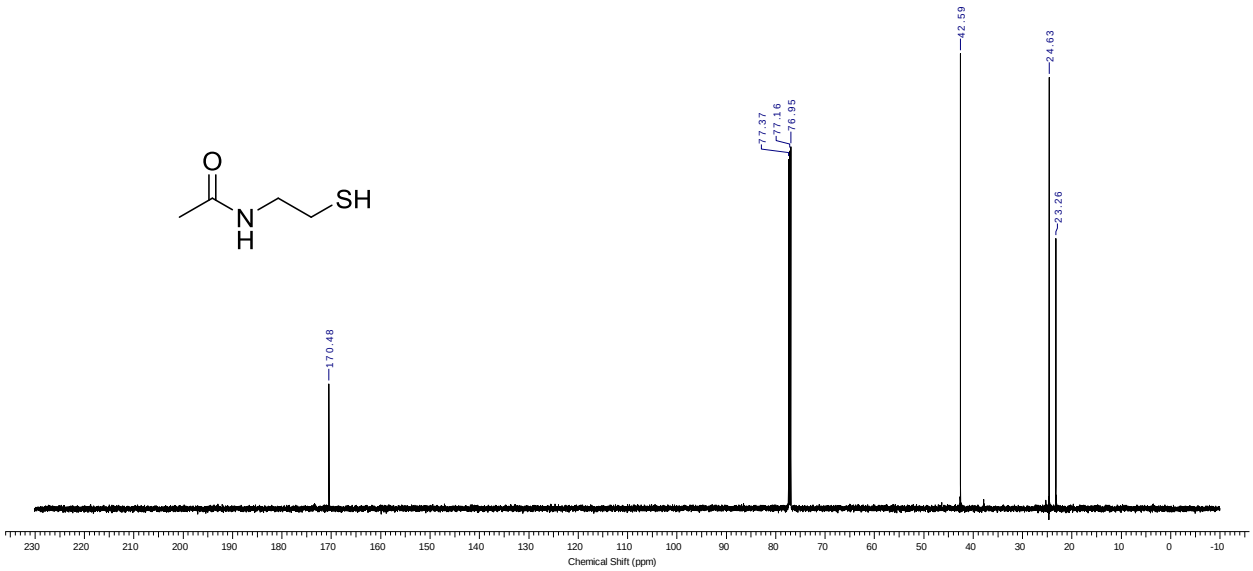


Figure S4. ^{13}C{^{1}H} NMR spectrum of N-acetylcysteamine.

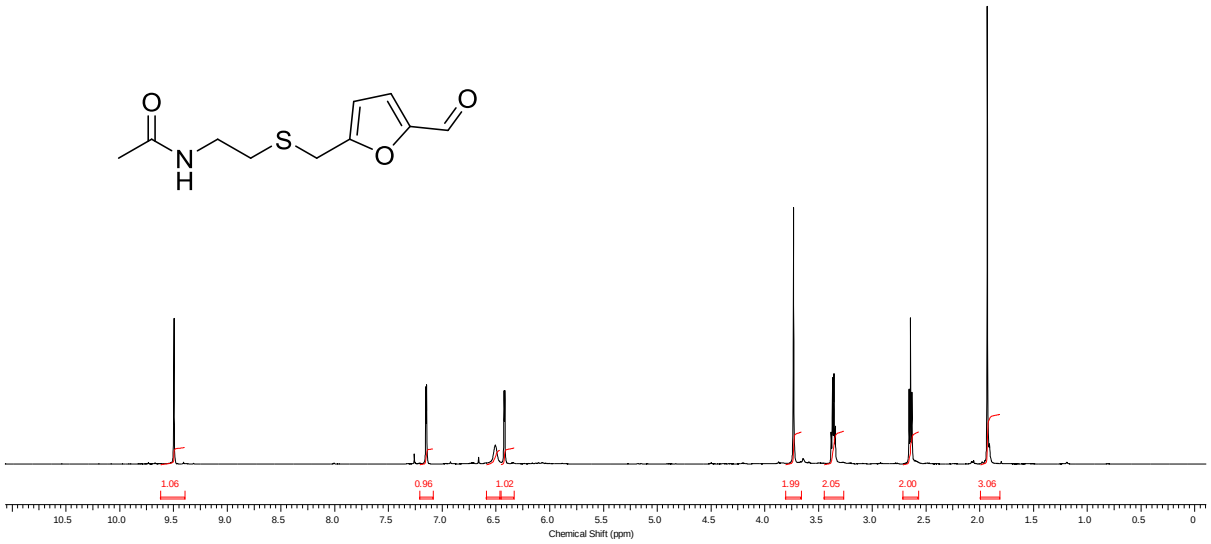


Figure S5. ^{1}H NMR spectrum of 5-[[(2-acetamidoethyl)thio]methyl]furfural **2**.

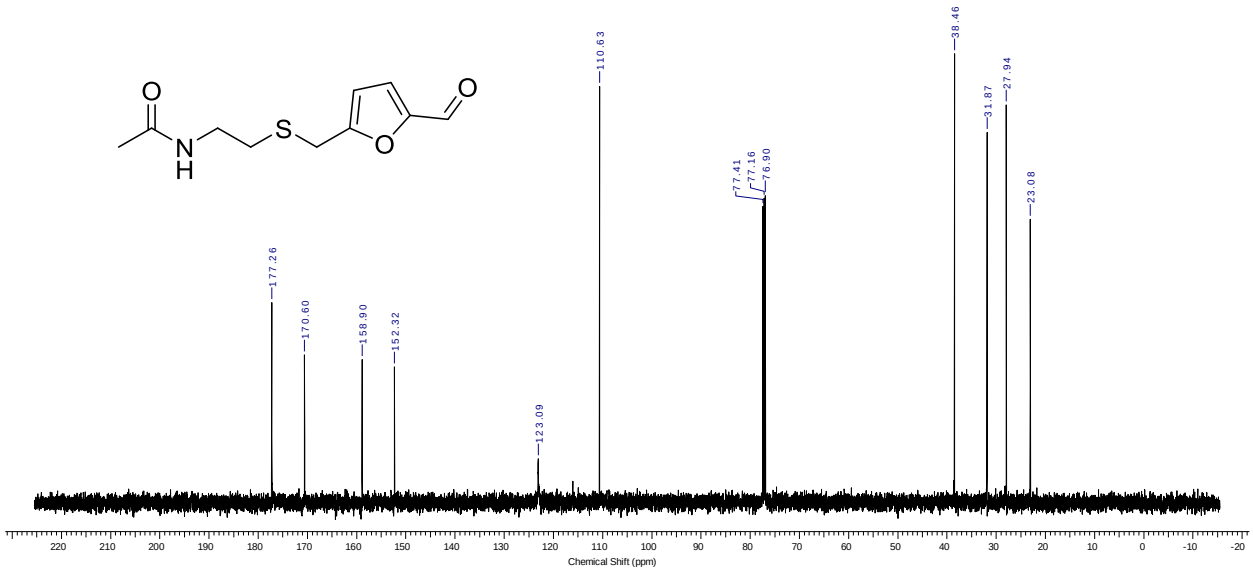


Figure S6. ^{13}C{^{1}H} NMR spectrum of 5-[[(2-acetamidoethyl)thio]methyl]furfural **2**.

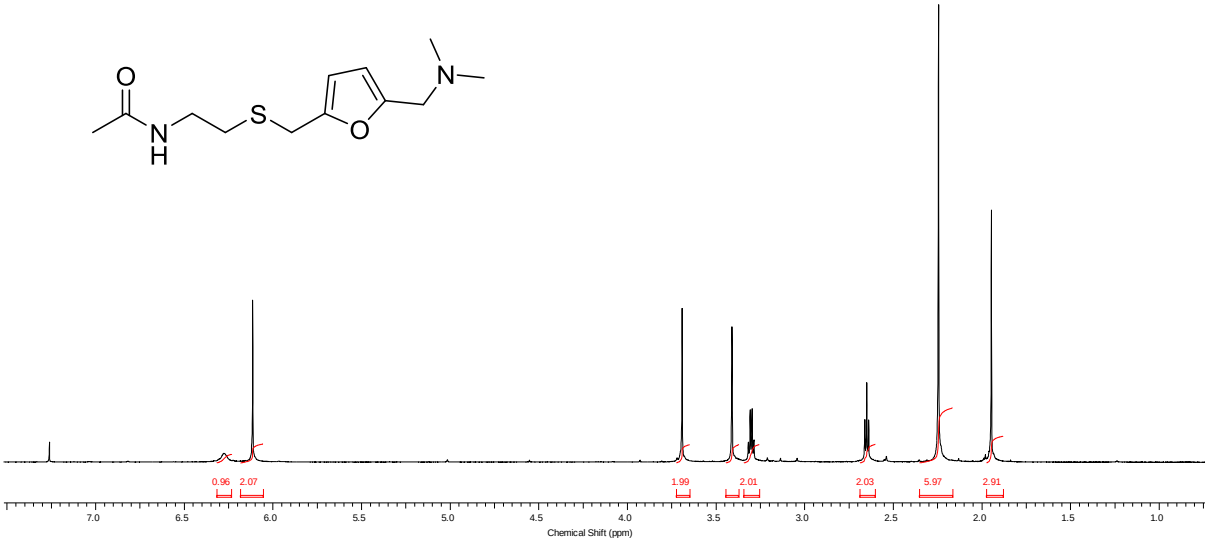


Figure S7. ^{1}H NMR spectrum of 5-[[(2-acetamidoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine **3**.

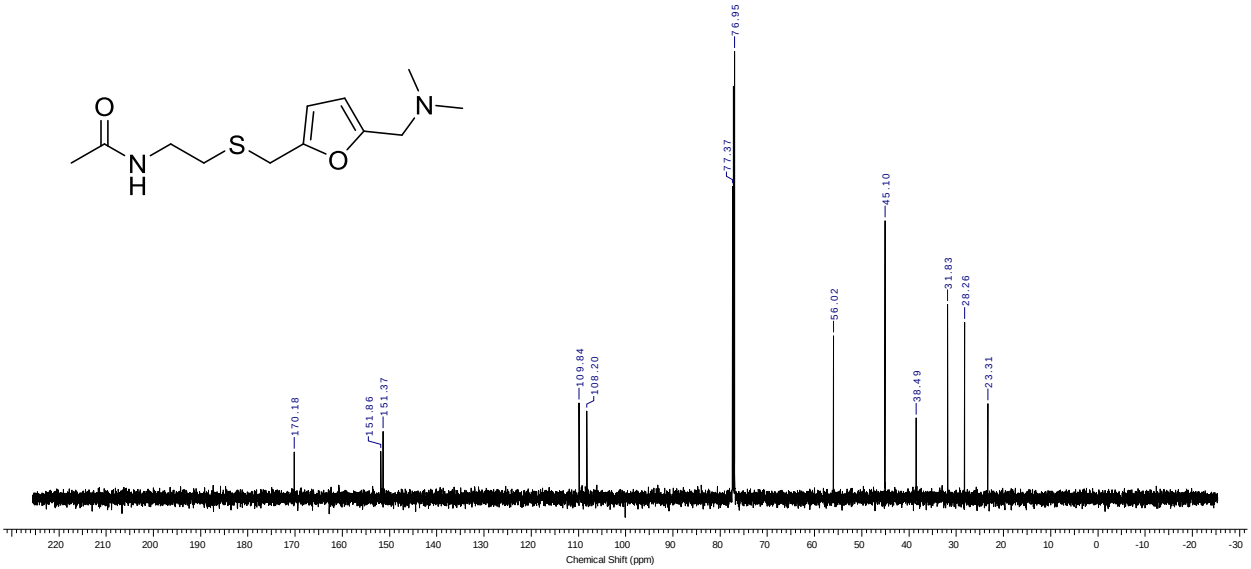


Figure S8. ^{13}C{^{1}H} NMR spectrum of 5-[[(2-acetamidoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine **3**.

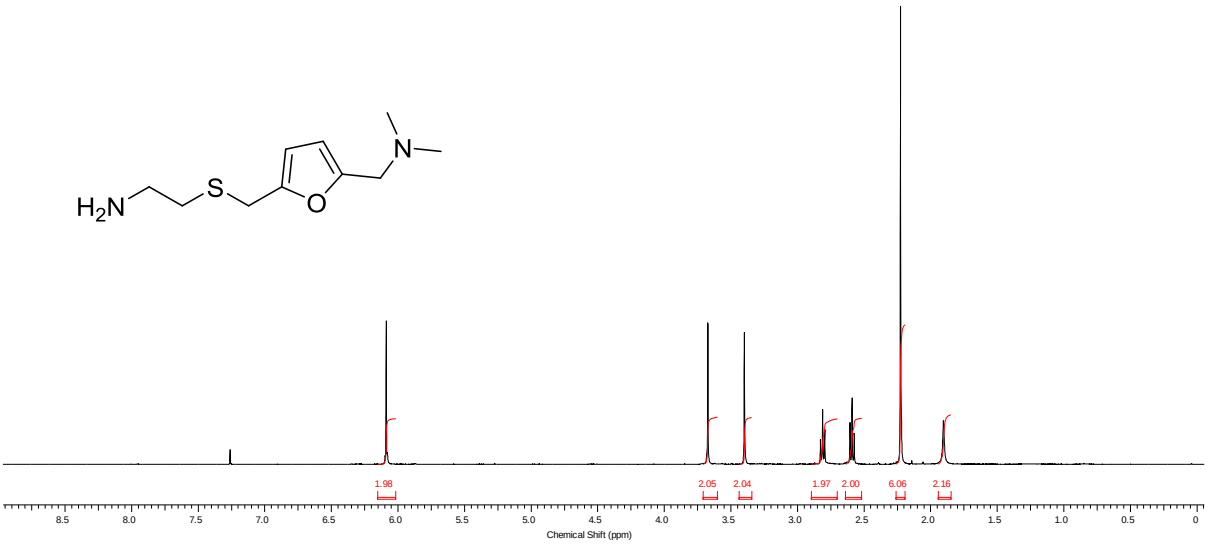


Figure S9. ^{1}H NMR spectrum of 5-[[(2-aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine **4**.

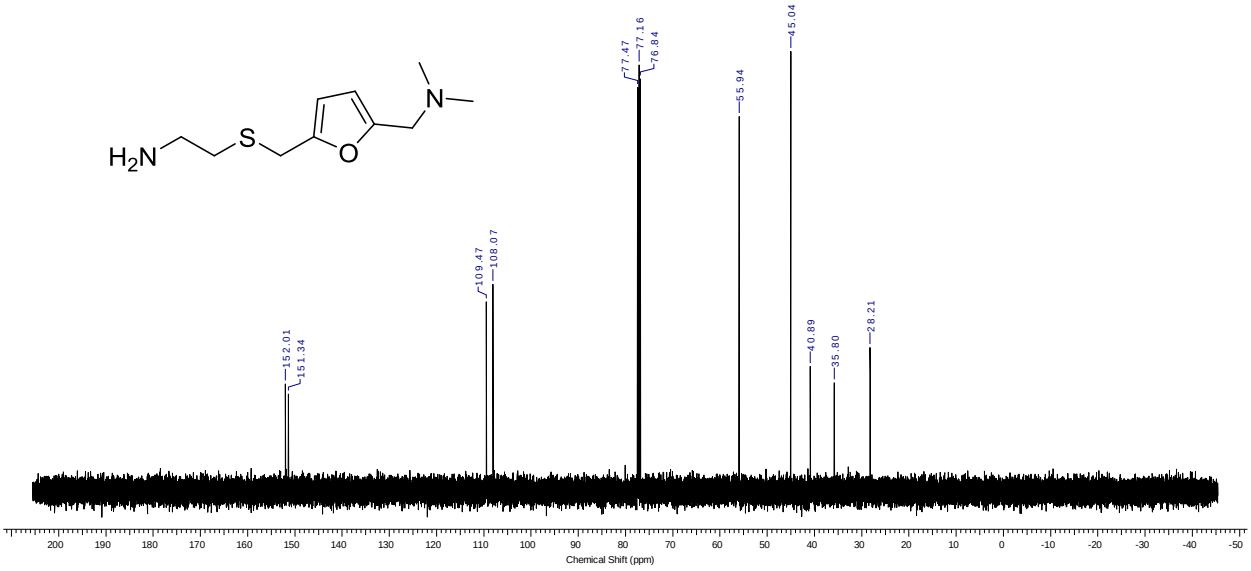


Figure S10. ^{13}C{^{1}H} NMR spectrum of 5-[[(2-aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine **4**.

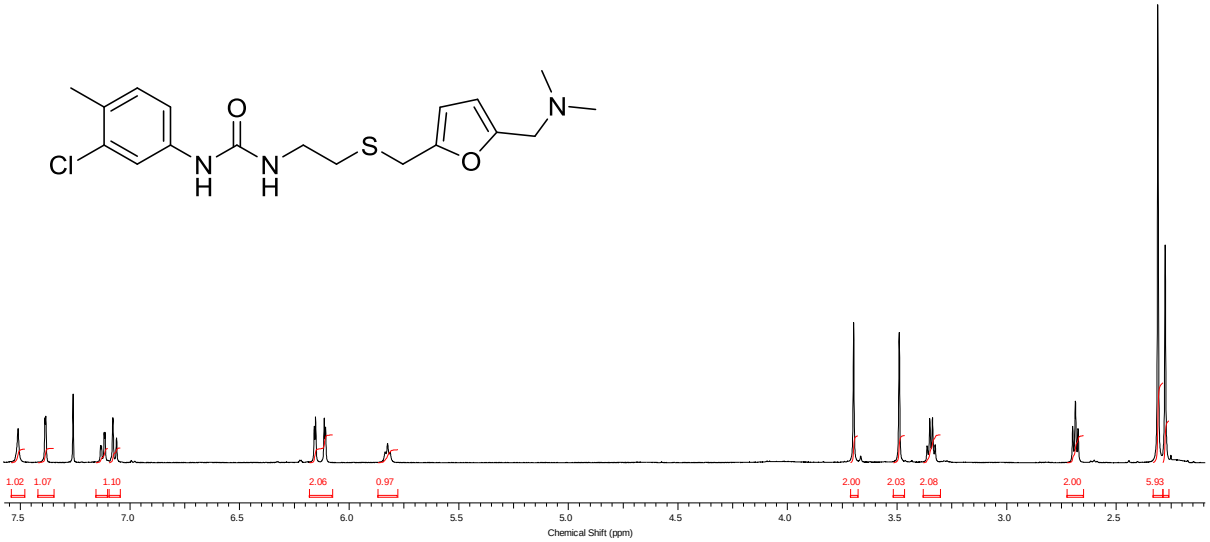


Figure S11. ^{1}H NMR spectrum of 1-(3-chloro-4-methylphenyl)-3-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)urea (**CAP-1**).

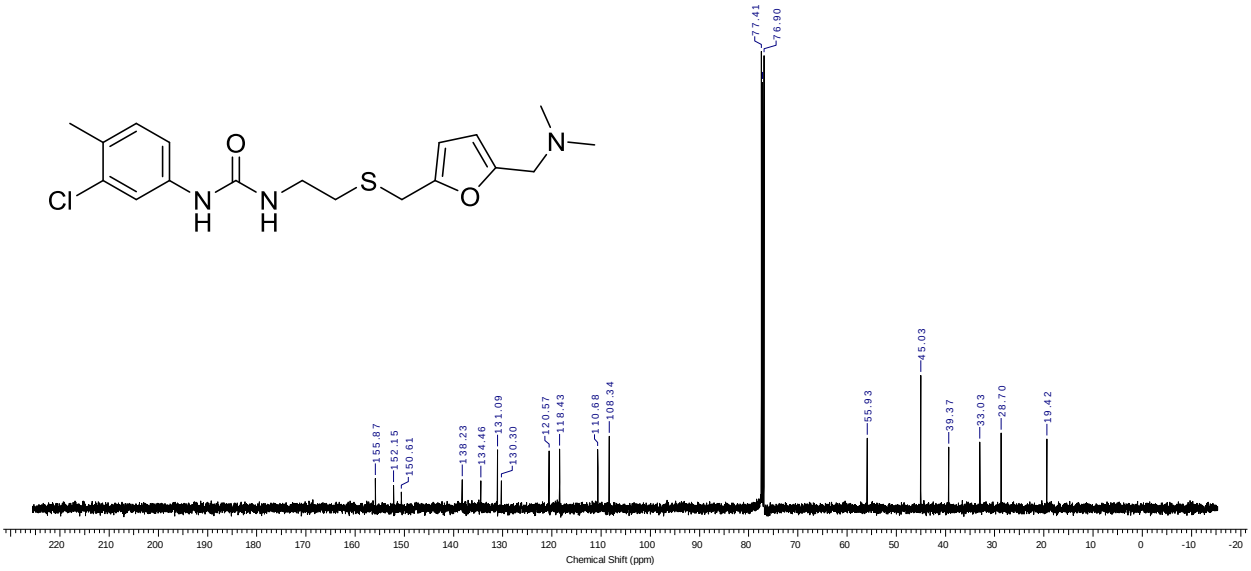


Figure S12. $^{13}C\{^{1}H\}$ NMR spectrum of 1-(3-chloro-4-methylphenyl)-3-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)urea (**CAP-1**).

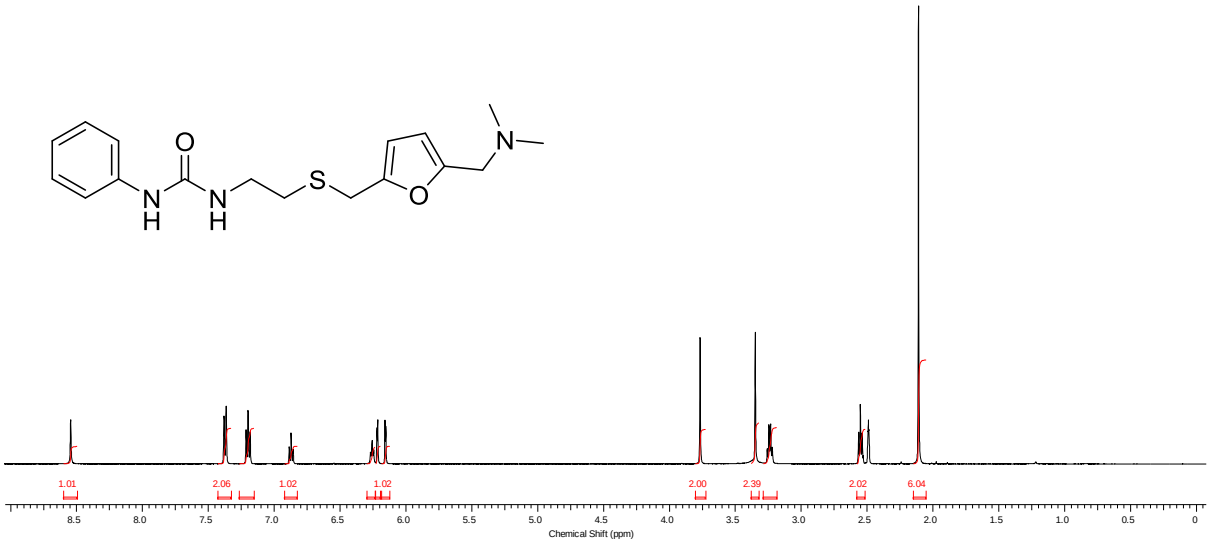


Figure S13. ^{1}H NMR spectrum of 1-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)-3-phenylurea **5a**.

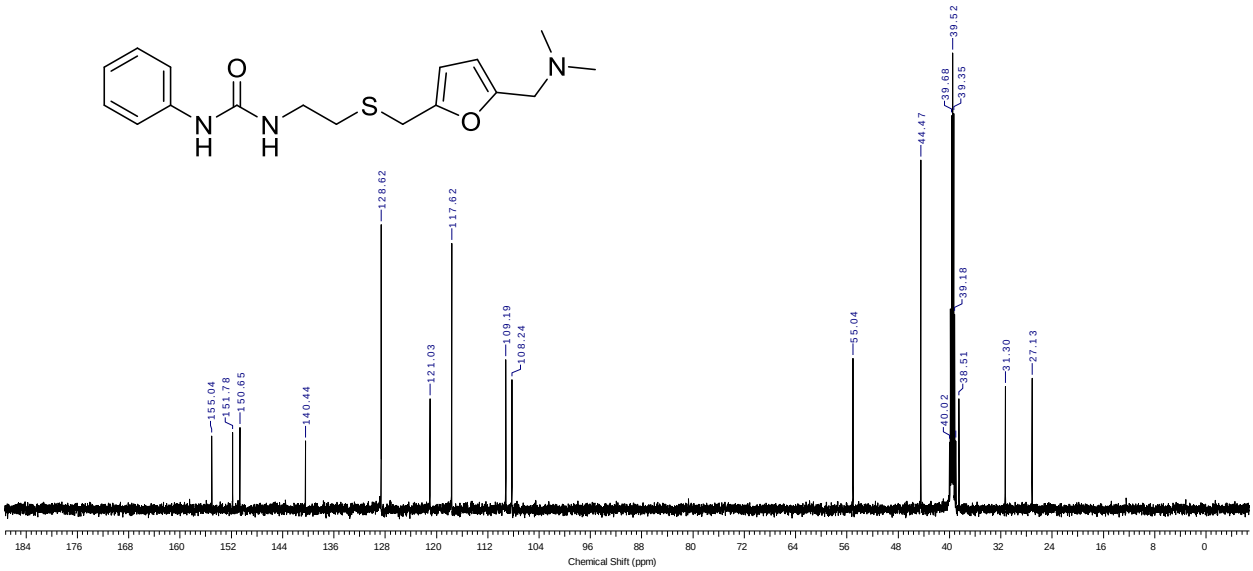


Figure S14. ^{13}C{^{1}H} NMR spectrum of 1-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)-3-phenylurea **5a**.

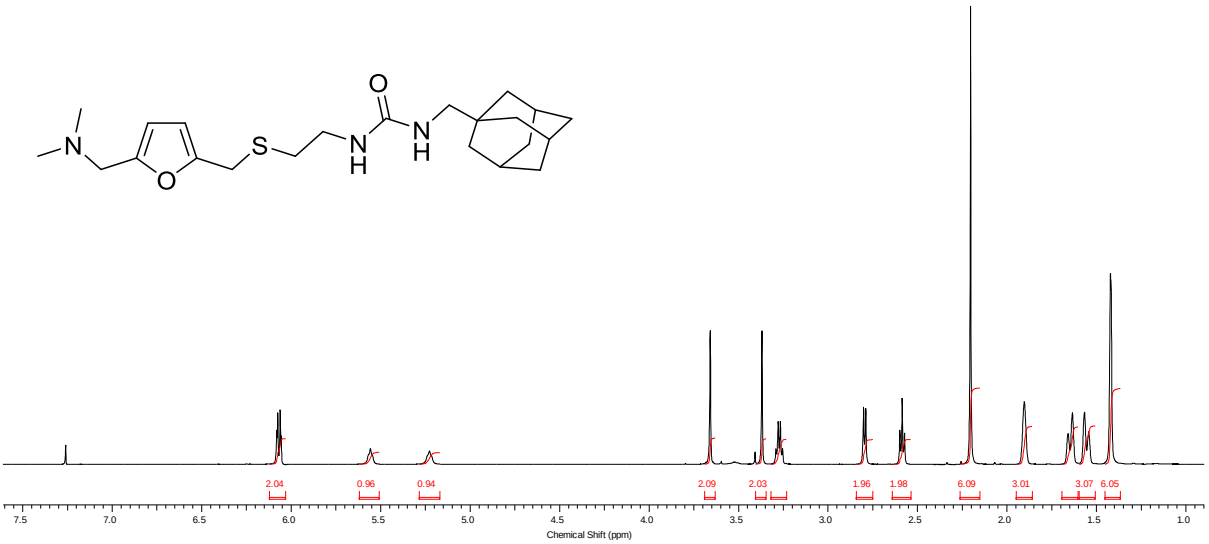


Figure S15. ^{1}H NMR spectrum of 1-((adamantan-1-yl)methyl)-3-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio) ethyl)urea **5b**.

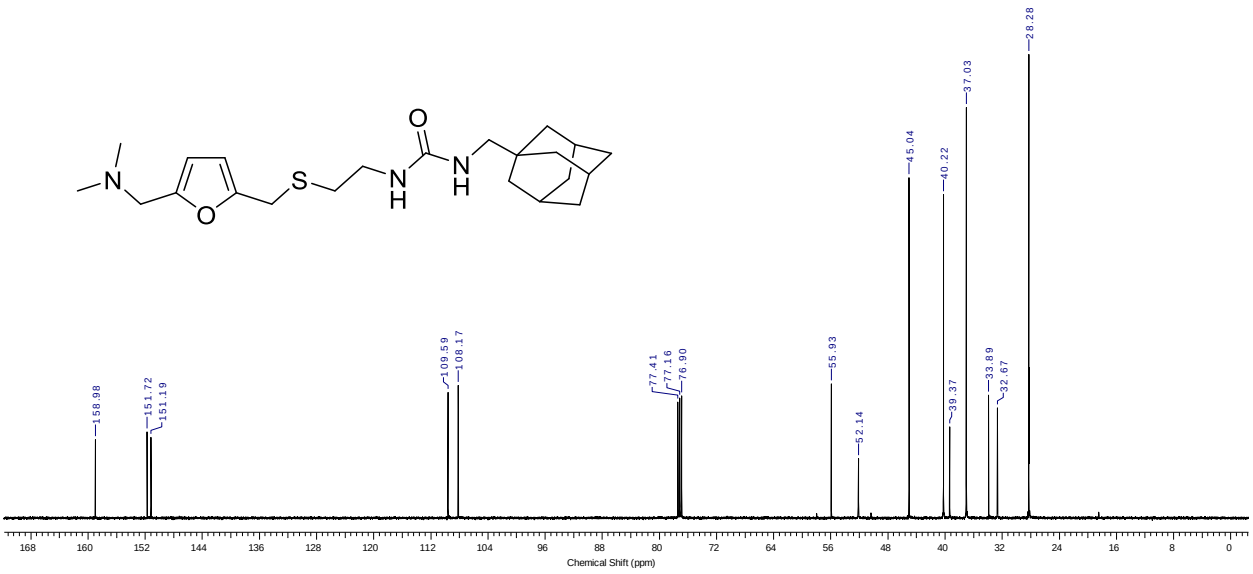


Figure S16. $^{13}C\{^{1}H\}$ NMR spectrum of 1-((adamantan-1-yl)methyl)-3-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio) ethyl)urea **5b**.

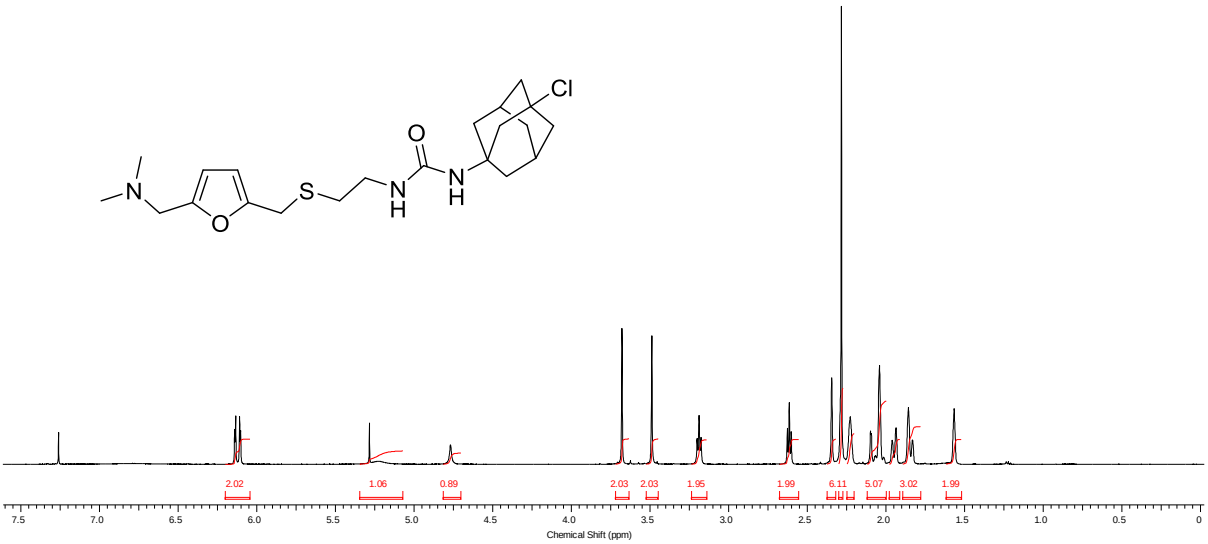


Figure S17. ^{1}H NMR spectrum of 1-(-3-chloroadamantan-1-yl)-3-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio) ethyl)urea **5c**.

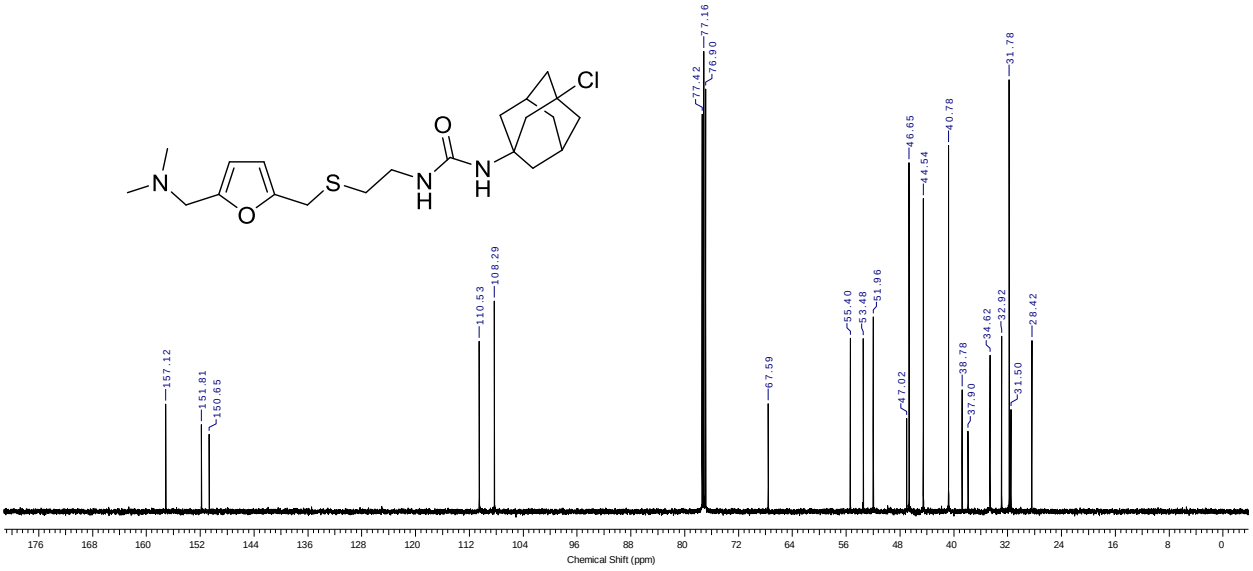


Figure S18. $^{13}C\{^{1}H\}$ NMR spectrum of 1-(-3-chloroadamantan-1-yl)-3-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio) ethyl)urea **5c**.

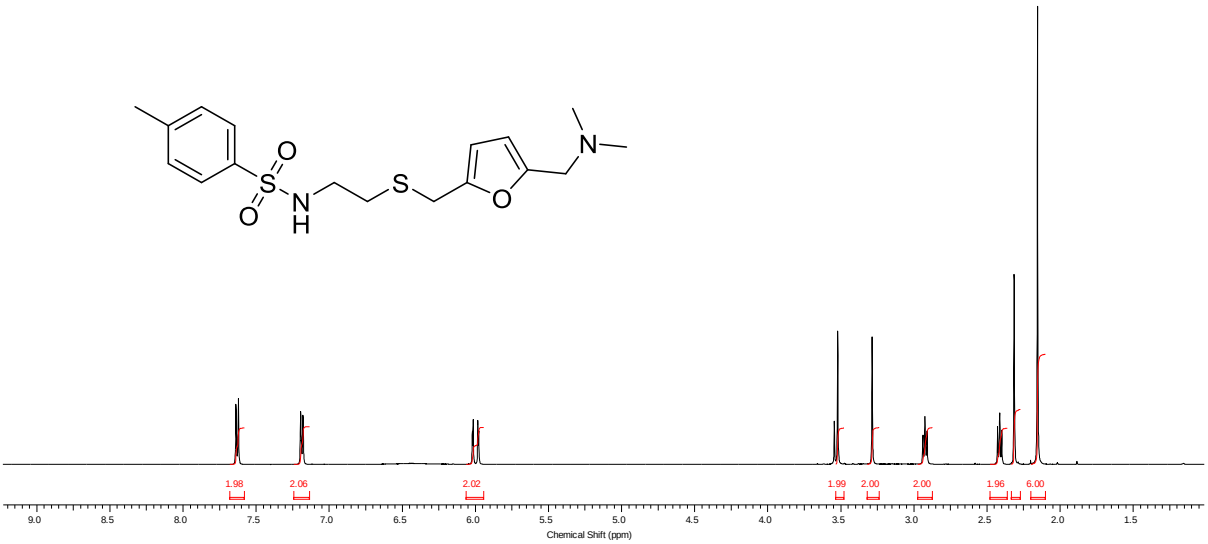


Figure S19. ^{1}H NMR spectrum of N-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)-4-methylbenzene-sulfonamide **6a**.

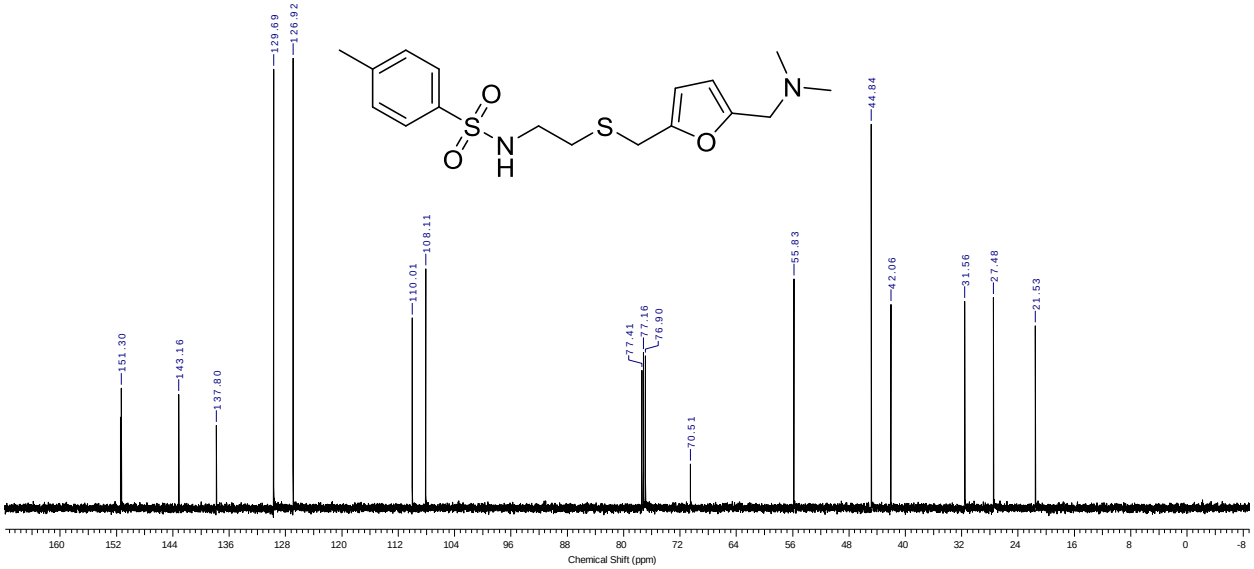


Figure S20. ^{13}C{^{1}H} NMR N-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)-4-methylbenzene-sulfonamide **6a**.

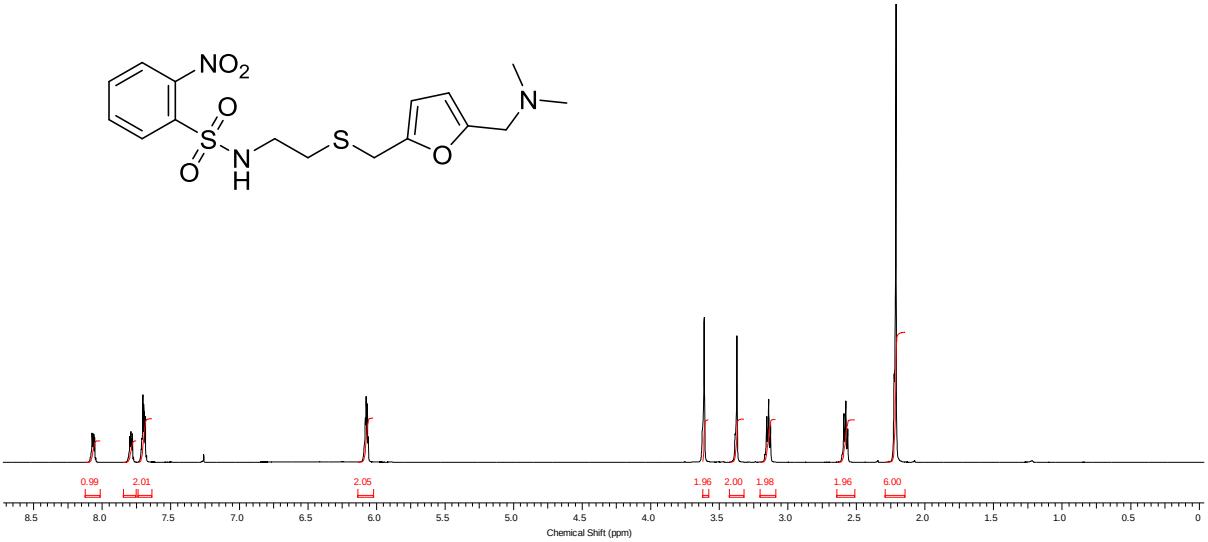


Figure S21. ^{1}H NMR spectrum of N-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)-2-nitrobenzene sulfonamide **6b**.

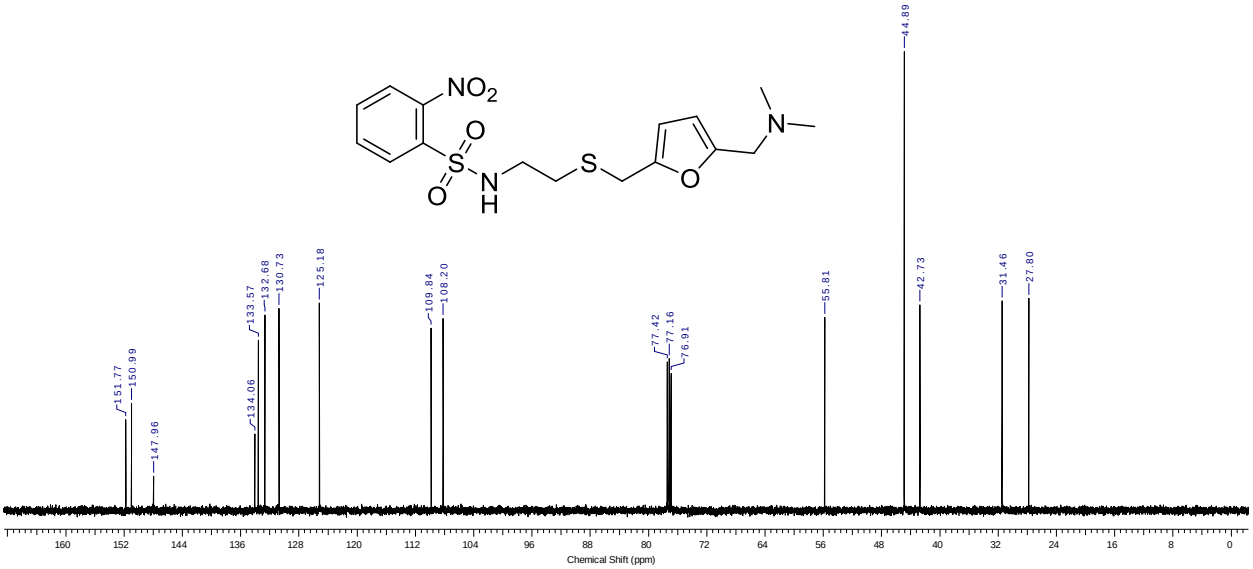


Figure S22. $^{13}C\{^{1}H\}$ NMR spectrum of N-(2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)-2-nitrobenzene sulfonamide **6b**.

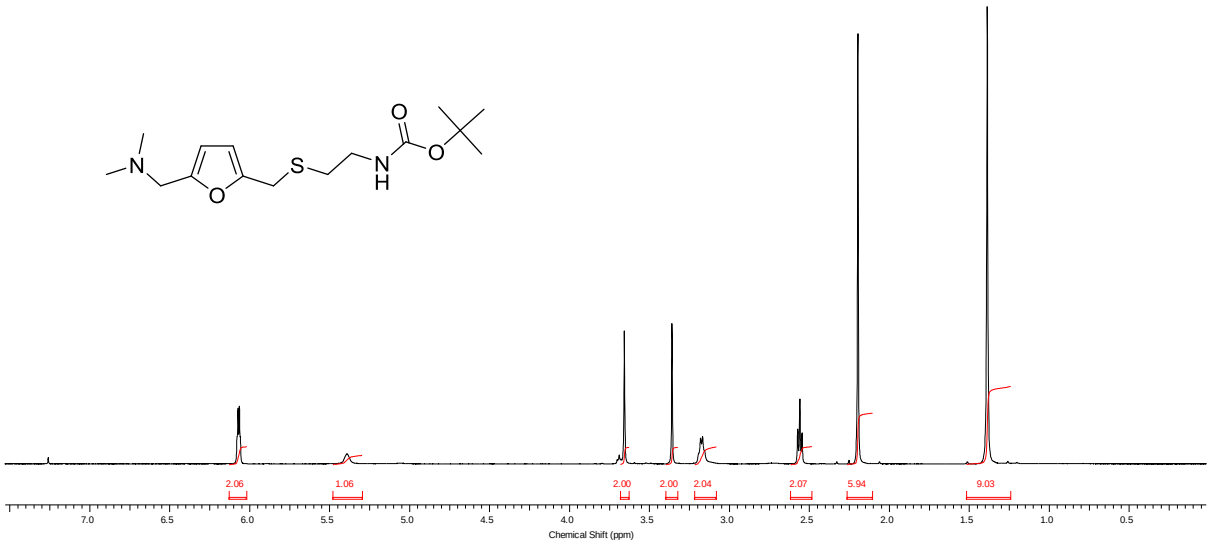


Figure S23. ^{1}H NMR spectrum of *tert*-butyl (2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)carbamate **7**.

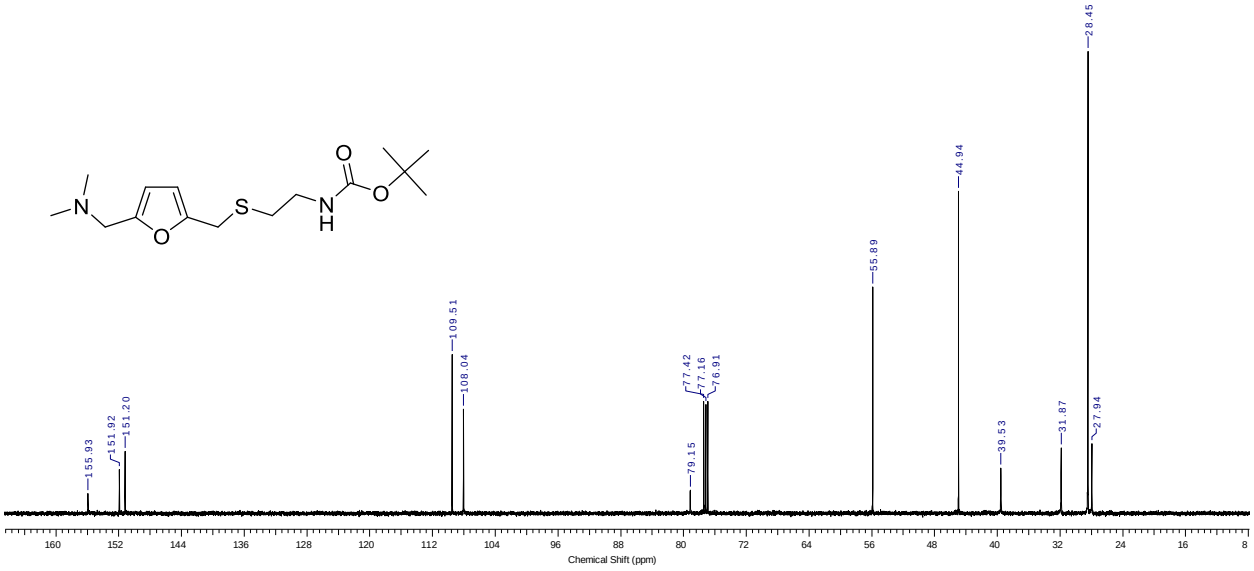


Figure S24. ^{13}C{^{1}H} NMR spectrum of *tert*-butyl (2-(((5-((dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)carbamate **7**.

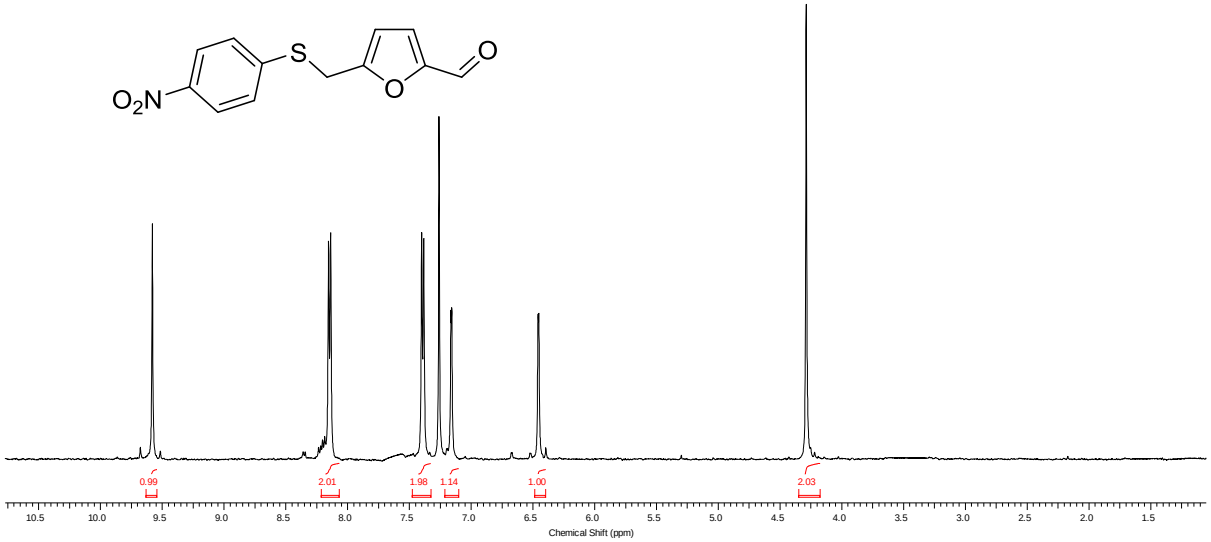


Figure S25. ^{1}H NMR spectrum of 5-(((4-nitrophenyl)thio)methyl)furan-2-carbaldehyde **8**.

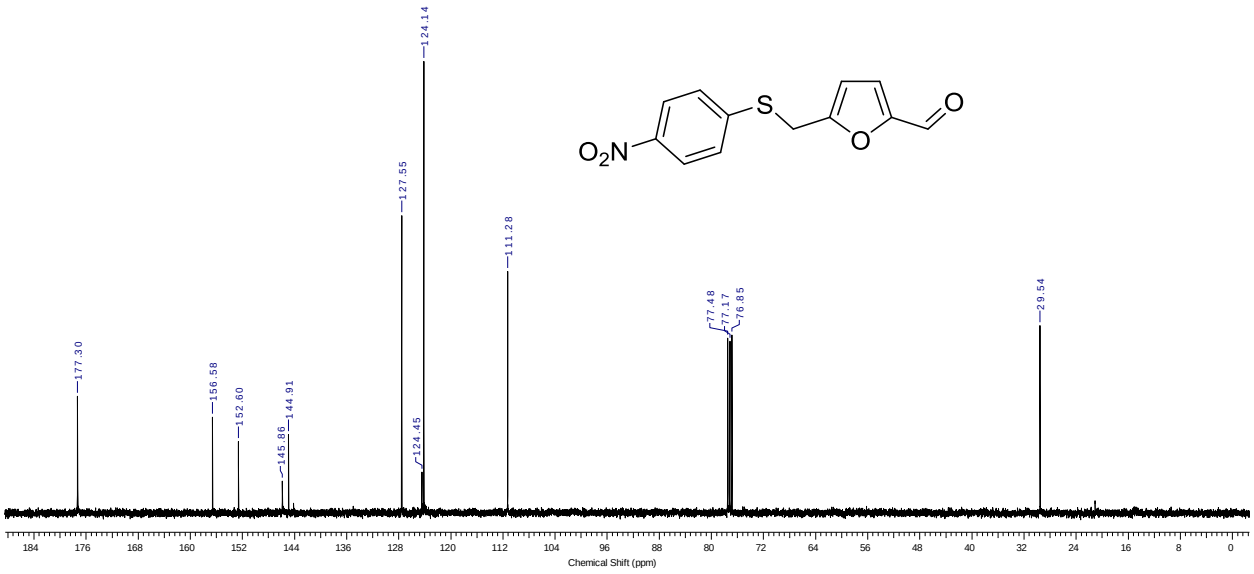


Figure S26. ^{13}C{^{1}H} NMR spectrum of 5-(((4-nitrophenyl)thio)methyl)furan-2-carbaldehyde **8**.

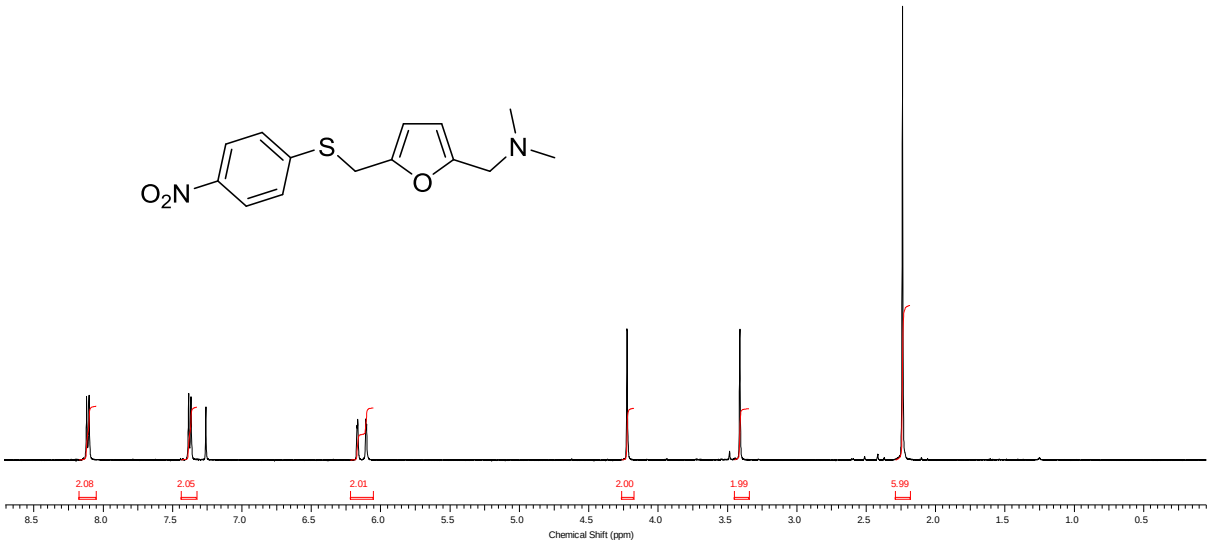


Figure S27. ^{1}H NMR spectrum of N,N-dimethyl-1-(5-(((4-nitrophenyl)thio)methyl)furan-2-yl)methanamine **9**.

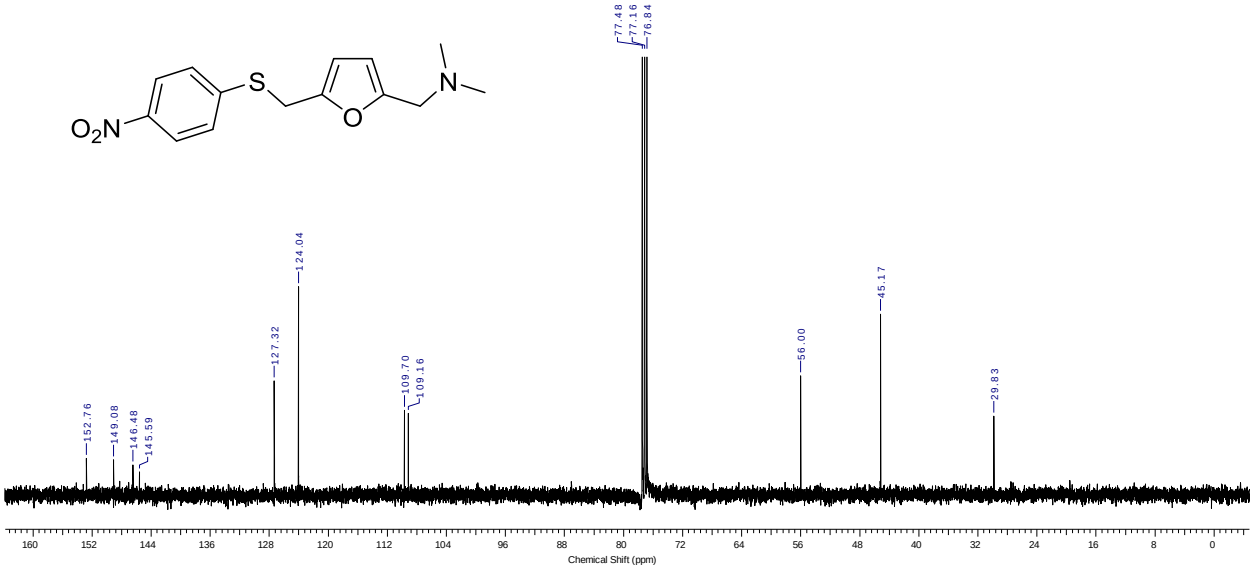


Figure S28. ^{13}C{^{1}H} NMR spectrum of N,N-dimethyl-1-(5-(((4-nitrophenyl)thio)methyl)furan-2-yl)methanamine **9**.

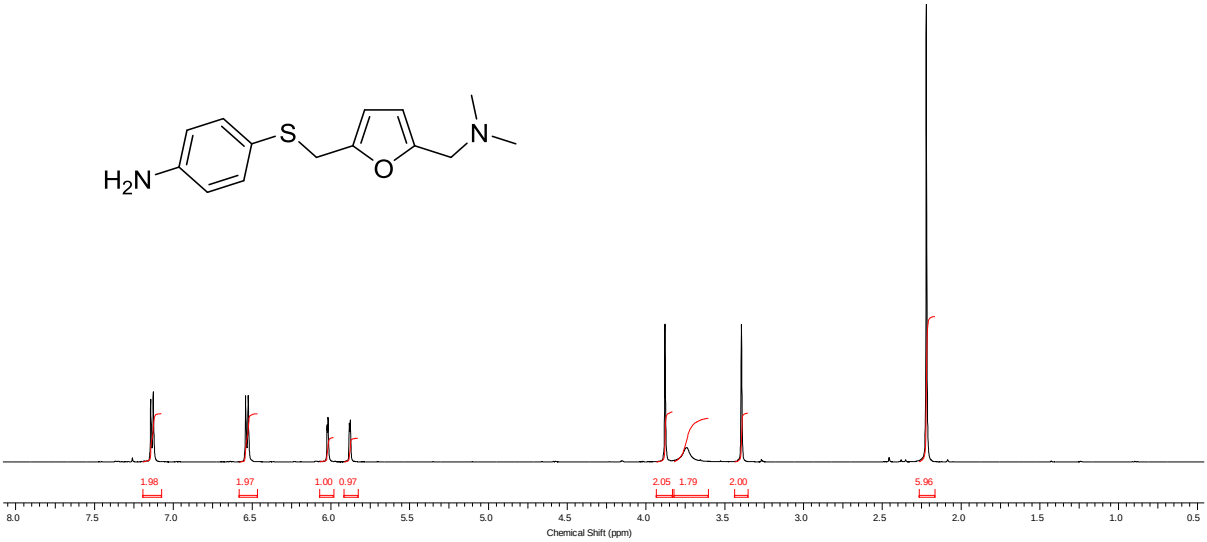


Figure S29. ^{1}H NMR spectrum of 4-(((5-((Dimethylamino)methyl)furan-2-yl)methyl)thio)aniline **10**.

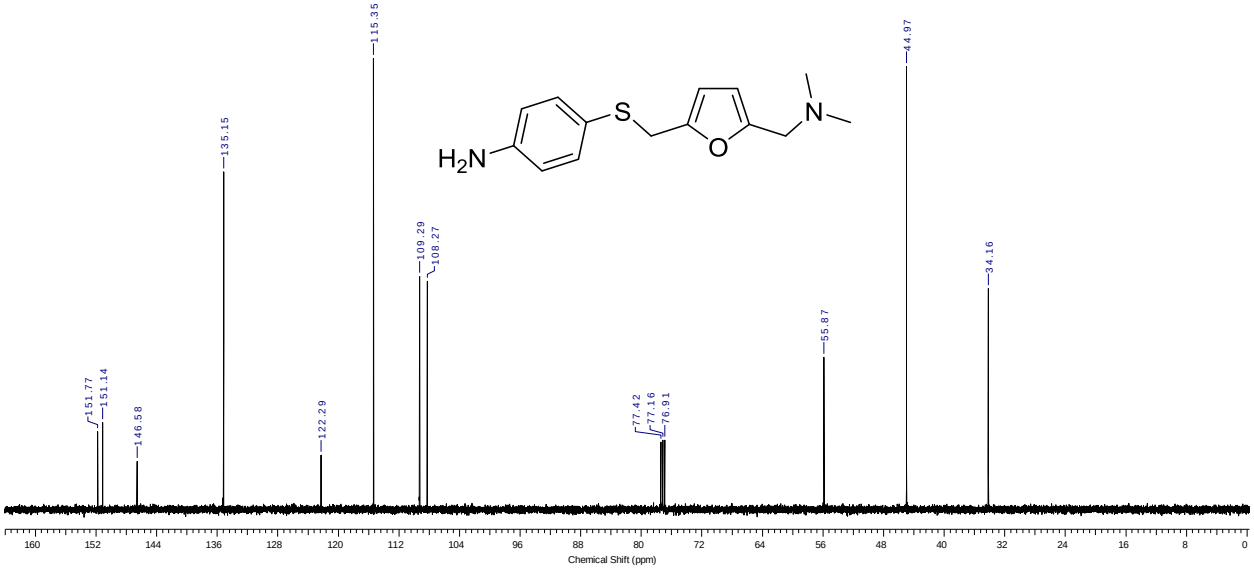


Figure S30. ^{13}C{^{1}H} NMR spectrum of 4-(((5-((Dimethylamino)methyl)furan-2-yl)methyl)thio)aniline **10**.

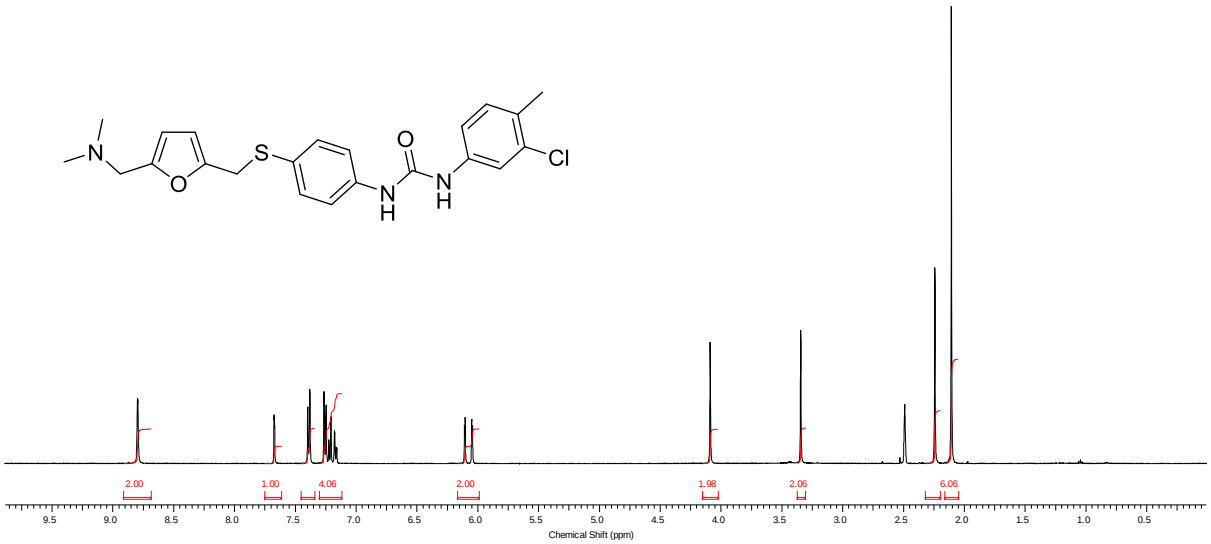


Figure S31. ^{1}H NMR spectrum of 1-(3-chloro-4-methylphenyl)-3-(4-(((5-((dimethylamino) methyl)furan-2-yl)methyl)thio)phenyl)urea **11**.

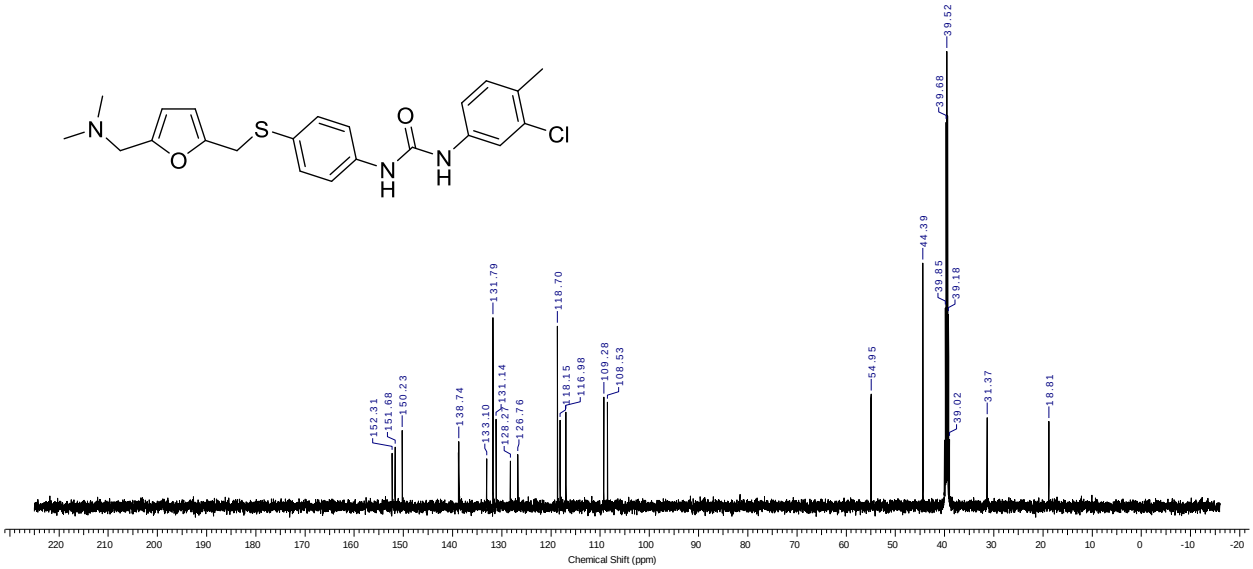


Figure S32. ^{13}C{^{1}H} NMR spectrum of 1-(3-chloro-4-methylphenyl)-3-(4-(((5-((dimethylamino) methyl)furan-2-yl)methyl)thio)phenyl)urea **11**.

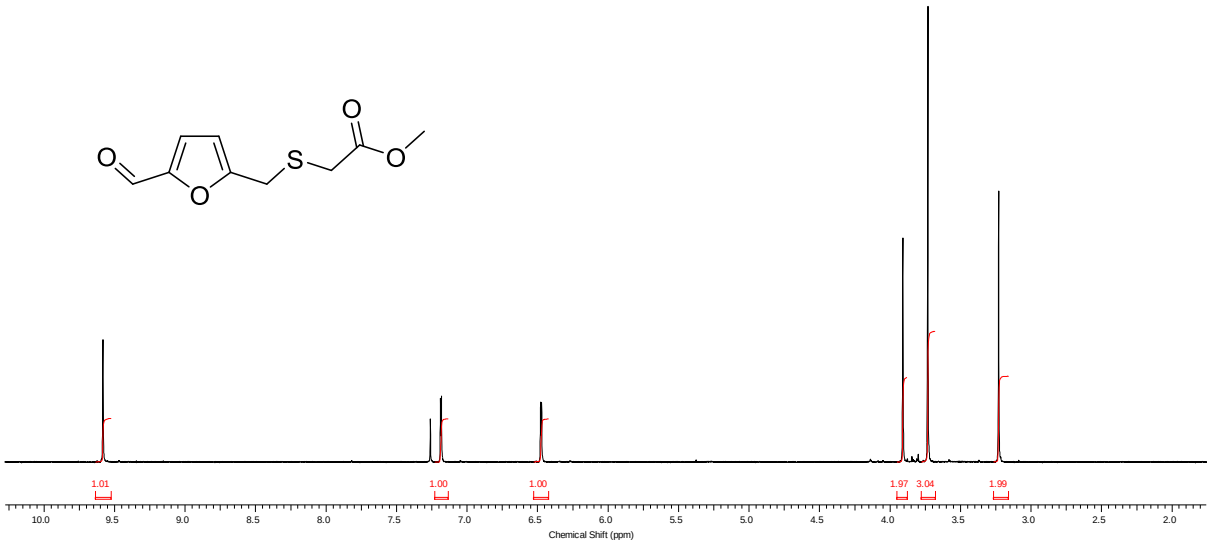


Figure S33. ^{1}H NMR spectrum of methyl 2-(((5-formylfuran-2-yl)methyl)thio)acetate **12**.

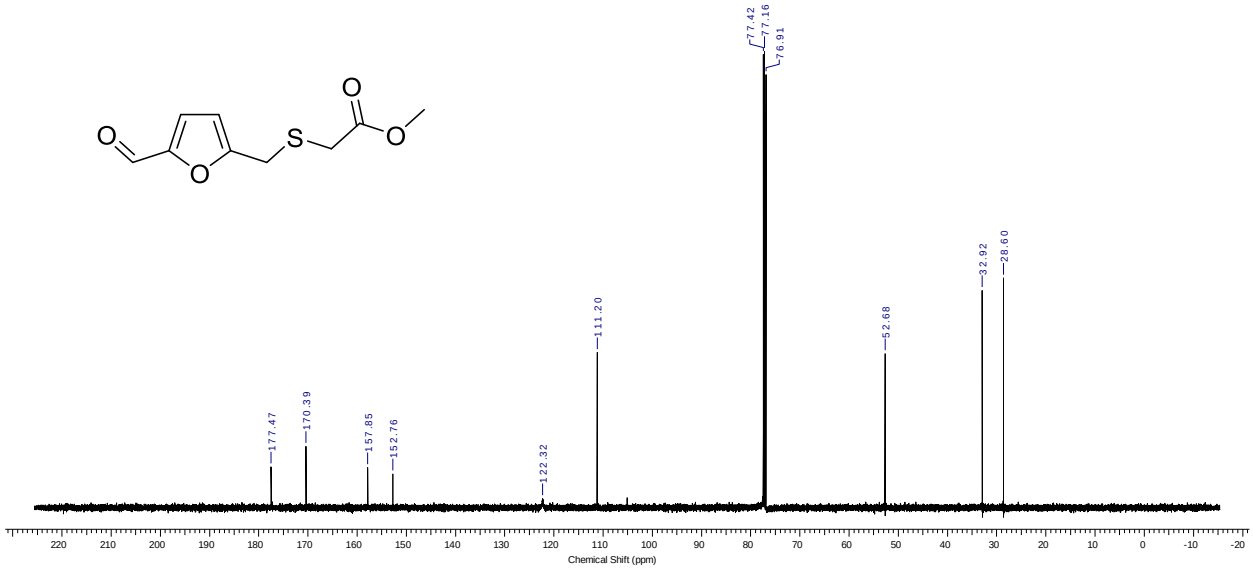


Figure S34. ^{13}C{^{1}H} NMR spectrum of methyl 2-(((5-formylfuran-2-yl)methyl)thio)acetate **12**.

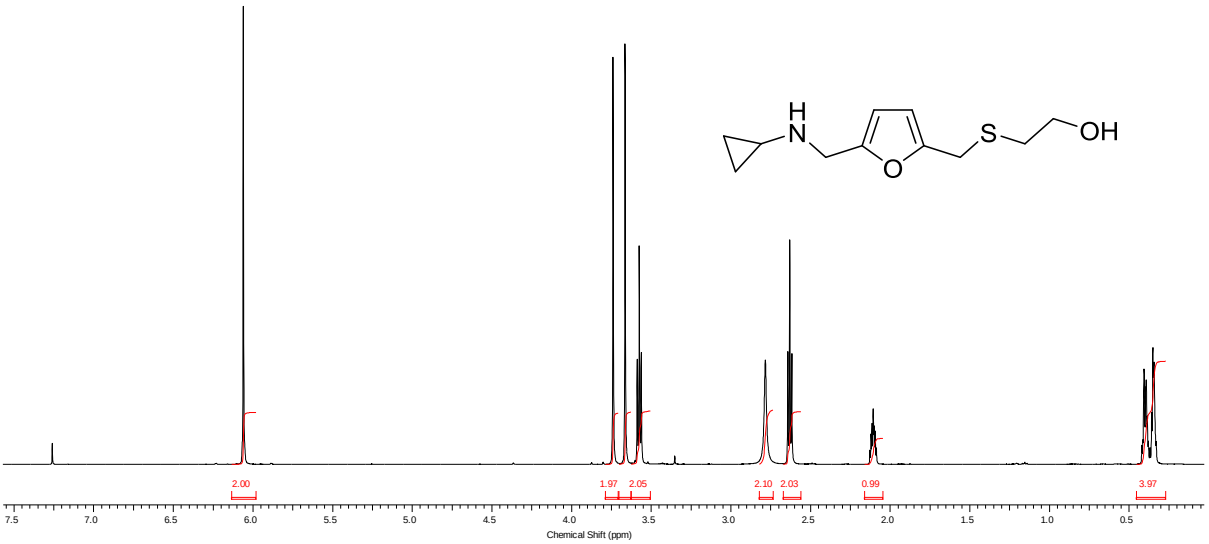


Figure S35. ^{1}H NMR spectrum of 2-(((5-((cyclopropylamino)methyl)furan-2-yl)methyl)thio)ethan-1-ol **13**.

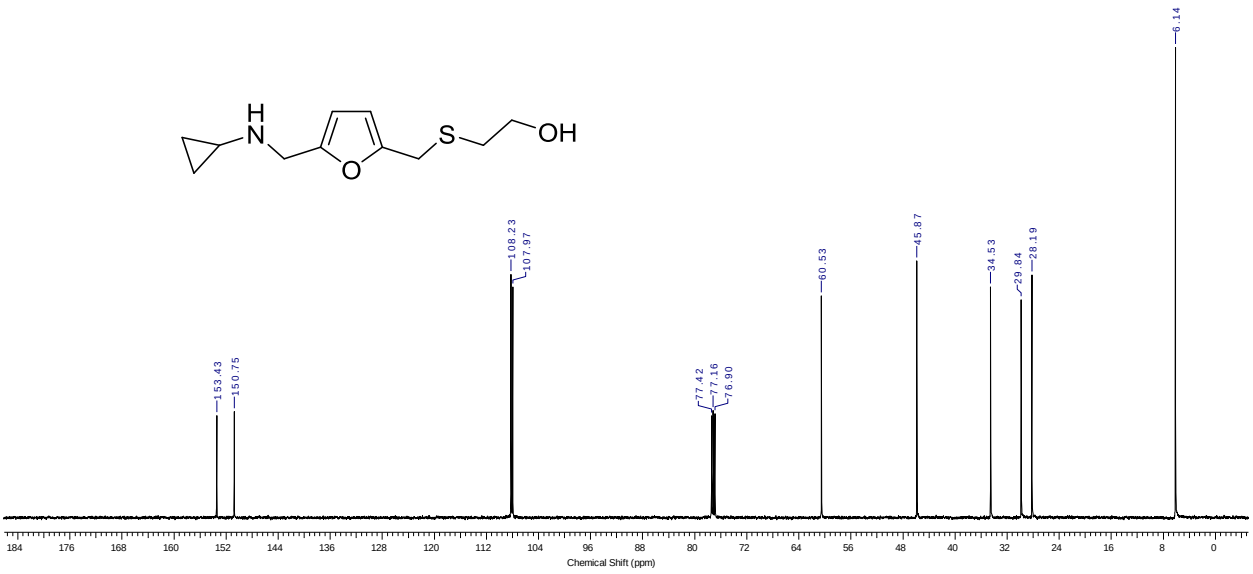
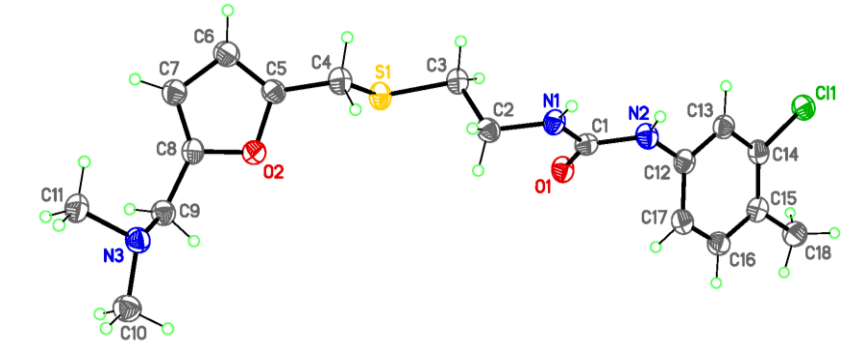


Figure S36. ^{13}C{^{1}H} NMR spectrum of 2-(((5-((cyclopropylamino)methyl)furan-2-yl)methyl)thio)ethan-1-ol **13**.

X-Ray data for CAP-1



CCDC 1497315

Table S1. Crystal data and structure refinement for ***CAP1***.

Identification code	**CAP1**	
Empirical formula	C18 H24 Cl N3 O2 S	
Formula weight	381.91	
Temperature	100(2) K	
Wavelength	0.96990 Å	
Crystal system	Monoclinic	
Space group	Cc	
Unit cell dimensions	a = 38.822(8) Å	α = 90°.
	b = 4.5920(9) Å	β = 99.08(3)°.
	c = 10.705(2) Å	γ = 90°.
Volume	1884.5(7) $Å^3$	
Z	4	
Density (calculated)	1.346 Mg/m^3	
Absorption coefficient	0.775 mm^{-1}	
F(000)	808	
Crystal size	0.10 x 0.10 x 0.10 mm^3	
Theta range for data collection	1.450 to 38.476°.	
Index ranges	-49<=h<=49, -5<=k<=5, -12<=l<=12	
Reflections collected	13010	
Independent reflections	3654 [R(int) = 0.0535]	
Completeness to theta = 35.587°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.900 and 0.900	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3654 / 2 / 235	
Goodness-of-fit on F^2	1.068	
Final R indices [for 3288 rflns with I>2σ(I)]	R1 = 0.0476, wR2 = 0.1167	
R indices (all data)	R1 = 0.0557, wR2 = 0.1233	
Absolute structure parameter	0.185(13)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.624 and -0.475 $e.Å^{-3}$	

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for ***CAP1***. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Cl(1)	7138(1)	9166(2)	8147(1)	45(1)
S(1)	4752(1)	5891(1)	2367(1)	38(1)
O(1)	5561(1)	6194(4)	5940(2)	38(1)
O(2)	3897(1)	4946(5)	1877(2)	35(1)
N(1)	5303(1)	10522(5)	5304(2)	33(1)
N(2)	5825(1)	10444(5)	6663(3)	35(1)
N(3)	3114(1)	2995(5)	1951(2)	37(1)
C(1)	5562(1)	8892(6)	5962(3)	32(1)
C(2)	5001(1)	9126(6)	4554(3)	34(1)
C(3)	5077(1)	8266(7)	3241(3)	36(1)
C(4)	4380(1)	8379(7)	1931(3)	37(1)
C(5)	4092(1)	6677(6)	1190(3)	34(1)
C(6)	3979(1)	6346(7)	-60(3)	41(1)
C(7)	3696(1)	4294(6)	-180(3)	40(1)
C(8)	3656(1)	3494(6)	1009(3)	35(1)
C(9)	3417(1)	1494(6)	1573(3)	37(1)
C(10)	2955(1)	1148(7)	2830(3)	44(1)
C(11)	2858(1)	3678(8)	822(3)	43(1)
C(12)	6094(1)	9077(6)	7512(3)	34(1)
C(13)	6442(1)	9688(6)	7442(3)	36(1)
C(14)	6701(1)	8384(7)	8305(3)	36(1)
C(15)	6635(1)	6491(7)	9249(3)	38(1)
C(16)	6282(1)	5902(6)	9290(3)	38(1)
C(17)	6015(1)	7172(6)	8453(3)	38(1)
C(18)	6920(1)	5153(8)	10191(3)	45(1)

Table S3. Bond lengths [Å] and angles [°] for ***CAP1***.

Cl(1)-C(14)	1.768(3)	C(6)-H(6)	0.9500
S(1)-C(3)	1.813(3)	C(7)-C(8)	1.358(5)
S(1)-C(4)	1.843(3)	C(7)-H(7)	0.9500
O(1)-C(1)	1.239(3)	C(8)-C(9)	1.497(4)
O(2)-C(8)	1.382(4)	C(9)-H(9A)	0.9900
O(2)-C(5)	1.387(4)	C(9)-H(9B)	0.9900
N(1)-C(1)	1.359(4)	C(10)-H(10A)	0.9800
N(1)-C(2)	1.460(4)	C(10)-H(10B)	0.9800
N(1)-H(1)	0.83(4)	C(10)-H(10C)	0.9800
N(2)-C(1)	1.368(4)	C(11)-H(11A)	0.9800
N(2)-C(12)	1.417(4)	C(11)-H(11B)	0.9800
N(2)-H(2)	0.80(4)	C(11)-H(11C)	0.9800
N(3)-C(11)	1.473(4)	C(12)-C(13)	1.392(4)
N(3)-C(10)	1.473(4)	C(12)-C(17)	1.404(4)
N(3)-C(9)	1.475(4)	C(13)-C(14)	1.390(4)
C(2)-C(3)	1.534(5)	C(13)-H(13)	0.9500
C(2)-H(2A)	0.9900	C(14)-C(15)	1.387(5)
C(2)-H(2B)	0.9900	C(15)-C(16)	1.405(4)
C(3)-H(3A)	0.9900	C(15)-C(18)	1.505(4)
C(3)-H(3B)	0.9900	C(16)-C(17)	1.388(4)
C(4)-C(5)	1.487(4)	C(16)-H(16)	0.9500
C(4)-H(4A)	0.9900	C(17)-H(17)	0.9500
C(4)-H(4B)	0.9900	C(18)-H(18A)	0.9800
C(5)-C(6)	1.349(5)	C(18)-H(18B)	0.9800
C(6)-C(7)	1.438(4)	C(18)-H(18C)	0.9800

C(3)-S(1)-C(4)	102.25(14)	O(1)-C(1)-N(2)	122.2(3)
C(8)-O(2)-C(5)	106.8(2)	N(1)-C(1)-N(2)	115.2(2)
C(1)-N(1)-C(2)	120.5(2)	N(1)-C(2)-C(3)	111.3(3)
C(1)-N(1)-H(1)	121(2)	N(1)-C(2)-H(2A)	109.4
C(2)-N(1)-H(1)	118(2)	C(3)-C(2)-H(2A)	109.4
C(1)-N(2)-C(12)	122.1(2)	N(1)-C(2)-H(2B)	109.4
C(1)-N(2)-H(2)	116(3)	C(3)-C(2)-H(2B)	109.4
C(12)-N(2)-H(2)	122(3)	H(2A)-C(2)-H(2B)	108.0
C(11)-N(3)-C(10)	110.5(2)	C(2)-C(3)-S(1)	114.1(2)
C(11)-N(3)-C(9)	109.8(3)	C(2)-C(3)-H(3A)	108.7
C(10)-N(3)-C(9)	109.9(2)	S(1)-C(3)-H(3A)	108.7
O(1)-C(1)-N(1)	122.7(3)	C(2)-C(3)-H(3B)	108.7

S(1)-C(3)-H(3B)	108.7	H(10B)-C(10)-H(10C)	109.5
H(3A)-C(3)-H(3B)	107.6	N(3)-C(11)-H(11A)	109.5
C(5)-C(4)-S(1)	107.6(2)	N(3)-C(11)-H(11B)	109.5
C(5)-C(4)-H(4A)	110.2	H(11A)-C(11)-H(11B)	109.5
S(1)-C(4)-H(4A)	110.2	N(3)-C(11)-H(11C)	109.5
C(5)-C(4)-H(4B)	110.2	H(11A)-C(11)-H(11C)	109.5
S(1)-C(4)-H(4B)	110.2	H(11B)-C(11)-H(11C)	109.5
H(4A)-C(4)-H(4B)	108.5	C(13)-C(12)-C(17)	119.2(3)
C(6)-C(5)-O(2)	110.0(2)	C(13)-C(12)-N(2)	119.9(3)
C(6)-C(5)-C(4)	133.4(3)	C(17)-C(12)-N(2)	120.9(3)
O(2)-C(5)-C(4)	116.5(3)	C(14)-C(13)-C(12)	118.9(3)
C(5)-C(6)-C(7)	106.6(3)	C(14)-C(13)-H(13)	120.5
C(5)-C(6)-H(6)	126.7	C(12)-C(13)-H(13)	120.5
C(7)-C(6)-H(6)	126.7	C(15)-C(14)-C(13)	123.9(3)
C(8)-C(7)-C(6)	107.0(3)	C(15)-C(14)-Cl(1)	119.1(2)
C(8)-C(7)-H(7)	126.5	C(13)-C(14)-Cl(1)	117.0(2)
C(6)-C(7)-H(7)	126.5	C(14)-C(15)-C(16)	115.9(3)
C(7)-C(8)-O(2)	109.5(3)	C(14)-C(15)-C(18)	122.9(3)
C(7)-C(8)-C(9)	135.6(3)	C(16)-C(15)-C(18)	121.3(3)
O(2)-C(8)-C(9)	114.9(3)	C(17)-C(16)-C(15)	122.2(3)
N(3)-C(9)-C(8)	113.3(2)	C(17)-C(16)-H(16)	118.9
N(3)-C(9)-H(9A)	108.9	C(15)-C(16)-H(16)	118.9
C(8)-C(9)-H(9A)	108.9	C(16)-C(17)-C(12)	119.9(3)
N(3)-C(9)-H(9B)	108.9	C(16)-C(17)-H(17)	120.0
C(8)-C(9)-H(9B)	108.9	C(12)-C(17)-H(17)	120.0
H(9A)-C(9)-H(9B)	107.7	C(15)-C(18)-H(18A)	109.5
N(3)-C(10)-H(10A)	109.5	C(15)-C(18)-H(18B)	109.5
N(3)-C(10)-H(10B)	109.5	H(18A)-C(18)-H(18B)	109.5
H(10A)-C(10)-H(10B)	109.5	C(15)-C(18)-H(18C)	109.5
N(3)-C(10)-H(10C)	109.5	H(18A)-C(18)-H(18C)	109.5
H(10A)-C(10)-H(10C)	109.5	H(18B)-C(18)-H(18C)	109.5

Table S4. Anisotropic displacement parameters ($Å^2$ x 10^3) for ***CAP1***. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	32(1)	56(1)	45(1)	0(1)	4(1)	-3(1)
S(1)	36(1)	33(1)	43(1)	-6(1)	0(1)	1(1)
O(1)	42(1)	28(1)	42(1)	-1(1)	-2(1)	0(1)
O(2)	36(1)	36(1)	34(1)	1(1)	4(1)	-1(1)
N(1)	35(1)	28(1)	33(1)	-2(1)	0(1)	2(1)
N(2)	37(1)	25(1)	42(2)	1(1)	0(1)	0(1)
N(3)	34(1)	37(1)	40(2)	3(1)	4(1)	0(1)
C(1)	36(1)	31(1)	31(2)	1(1)	7(1)	1(1)
C(2)	32(1)	31(1)	40(2)	2(1)	5(1)	0(1)
C(3)	33(1)	35(1)	39(2)	-3(1)	1(1)	0(1)
C(4)	36(1)	32(1)	42(2)	-3(1)	3(1)	1(1)
C(5)	35(1)	29(1)	38(2)	0(1)	6(1)	-2(1)
C(6)	39(1)	42(2)	43(2)	2(1)	8(1)	-1(1)
C(7)	40(2)	42(2)	38(2)	-3(1)	6(1)	-3(1)
C(8)	34(1)	34(1)	35(2)	-4(1)	2(1)	-1(1)
C(9)	37(1)	36(1)	39(2)	-1(1)	5(1)	-2(1)
C(10)	43(2)	47(2)	44(2)	1(1)	11(1)	1(1)
C(11)	34(1)	54(2)	40(2)	1(2)	-1(1)	1(1)
C(12)	39(1)	28(1)	35(2)	-6(1)	4(1)	1(1)
C(13)	39(1)	34(1)	34(2)	-4(1)	3(1)	-2(1)
C(14)	32(1)	37(1)	39(2)	-7(1)	5(1)	-2(1)
C(15)	38(1)	37(1)	37(2)	-3(1)	1(1)	3(1)
C(16)	40(2)	36(2)	39(2)	1(1)	4(1)	-2(1)
C(17)	35(1)	36(1)	41(2)	-4(1)	6(1)	-3(1)
C(18)	41(2)	46(2)	46(2)	4(2)	2(1)	3(1)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for ***CAP1***.

Atom	x	y	z	U(iso)
H(1)	5301(9)	12320(80)	5370(30)	39
H(2)	5815(9)	12170(80)	6590(40)	42
H(2A)	4800	10479	4460	41
H(2B)	4938	7367	5001	41
H(3A)	5307	7278	3339	43
H(3B)	5094	10058	2740	43
H(4A)	4304	9188	2701	44
H(4B)	4447	10015	1418	44
H(6)	4069	7286	-730	49
H(7)	3562	3624	-947	48
H(9A)	3333	-39	949	45
H(9B)	3551	530	2324	45
H(10A)	2894	-746	2435	66
H(10B)	2744	2095	3031	66
H(10C)	3122	867	3610	66
H(11A)	2970	4832	230	65
H(11B)	2665	4793	1073	65
H(11C)	2768	1864	412	65
H(13)	6501	10976	6814	43
H(16)	6224	4591	9911	46
H(17)	5779	6754	8516	45
H(18A)	7091	4210	9740	67
H(18B)	6819	3703	10699	67
H(18C)	7036	6677	10746	67

Table S6. Torsion angles [°] for ***CAP1***.

C(2)-N(1)-C(1)-O(1)	1.7(5)
C(2)-N(1)-C(1)-N(2)	-177.9(3)
C(12)-N(2)-C(1)-O(1)	-6.8(5)
C(12)-N(2)-C(1)-N(1)	172.7(3)
C(1)-N(1)-C(2)-C(3)	-83.9(3)
N(1)-C(2)-C(3)-S(1)	168.33(19)
C(4)-S(1)-C(3)-C(2)	72.3(2)
C(3)-S(1)-C(4)-C(5)	179.6(2)
C(8)-O(2)-C(5)-C(6)	0.2(3)
C(8)-O(2)-C(5)-C(4)	-177.8(2)
S(1)-C(4)-C(5)-C(6)	-97.6(4)
S(1)-C(4)-C(5)-O(2)	79.7(3)
O(2)-C(5)-C(6)-C(7)	0.1(3)
C(4)-C(5)-C(6)-C(7)	177.5(3)
C(5)-C(6)-C(7)-C(8)	-0.3(3)
C(6)-C(7)-C(8)-O(2)	0.4(3)
C(6)-C(7)-C(8)-C(9)	179.9(3)
C(5)-O(2)-C(8)-C(7)	-0.3(3)
C(5)-O(2)-C(8)-C(9)	-179.9(2)
C(11)-N(3)-C(9)-C(8)	75.6(3)
C(10)-N(3)-C(9)-C(8)	-162.7(3)
C(7)-C(8)-C(9)-N(3)	-95.7(4)
O(2)-C(8)-C(9)-N(3)	83.7(3)
C(1)-N(2)-C(12)-C(13)	128.5(3)
C(1)-N(2)-C(12)-C(17)	-53.5(4)
C(17)-C(12)-C(13)-C(14)	0.2(4)
N(2)-C(12)-C(13)-C(14)	178.3(3)
C(12)-C(13)-C(14)-C(15)	-0.2(5)
C(12)-C(13)-C(14)-Cl(1)	178.4(2)
C(13)-C(14)-C(15)-C(16)	0.6(5)
Cl(1)-C(14)-C(15)-C(16)	-178.0(2)
C(13)-C(14)-C(15)-C(18)	-178.7(3)
Cl(1)-C(14)-C(15)-C(18)	2.7(4)
C(14)-C(15)-C(16)-C(17)	-1.1(5)
C(18)-C(15)-C(16)-C(17)	178.2(3)
C(15)-C(16)-C(17)-C(12)	1.1(5)
C(13)-C(12)-C(17)-C(16)	-0.7(4)
N(2)-C(12)-C(17)-C(16)	-178.7(3)

Table S7. Hydrogen bonds for ***CAP1*** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(1)#1	0.83(4)	2.09(4)	2.835(3)	150(3)
N(2)-H(2)...O(1)#1	0.80(4)	2.16(4)	2.894(3)	154(3)

Symmetry transformations used to generate equivalent atoms:

#1 x, y+1, z