Supporting Information

WATER MEDIATED SYNTHESIS OF BENZAZOLE AND THIOUREA MOTIFS BY REACTING NATURALLY OCCURRING ISOTHIOCYANATE WITH AMINES

Ritika Sharma,¹ Manju Bala,^{1,2} Praveen Kumar Verma,^{1,2} Bikram Singh^{1,2,*}

¹ *Natural Product Chemistry and Process Development Division, CSIR-Institute of Himalayan Bioresource Technology, Palampur, Himachal Pradesh-176061, India.*

² *Academy of Scientific & Innovative Research, New Delhi, India*

Table of content:

General information

Isolation of erucin

General procedure for synthesis of benzazoles analogue of isothiocyanate

General procedure for synthesis of thiourea analogues of erucin

Characterization data of compounds

References

General Information

Erucin was isolated in lab from seeds of *Eruca sativa*. Amino phenols, amino thiols, anilines, phenyl ethyl amines, different isothiocyanates and secondary amines were purchased from Sigma- Aldrich, USA. Silica gel (60- 120 mesh) used for column chromatography was purchased from Sisco Research Laboratories Pvt. Ltd. India, and all other chemicals were purchased from spectrochem, India, Merck, Germany, and Sigma- Aldrich, USA, and were used without further purification. NMR spectra were recorded on a Bruker Avance-300 and 600 spectrometers. Mass spectra were recorded on QTOF- Micro of Water Micromass. The GC-MS analysis was carried out on a Shimadzu (QP2010) series Gas Chromatogram-Mass Spectrometer (Tokyo, Japan), AOC-20i auto-sampler coupled, and a DB-5MS capillary column, (30 m $\times$ 0.25 mm i.d., 0.25 μ m). The initial temperature of column was 70 $^{\circ}$ C, which was held for 4 min and then programmed to 230 $^{\circ}$ C with a heat rate of 4 $^{\circ}$ C min $^{-1}$, and then held for 15 min at 230 $^{\circ}$ C; the sample injection volume was 2 μ l in GC grade dichloromethane. Helium was used as the carrier gas at a flow rate of 1.1 ml min $^{-1}$ on split mode (1: 50). Melting points were determined on a Bronsted Electrothermal 9100.

Isolation of Erucin

Seeds of *Eruca sativa* were crushed and hydro distillation was carried out using distilled water in a Clevenger apparatus for 3 h. Oil was collected in the inner tubes of Clevenger apparatus which was further extracted three times with DCM and passed through anhydrous sodium sulphate.¹ Extracted oil was purified by column chromatography to yield pure erucin (4-methylthiobutylisothiocyanate).

General procedure for synthesis of benzazole analogues of isothiocyanate

The stirred suspension of isothiocyanate (1 mmol), *o*-substituted anilines (1 mmol) in H₂O (5 ml) was refluxed at 120 $^{\circ}$ C for 48 h. On completion (as monitored by TLC), the reaction mixture was extracted with ethyl acetate, filtered, passed through anhydrous Na₂SO₄ and dried under vacuum. The crude product was analyzed by GC-MS and purified by column chromatography over silica-gel (60-120 mesh) with appropriate mixture of *n*-hexane and ethyl acetate. The yields of products were calculated on the basis of isothiocyanate reactants.

General procedure for synthesis of thiourea analogues of erucin

The stirred suspension of erucin (1 mmol), amines (1 mmol) in H₂O (5 ml) was refluxed at 120 $^{\circ}$ C for 48 h. On completion (as monitored by TLC), the reaction mixture was extracted with ethyl acetate, filtered, passed through anhydrous Na₂SO₄ and dried under vacuum. The crude

product was analyzed by GC-MS and purified by column chromatography over silica-gel (60-120 mesh) with appropriate mixture of *n*-hexane and ethyl acetate. The yields of products were calculated on the basis of erucin reactant.

Characterization data of compounds

Erucin (4-methylthiobutylisothiocyanate)¹

Erucin was isolated as colorless oil. Purity was checked by GC analysis and was found 99% pure.

¹H NMR (600 MHz, CDCl₃): δ 3.51-3.55 (m, 2H), 2.47-2.50 (m, 2H), 2.05 (s, 3H), 1.69-1.79 (m, 4H).

¹³C NMR (150 MHz, CDCl₃): δ 129.8, 44.6, 33.1, 28.7, 25.6, 15.2.

***N*-(4-(Methylthio)butyl)benzo[d]thiazol-2-amine (Table 2, entry 3a):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as yellow powder.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.60 (d, *J* = 6.0 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.21-7.23 (m, 1H), 7.10 (s, NH), 7.00-7.02 (m, 1H), 3.50-3.55 (m, 2H), 2.84 (s, 2H), 2.50-2.55 (m, 3H), 1.71-1.85 (m, 4H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 166.4, 153.2, 130.7, 125.4, 121.0, 120.9, 118.4, 44.0, 33.3, 28.3, 26.3, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₂H₁₆N₂S₂ [M+H]⁺ 253.0828, found 253.0817.

IR (KBr) (cm⁻¹): 2958, 2918, 2856, 1730, 1598, 1543, 1442, 1282, 1122, 1016, 873, 750.

Mp: 42-44 °C

***5-Chloro-N*-(4-(methylthio)butyl)benzo[d]thiazol-2-amine (Table 2, entry 3b):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as yellow oily liquid.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.61-7.62 (d, *J* = 6.0 Hz, 1H), 7.39 (s, 1H), 7.31 (s, NH), 7.02 (d, *J* = 6.0 Hz, 1H), 3.50-3.51 (m, 2H), 2.82-2.85 (m, 2H), 2.51-2.55 (m, 3H), 1.76-1.81 (m, 2H), 1.69-1.73 (m, 2H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 168.0, 154.5, 130.9, 129.3, 121.6, 120.7, 117.9, 44.0, 33.3, 28.2, 26.2, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₂H₁₅ClN₂S₂ [M+H]⁺ 287.0438, found 287.0429.

IR (KBr) (cm⁻¹): 2956, 2926, 2854, 1726, 1600, 1562, 1543, 1462, 1377, 1269, 1122, 1070, 918, 738.

***N*-(4-(Methylthio)butyl)benzo[d]oxazole-2-amine (Table 3, entry 3c):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid brown precipitates.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.21 (d, *J* = 6.0 Hz, 2H), 7.07-7.10 (m, 1H), 6.94-6.96 (m, 1H), 6.89 (s, NH), 3.44-3.47 (m, 2H), 2.83 (s, 3H), 2.49-2.53 (m, 2H), 1.75-1.79 (m, 2H), 1.69-1.71 (m, 2H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 162.6, 148.6, 143.9, 123.4, 120.1, 115.78, 108.2, 42.3, 33.3, 28.5, 26.1, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₂H₁₆N₂OS [M+H]⁺ 237.1056, found 237.1041.

IR (KBr) (cm⁻¹): 2939, 1689, 1643, 1581, 1460, 1244, 1031, 891, 742.

Mp: 86-89 °C.

***5-Chloro-N*-(4-(methylythio)butyl)benzo[d]oxazole-2-amine (Table 2, entry 3d):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid orange powder.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.21-7.24 (m, 2H), 7.13 (s, NH), 6.97 (d, *J* = 8.4 Hz, 1H), 3.45-3.51 (m, 2H), 2.83 (s, 3H), 2.50-2.54 (m, 2H), 1.75-1.81 (m, 2H), 1.68-1.71 (m, 2H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 163.7, 147.4, 145.5, 128.4, 119.8, 115.5, 109.1, 42.3, 43.2, 33.3, 26.1, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₂H₁₅ClN₂OS [M+H]⁺ 271.0606, found 271.0651.

IR (KBr) (cm⁻¹): 2940, 1681, 1658, 1573, 1446, 1371, 1251, 1182, 1018, 918, 794.

Mp: 51-53 °C

5-Methyl-N-(4-(methylthio)butyl)benzo[d]oxazole-2-amine (Table 3, entry 3e): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid brown crystals.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.08-7.10 (m, 1H), 7.05 (s, 1H), 6.83 (s, NH), 6.77-6.78 (m, 1H), 2.43-3.47 (m, 2H), 2.52-2.55 (m, 2H), 2.33 (s, 3H), 2.04 (s, 3H, overlapped with solvent), 1.75-1.80 (m, 2H), 1.68-1.72 (m, 2H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 162.7, 146.8, 144.0, 132.8, 120.6, 116.2, 107.6, 42.3, 33.3, 26.1, 20.5, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₂H₁₅ClN₂OS [M+H]⁺ 251.1213, found 251.1202.

IR (KBr) (cm⁻¹): 2933, 2845, 1658, 1585, 1548, 1467, 1332, 1259, 1184, 1028, 950, 794.

Mp: 67-70 °C.

4-Methyl-N-(4-(methylthio)butyl)benzo[d]oxazole-2-amine (Table 3, entry 3f): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid dark orange crystalline powder.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.06 (d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.85-6.87 (m, 1H + NH), 3.46-3.49 (m, 2H), 2.52-2.55 (m, 2H), 2.39 (s, 3H), 2.04 (s, 3H, overlapped with solvent), 1.76-1.81 (m, 2H), 1.68-1.72 (m, 2H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 162.1, 148.1, 142.5, 125.7, 124.2, 119.9, 105.7, 42.3, 33.3, 28.5, 26.2, 15.5, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₃H₁₈N₂OS [M+H]⁺ 251.1213, found 251.1203.

IR (KBr) (cm⁻¹): 2930, 1668, 1639, 1585, 1423, 1373, 1338, 1244, 1172, 1099, 1066, 1029, 933, 875, 740.

Mp: 63-66 °C.

N-(4-(Methylthio)butyl)-5-nitrobenzo[d]oxazole-2-amine (Table 3, entry 3g): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as yellow precipitates.

¹H NMR (600 MHz, CD₃COCD₃): δ 8.02 (s, 1H), 7.96-7.98 (m, 1H), 7.46-7.47 (s, 1H), 3.50-3.54 (m, 2H), 2.52-2.55 (m, 2H), 2.08 (s, 3H), 1.78-1.81 (m, 2H), 1.70-1.74 (m, 2H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 164.5, 152.8, 145.0, 144.8, 116.6, 110.5, 108.3, 42.4, 33.2, 28.2, 26.0, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₂H₁₅N₂O₃S [M+H]⁺ 282.0907, found 282.0901.

IR (KBr) (cm⁻¹): 2927, 1681, 1583, 1516, 1458, 1435, 1338, 1251, 1120, 956, 866, 736.

Mp: 60-62 °C.

4-Methyl-N-phenethylbenzo[d]oxazole-2-amine (Table 3, entry 6a): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid orange crystals.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.31-7.33 (m, 2H), 7.23-7.26 (m, 3H), 7.07-7.09 (m, 1H), 6.97-6.98 (m, 1H), 6.92-6.94 (m, 1H), 5.29 (s, NH), 3.75-3.77 (m, 2H), 2.97-2.99 (m, 2H), 2.49 (s, 3H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 161.4, 148.1, 141.8, 138.3, 128.8, 128.7, 126.7, 126.5, 124.7, 120.4, 106.2, 44.1, 35.9, 16.4.

HRMS (ESI-TOF) *m/z* calculated for C₁₆H₁₆N₂O [M+H]⁺ 253.1335, found 253.1329.

IR (KBr) (cm⁻¹): 2927, 1643, 1587, 1452, 1371, 1344, 1261, 1244, 1188, 1101, 1012, 937, 877, 744.

Mp: 135-138 °C.

4-Methyl-N-m-tolylbenzo[d]oxazol-2-amine (Table 3, entry 6b): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid red precipitates.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.40-7.42 (m, 1H), 7.34 (s, 1H), 6.91-6.94 (m, 1H), 6.84-6.86 (m, 1H), 6.66-6.73 (m, 2H), 6.54-6.55 (m, 1H), 2.73 (s, 3H), 2.35 (s, 3H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 157.5, 147.1, 141.8, 139.1, 138.5, 128.9, 126.9, 124.5, 122.9, 121.4, 118.2, 114.8, 106.1, 20.7, 15.4.

HRMS (ESI-TOF) *m/z* calculated for C₁₅H₁₄N₂O [M+H]⁺ 239.1179, found, 239.1165.

IR (KBr) (cm⁻¹): 1635, 1602, 1571, 1479, 1340, 1242, 1213, 1168, 1072, 1031, 975, 744.

Mp: 45-47 °C.

4-methyl-N-phenylbenzo[d]oxazol-2-amine (Table 3, entry 6c) Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid orange powder.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.36-7.39 (m, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 6.99-7.05 (m, 3H), 2.98 (s, NH), 2.50 (s, 3H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 157.5, 147.1, 141.8, 139.1, 128.9, 127.0, 124.6, 122.1, 121.4, 117.6, 106.1, 15.5.

HRMS (ESI-TOF) *m/z* calculated for C₁₄H₁₂N₂O [M+H]⁺ 225.1022, found, 225.1012.

IR (KBr) (cm⁻¹): 1639, 1568, 1483, 1367, 1244, 1203, 1076, 1031, 968, 833, 744.

Mp: 119-121 °C.

N-(3-Chlorophenyl)-4-methylbenzo[d]oxazole-2-amine (Table 3, entry 6d): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid light orange powder.

¹H NMR (600 MHz, CD₃COCD₃): δ 8.10-8.11 (m, 1H), 7.73-7.75 (m, 1H), 7.36-7.39 (m, 1H), 7.19-7.21 (m, 1H), 7.02-7.07 (m, 3H), 2.53 (s, 3H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 156.9, 147.1, 141.4, 140.5, 134.1, 130.3, 127.3, 124.7, 121.9, 117.2, 115.9, 106.2, 15.4.

HRMS (ESI-TOF) *m/z* calculated for C₁₄H₁₁ClN₂O [M+H]⁺ 259.0560, found, 259.0624.

IR (KBr) (cm⁻¹): 1645, 1589, 1556, 1456, 1361, 1342, 1244, 1203, 1031, 979, 860, 746.

Mp: 116-118 °C.

N-Cyclohexyl-4-methylbenzo[d]oxazole-2-amine (Table 3, entry 6e): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid orange powder.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.03-7.04 (s, 1H), 6.90-6.92 (m, 1H), 6.83-6.86 (m, 1H), 3.72 (s, NH), 2.88 (m, 2H), 2.38 (s, 3H), 1.77-1.79 (m, 2H), 1.62-1.63 (m, 1H), 1.36-1.42 (m, 4H), 1.21-1.23 (m, 2H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 161.3, 148.0, 142.6, 125.8, 124.2, 119.7, 113.3, 105.6, 51.9, 32.8, 25.4, 24.7, 15.5.

HRMS (ESI-TOF) m/z calculated for $C_{14}H_{18}N_2O$ $[M+H]^+$ 231.1492, found, 231.1484.

IR (KBr) (cm^{-1}): 2927, 2856, 1639, 1618, 1587, 1234, 1068, 1031, 746.

Mp: 77-80 °C.

N-m-Tolylbenzo[d]thiazol-2-amine (Table 3, entry 6f): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid brown precipitates.

1H NMR (600MHz, CD_3COCD_3): δ 7.74 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.60-7.63 (m, 2H), 7.32-7.35 (m, 1H), 7.23-7.26 (m, 1H), 7.14-7.17 (m, 1H), 6.88 (d, J = 6.0 Hz, 1H), 2.88 (s, NH), 2.34 (s, 3H).

^{13}C NMR (150MHz, CD_3COCD_3): δ 161.9, 152.6, 140.8, 138.6, 130.4, 128.8, 125.8, 123.2, 122.3, 120.7, 119.5, 118.8, 115.5, 20.7.

HRMS (ESI-TOF) m/z calculated for $C_{14}H_{12}N_2S$ $[M+H]^+$ 241.0794, found, 241.0784.

IR (KBr) (cm^{-1}): 1622, 1568, 1489, 1446, 1273, 1246, 1031, 879, 744.

Mp: 97-99 °C.

N-Phenylbenzo[d]thiazol-2-amine (Table 3, entry 6g): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid light yellow crystals.

1H NMR (600 MHz, CD_3COCD_3): δ 7.84-7.87 (m, 2H), 7.72-7.74 (m, 1H), 7.62-7.64 (m, 1H), 7.32-7.38 (m, 3H), 7.14-7.17 (m, 1H), 7.04-7.05 (m, 1H), 2.97 (s, NH).

^{13}C NMR (600 MHz, CD_3COCD_3): δ 161.9, 152.7, 140.9, 130.4, 128.9, 125.8, 122.4, 120.7, 119.6, 118.2.

HRMS (ESI-TOF) m/z calculated for $C_{13}H_{10}N_2S$ $[M+H]^+$ 227.0637, found, 227.0628.

IR (KBr) (cm^{-1}): 1620, 1550, 1247, 1018, 920, 742.

Mp: 156-158 °C; (Lit.²: 158-160)

N-(3-Chlorophenyl)benzo[d]thiazol-2-amine (Table 3, entry 6h): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid brown precipitates.

¹H NMR (600 MHz, CD₃COCD₃): δ 8.15 (s, 1H), 7.68-7.76 (m, 1H), 7.65-7.67 (m, 2H), 7.34-7.38 (m, 2H), 7.18-7.20 (m, 1H), 7.04-7.06 (m, 1H) 2.91 (s, NH).

¹³C NMR (150 MHz, CD₃COCD₃): δ 161.3, 152.4, 142.2, 134.1, 130.4, 130.3, 125.9, 122.8, 121.9, 120.8, 119.9, 117.6, 116.2.

HRMS (ESI-TOF) *m/z* calculated for C₁₃H₉ClN₂S [M+H]⁺ 261.0248, found, 261.0239.

IR (KBr) (cm⁻¹): 1622, 1593, 1566, 1462, 1444, 1321, 1269, 1022, 939, 858, 740.

Mp: 157-159 °C.

***N*-Cyclohexylbenzo[d]thiazol-2-amine (Table 3, entry 6i):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as orange oily compound.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.4, 1H), 7.20-7.22 (m, 1H), 6.99-7.01 (m, 1H + NH), 2.09-2.11 (m, 2H), 1.75-1.78 (m, 2H), 1.61-1.63 (m, 1H), 1.33-1.42 (m, 4H), 1.17-1.23 (m, 2H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 165.5, 153.2, 130.6, 125.4, 120.6, 120.5, 118.3, 53.4, 32.7, 25.5, 24.7.

HRMS (ESI-TOF) *m/z* calculated for C₁₃H₁₆N₂S [M+H]⁺ 233.1107, found, 233.1117.

IR (KBr) (cm⁻¹): 2929, 2854, 1595, 1537, 1440, 1365, 1205, 1022, 885, 748.

***1*-Benzyl-3-(4-(methylthio)butyl)thiourea (Table 4, entry 8a):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as yellow oily compound.

¹H NMR (600 MHz, CD₃COCD₃): δ 8.81 (s, NH), 7.40 (d, *J* = 7.8 Hz, 2H), 7.32-7.35 (m, 2H), 7.25 (s, NH), 7.13-7.16 (m, 1H), 3.62-3.65 (m, 2H), 2.85 (s, 2H), 2.49-2.52 (m, 3H), 1.69-1.74 (m, 2H), 1.62-1.64 (m, 2H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 181.4, 138.7, 129.3, 124.9, 124.0, 44.0, 33.4, 28.0, 26.3, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₃H₂₀N₂S₂ [M+H]⁺ 269.1132, found 269.1141.

IR (KBr) (cm⁻¹): 2916, 2852, 1589, 1537, 1450, 1315, 1238, 1028, 806, 748.

1-(2,3-dimethylphenyl)-3-(4-(methylthio)butyl)thiourea (Table 4, entry 8b): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid white powder.

¹H NMR (300 MHz, CDCl₃): δ 7.77 (s, NH), 7.03-7.27 (m, 3H), 5.63 (s, NH), 3.58-3.62 (m, 2H), 2.45-2.49 (m, 2H), 2.31 (s, 3H), 2.17 (s, 3H), 2.03 (s, 3H), 1.60 (s, 4H).

¹³C NMR (75 MHz, CDCl₃): δ 181.4, 139.6, 135.1, 134.5, 130.5, 127.2, 125.7, 45.2, 34.1, 28.6, 26.5, 20.8, 15.8, 14.5.

HRMS (ESI-TOF) *m/z* calculated for C₁₄H₂₂N₂S₂ [M+H]⁺ 283.1297, found, 283.1283.

IR (KBr) (cm⁻¹): 2914, 2852, 1540, 1531, 1462, 1261, 1217, 1165, 1101, 1031, 958, 810, 713.

Mp: 55-58 °C.

1-(Benzo[d]thiazol-2-yl)-3-(3-(methylthio)butyl)thiourea (Table 4, entry 8c): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid white crystals.

¹H NMR (600 MHz, CDCl₃): δ 7.69 -7.72 (m, 2H), 7.40-7.42 (m, 1H), 7.26-7.29 (m, 1H), 3.82-3.85 (m, 2H), 2.59-2.62 (m, 2H), 2.11 (s, 3H, overlapped with solvent signal), 1.89-1.94 (m, 2H), 1.78-1.82 (m, 2H).

¹³C NMR (150 MHz, CDCl₃) δ 177.8, 160.3, 149.5, 129.8, 126.5, 124.4, 121.2, 120.6, 45.2, 33.8, 27.7, 26.5, 15.5.

HRMS (ESI-TOF) *m/z* calculated for C₁₃H₁₇N₃S₃ [M+H]⁺ 312.0657, found, 312.0649.

IR (KBr) (cm⁻¹): 1554, 1525, 1440, 1338, 1269, 1197, 1031, 744.

Mp: 99-101 °C.

1-(3,4-Dimethoxyphenethyl)-3-(4-(methylthio)butyl)thiourea (Table 4, entry 8d): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography yellow oily compound.

¹H NMR (600 MHz, CD₃COCD₃): δ 6.97 (s, NH), 6.83-6.86 (m, 2H + NH), 6.73-6.74 (m, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.70 (s, 2H), 3.50 (s, 2H), 2.80-2.86 (m, 3H), 2.47-2.50 (m, 2H), 2.07 (s, 2H), 1.60-1.66 (m, 4H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 183.1, 149.4, 148.0, 132.1, 120.7, 113.0, 112.1, 55.4, 55.2, 45.4, 43.4, 34.7, 33.4, 26.3, 14.3.

HRMS (ESI-TOF) m/z calculated for $C_{16}H_{26}N_2O_2S_2 [M+H]^+$ 343.1436, found, 343.1501.

IR (KBr) (cm^{-1}): 2962, 2914, 1546, 1514, 1257, 1089, 1018, 860, 794.

1-(2-Fluorophenethyl)-3-(4-(methylthio)butyl)thiourea (Table 4, entry 8e): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography solid white compound.

1H NMR (600 MHz, CD_3COCD_3): δ 7.29-7.32 (m, 1H), 7.22-7.26 (m, 1H), 7.10-7.12 (m, 1H), 7.04-7.07 (m, 1H), 6.97-6.99 (m, 2 x NH), 3.75 (s, 2H), 3.50 (s, 2H), 2.94-2.96 (m, 2H), 2.48-2.50 (m, 2H), 2.04 (s, 3H, overlapped with solvent signal), 1.59-1.67 (m, 4H).

^{13}C NMR (150 MHz, CD_3COCD_3): δ 183.2, 161.2 (d, $J = 243$ Hz), 131.3, (d, $J = 4.5$ Hz), 128.2 (d, $J = 7.5$ Hz), 126.2 (d, $J = 16.5$ Hz), 124.2 (d, $J = 4.5$ Hz), 115.0 (d, $J = 22.5$ Hz), 43.9, 43.3, 33.4, 26.2, 14.4.

HRMS (ESI-TOF) m/z calculated for $C_{14}H_{21}FN_2S_2 [M+H]^+$ 301.1203, found, 301.1212.

IR (KBr) (cm^{-1}): 3199, 2927, 2858, 1550, 1516, 1490, 1469, 1438, 1228, 1190, 1120, 1031, 999, 752.

Mp: 40-42 °C.

1-(2-Bromophenethyl)-3-(4-(methylthio)butyl)thiourea (Table 4, entry 8f): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography yellow oily compound.

1H NMR (600 MHz, CD_3COCD_3): δ 7.55-7.56 (m, 1H), 7.35-7.36 (m, 1H), 7.29-7.32 (m, 1H), 7.13-7.16 (m, 1H), 6.98-6.99 (s, 2 x NH), 3.76 (s, 2H), 3.50 (s, 2H), 3.04-3.07 (m, 2H), 2.48-2.50 (m, 2H), 2.05 (s, 3H, overlapped with solvent signal), 1.59-1.67 (m, 4H).

^{13}C NMR (150 MHz, CD_3COCD_3): δ 182.0, 138.8, 132.8, 131.2, 128.2, 127.7, 124.1, 43.6, 35.3, 33.4, 26.2, 14.4.

HRMS (ESI-TOF) m/z calculated for $C_{14}H_{21}BrN_2S_2 [M+H]^+$ 361.0402, found, 361.0417.

IR (KBr) (cm^{-1}): 2914, 2854, 1546, 1539, 1469, 1435, 1282, 1026, 956, 748.

1-(4-(Methylthio)butyl)-3-phenethylthiourea (Table 4, entry 8g): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography solid white compound.

¹H NMR (300 MHz, CDCl₃): δ 7.22-7.31 (m, 5H), 6.00-6.11 (m, 2 x NH), 2.73 (s, 2H), 3.31 (s, 2H), 2.91-2.93 (m, 2H), 2.48 (s, 2H), 2.06 (s, 3H, overlapped with solvent signal), 1.61 (s, 4H).

¹³C NMR (75 MHz, CDCl₃): δ 182.0, 138.8, 129.1, 127.1, 46.0, 44.0, 35.6, 34.1, 28.1, 26.4, 15.8.

HRMS (ESI-TOF) *m/z* calculated for C₁₄H₂₂N₂S₂ [M+H]⁺ 283.1297, found, 283.1285.

IR (KBr) (cm⁻¹): 3203, 2935, 2852, 1550, 1516, 1433, 1246, 1184, 1109, 1029, 777, 742.

Mp: 37-39 °C.

1-(4-Methoxyphenethyl)-3-(4-(methylthio)butyl)thiourea (Table 4, entry 8h): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography yellow oily compound.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.14-7.15 (m, 2H), 6.97 (s, NH), 6.83-6.87 (m, 2H + NH), 3.77 (s, 3H), 3.68 (s, 2H), 3.50 (s, 2H), 2.81-2.86 (m, 2H), 2.48-2.50 (m, 2H), 2.04 (s, 3H), 1.59-1.67 (m, 4H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 183.48, 158.3, 131.4, 129.6, 113.7, 54.5, 46.04, 43.27, 34.3, 33.4, 26.2, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₆H₂₆N₂OS₂ [M+H]⁺ 313.1403, found, 313.1410.

IR (KBr) (cm⁻¹): 2941, 2845, 1612, 1546, 1510, 1444, 1346, 1242, 1176, 1026, 817, 765.

1-(4-Hydroxyphenethyl)-3-(4-(methylthio)butyl)thiourea (Table 4, entry 8i): Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography yellow oily compound.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.04-7.05 (m, 2H), 6.95 (s, NH), 6.84 (s, NH), 6.73-6.76 (m, 2H), 3.66 (s, 2H), 3.50 (s, 2H), 2.77-2.79 (m, 2H), 2.48-2.50 (m, 2H), 2.05 (s, 3H, overlapped with solvent signal), 1.64-1.66 (4H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 183.8, 155.8, 129.6, 115.1, 45.6, 43.2, 33.4, 26.3, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₂H₁₈N₂S₂ [M+H]⁺ 255.0984, found, 255.0972.

IR (KBr) (cm⁻¹): 2933, 2862, 1612, 1548, 1512, 1440, 1346, 1242, 1217, 1105, 1018, 823, 715.

***N*¹, *N*⁴-Bis(4-(methylthio)butyl)piperazine-1,4-bis(carothioamide) (Table 5, entry 10a):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as pale yellow compound.

¹H NMR (600 MHz, CD₃COCD₃): δ 6.85 (s, 2 x NH), 3.86 (s, 12H), 3.49-3.52 (m, 3H), 2.66-2.69 (m, 4H), 2.34-2.37 (m, 3H), 1.54-1.59 (m, 4H), 1.45-1.49 (m, 4H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 182.3, 45.6, 44.9, 33.4, 28.2, 26.2, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₆H₃₂N₄S₄ [M+H]⁺ 409.1583, found 409.1579.

IR (KBr) (cm⁻¹): 3302, 2922, 2852, 1743, 1525, 1411, 1359, 1327, 1199, 997, 887, 798, 734.

Mp: 56-58 °C.

***N*-(4-(Methylthio)butyl)-4-(4-nitrophenyl)piperazine-1-carbothioamide (Table 5, entry 10b):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as solid orange powder.

¹H NMR (600 MHz, CD₃COCD₃): δ 8.09-8.12 (m, 2H), 6.94-6.96 (m, 2H), 5.76 (s, NH), 4.09-4.11 (m, 4H), 3.63-3.71 (m, 6H), 2.52-2.56 (m, 2H), 2.09 (s, 3H, overlapped with solvent signal), 1.67-1.77 (m, 4H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 182.4, 154.3, 137.8, 125.5, 111.8, 45.9, 45.4, 45.0, 33.5, 28.2, 26.3, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₆H₂₄N₄O₂S₂ [M+H]⁺ 369.1413, found 369.1408.

IR (KBr) (cm⁻¹): 1597, 1537, 1485, 1311, 1244, 1116, 1006, 933, 825, 752.

Mp: 94-97 °C.

***N*-(4-(Methylthio)butyl)pyrrolidine-1-carbothioamide (Table 5, entry 10c):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as colourless crystals.

¹H NMR (600 MHz, CD₃COCD₃): δ 6.56 (s, NH), 3.54-3.61 (m, 6H), 2.48-2.50 (m, 2H), 2.05 (s, 3H, overlapped with solvent signal), 1.92 (s, 4H), 1.65-1.70 (m, 4H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 179.3, 44.4, 44.2, 33.5, 26.3, 25.0, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₀H₂₀N₂S₂ [M+H]⁺ 232.1141, found 232.1134.

IR (KBr) (cm⁻¹): 2926, 2845, 1745, 1535, 1413, 1386, 1355, 1259, 1182, 1031, 958, 896, 761.

Mp: 61-63 °C.

***N*-(4-Methylthio)butyl)morpholine-4-carbothioamide (Table 5, entry 10d):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as colourless oily compound.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.09 (s, NH), 3.61-3.79 (m, 10H), 3.85-3.88 (m, 3H), 2.47-2.52 (m, 2H), 1.57-1.75 (m, 4H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 183.8, 66.3, 47.9, 45.5, 33.8, 26.6, 14.7.

HRMS (ESI-TOF) *m/z* calculated for C₁₀H₂₀N₂OS₂ [M+H]⁺ 249.1090, found 249.1081.

IR (KBr) (cm⁻¹): 2906, 2850, 1525, 1382, 1330, 1271, 1228, 1111, 1020, 885, 839.

***4*-Hydroxy-*N*-(4-(methylthio)butyl)piperidine-1-carbothioamide (Table 5, entry 10e):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as yellow oily compound.

¹H NMR (600 MHz, CD₃COCD₃): δ 7.00 (s, NH), 4.24-4.27 (m, 2H), 3.86 (s, 1H), 3.61-3.63 (m, 2H), 3.44-3.49 (m, 2H), 2.48-2.50 (m, 2H), 2.05 (s, 3H, overlapped with solvent signal), 1.78-1.81 (m, 2H), 1.67-1.70 (m, 2H), 1.58-1.60 (m, 2H), 1.43-1.45 (m, 2H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 181.9, 66.2, 45.2, 44.8, 33.9, 33.5, 28.2, 26.3, 14.3.

HRMS (ESI-TOF) *m/z* calculated for C₁₁H₂₂N₂OS₂ [M+H]⁺ 263.1246, found 263.1237.

IR (KBr) (cm⁻¹): 2927, 2846, 1531, 1384, 1327, 1211, 1056, 1022, 972, 862, 808.

***4*-Methyl-*N*-(4-(methylthio)butyl)piperidine-1-carbothioamide (Table 5, entry 10f):** Product was synthesized using general experimental procedure and isolated from crude reaction mixture after column chromatography as oily compound.

¹H NMR (600 MHz, CD₃COCD₃): δ 6.95 (s, NH), 4.69-4.72 (m, 2H), 3.61-3.64 (m, 2H), 2.90-2.94 (m, 2H), 2.48-2.50 (m, 2H), 2.05 (s, 3H, overlapped with solvent signal), 1.56-1.71 (m, 8H), 1.05-1.12 (m, 2H), 0.91-0.92 (m, 3H).

¹³C NMR (150 MHz, CD₃COCD₃): δ 181.9, 47.7, 45.1, 33.7, 33.5, 30.9, 28.3, 26.3, 21.1, 14.4.

HRMS (ESI-TOF) *m/z* calculated for C₁₂H₂₄N₂S₂ [M+H]⁺ 261.1454, found 261.1443.

IR (KBr) (cm⁻¹): 2914, 2862, 1529, 1382, 1301, 1220, 1128, 1082, 968, 956, 862.

References

1. Ganin, H.; Rayo, J.; Amara, N.; Levi, N.; Krief, P.; Meijler, M. M. *Med. Chem. Commun.*, **2013**, *4*, 175.
2. Ding, Q.; Cao, B.; Liu, X.; Zhong, Z.; Peng, Y. Y. *Green Chem.*, **2010**, *12*, 1607.