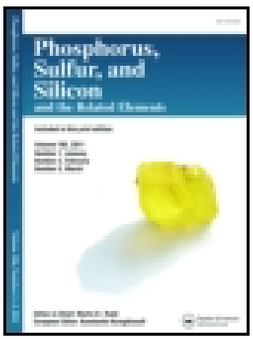

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Ugi reaction of thiouridocarboxylic acids: A synthesis of thiourea-peptoids

Elnaz Ghasemi[a], Ashraf S. Shahvelayati[b], and Issa Yavari[a]

[a]Department of Chemistry, Islamic Azad University, Science and Research Branch, Ponak, Tehran, Iran; [b]Department of Chemistry, Islamic Azad University, Shahr-e Ray Branch, Tehran, Iran

ABSTRACT
Benzoylthioureidocarboxylic acids, prepared from benzoyl chlorides, potassium thiocyanate, and α-aminoacids, are used as acid components in the Ugi reaction to produce thiourea-peptoids in moderate to good yields.

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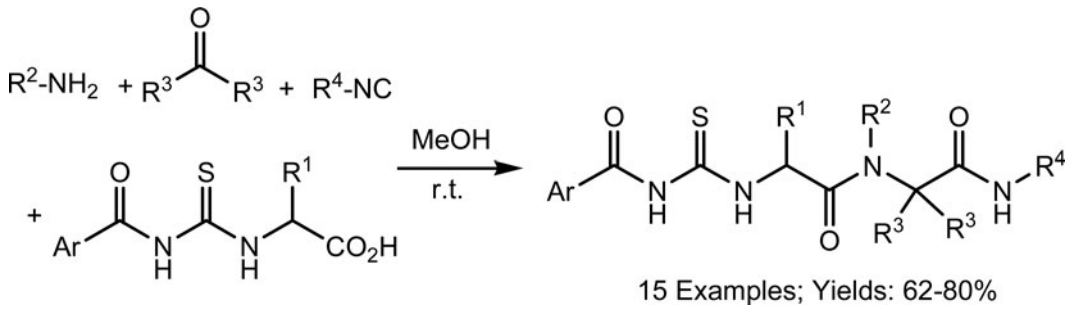
KEYWORDS
Ugi reaction; peptoid; peptide mimics; thioureidocarboxylic acid; isocyanide; α-amino acid

GRAPHICAL ABSTRACT



Introduction

Multicomponent reactions (MCRs) are not only an excellent tool for the creation of chemical diversity, they also represent a powerful methodology for the synthesis of small peptides and their simple analogues.[1] One of the most important MCRs is the Ugi four-component reaction (U-4CR),[2–5] which is of considerable interest owing to its exceptional synthetic efficiency and is widely used in modern combinatorial chemistry. In the U-4CR, an amine, an aldehyde (or ketone), a carboxylic acid and an isocyanide react simultaneously to afford peptide-like structures in high diversity. Small peptides are an important group of compounds in medicinal chemistry. Among them, compounds with various activities are found.[2–7]

Unnatural α-amino acids are important substances for different areas of chemistry,[8–10] and they have a wide biological activity and hence medicinal applications. The replacement of natural amino acids in peptides with nonproteinogenic derivatives has become an important task in synthetic organic chemistry because their incorporation into biologically relevant peptides may influence their properties.[7–10]

Peptoids are a developing class of peptide-like compounds originally invented for drug discovery in the early 1990s.[11,12] Because of their physicochemical features, ease of adaptation to combinatorial chemistry approaches, and their stabilities, they become an important class of peptidomimetics comprised of *N*-alkylglycine units that have been successfully developed for drug discovery process. Consequently, peptoid libraries have found application for discovering hits against a wide diversity of pharmaceutical targets, among which different examples of antibacterials are found.[13–16] As part of our continuing interest in MCRs,[17–21] research efforts addressed towards the synthesis and identification of thiourea-containing peptoids are reported. The synthesis of thiourea-peptoids can be attractive, since the thiourea residue is fairly rigid, and may play an important role in protein secondary structure, and its folding.

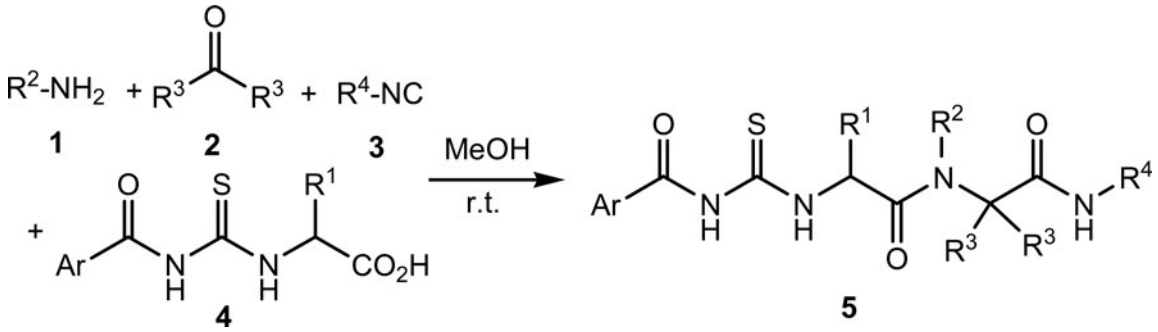
Results and discussion

The U-4CR between amines **1**, ketones **2**, isocyanides **3**, and benzoylthiouridocarboxylic acids **4** proceeded slowly in methanol at room temperature to afford the thioamidodipeptides **5a–o** with 62–80% yields (Table 1). The carboxylic acid **4** was prepared through a cascade reaction of benzoyl chlorides, potassium thiocyanate, and α-amino acids in acetonitrile.[22]

The structure of the compounds **5a–o** was characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data. The IR and ^{1}H NMR spectra of **5a–o** exhibited three characteristic peaks for the NH moieties. The proton decoupled ^{13}C NMR spectra of **5a–o** show four distinct resonances for C = O and C = S groups. The methylene protons of the $ArCH_2N$ groups in **5b–c**, **5f–m**, and **5o–r** are diastereotopic and exhibit characteristic AB-spin systems with significant $\Delta\nu$ values. For example, the

CONTACT Issa Yavari yavarisa@modares.ac.ir Department of Chemistry, Islamic Azad University, Science and Research Branch, Ponak, TehranIran.

Table 1. Formation of thiourea-peptoids **5a–o**.



Entry	Ar	R^1	R^2	R^3	R^4	Product	Yield (%)
1	Ph	Me	Ph	Me	cHex	**5a**	67
2	Ph	Me	Bn	Me	cHex	**5b**	75
3	Ph	^{i}Pr	Bn	Me	cHex	**5c**	73
4	Ph	Me	Et	Me	cHex	**5d**	70
5	Ph	^{i}Pr	Et	Me	cHex	**5e**	65
6	Ph	Me	Bn	Et	cHex	**5f**	62
7	4-$O_2NC_6H_4$	Me	Bn	Me	cHex	**5g**	64
8	*p*-Tol	Me	4-$MeOC_6H_4CH_2$	Me	cHex	**5h**	72
9	Ph	Me	Bn	Me	^{t}Bu	**5i**	77
10	Ph	^{i}Pr	Bn	$(CH_2)_4$	^{t}Bu	**5j**	65
11	Ph	Me	Et	$(CH_2)_4$	^{t}Bu	**5k**	80
12	Ph	H	Bn	$(CH_2)_5$	^{t}Bu	**5l**	78
13	Ph	^{i}Pr	Bn	Me	^{t}Bu	**5m**	80
14	Ph	Me	Et	Me	^{t}Bu	**5n**	68
15	Ph	H	Bn	Et/Me	^{t}Bu	**5o**	72

^{1}H NMR spectrum of **5b** in $CDCl_3$ showed two doublets (δ = 5.65, 11.06 ppm), and a singlet (δ = 8.92 ppm) for NH groups. The methyl protons exhibited a doublet (δ = 1.36 ppm) and two singlets (δ = 1.50 and 1.53 ppm). The methylene protons of **5b** exhibited an ABq (δ = 4.94 ppm, $\Delta\nu$ = 127 Hz, ^2J 18.2 Hz). The ^{1}H-decoupled ^{13}C NMR spectrum of **5b** showed 24 signals in agreement with the proposed structure. Partial assignments of aromatic and cyclohexyl resonances are given in the Experimental section. The methylene protons of the Et-N and $ArCH_2$-N groups in **5b–5o** are also diastereotopic and exhibit two distinct multiple peaks. Similarly, the methyl groups of the oxo moieties in **5e**, **5g–i**, **5m**, and **5n** are diastereotopic and exhibit two distinct signals in their NMR spectra.

These reactions follow the classical U-4CR mechanism, described in the literature.[2,3]

In summary, we have found that a variety of ketones participate in stepwise one-pot Ugi MCRs to give thiourea-peptoids in good yields. These products possess a number of different functional groups that can be utilized in various reactions. The introduction of a thiourea group in the peptoids **5** may increase the biological and antimicrobial properties of these compounds.

Experimental

Chemicals and apparatus

Chemicals were obtained from *Merck* and were used without further purification. Benzoylthioureidocarboxylic acids have been synthesized from reaction of benzoyl chlorides, KSCN and amino acids.[22] Melting points (m.p.) were obtained on an Electrothermal-9100 apparatus. IR Spectra (ν/cm^{-1}) were recorded as KBr pellets with a *Shimadzu IR-460* spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a *Bruker DRX-300 Avance* instrument using $CDCl_3$ as the deuterated solvent containing TMS as internal standard, at 300 and 75 MHz, respectively; δ in ppm, J in Hz. Elemental analyses (C, H, N) were obtained with a *Heraeus CHN-O-Rapid* analyzer.

General procedure for the preparation of compounds 5a–o

The isocyanide **4** (1 mmol) was added to a solution of amine **2** (1.1 mmol), ketone **3** (1 mmol), and acid **1** (1 mmol) in MeOH (10 mL) at room temperature, and the solution was stirred for 12 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (8 mL), washed with aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by crystallization from EtOH.

***N*-(1-(Phenyl(1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)amino)-1-oxopropan-2-ylcarbamothioyl) benzamide (5a)**

Pale yellow powder; m.p.: 160–163°C; yield: 0.33 g (67%); IR: ν = 3450, 3310, 3223, 1682, 1592, 1502, 1404, 1228, 1148; EI-MS: m/z = 494 (M^+, 2), 259 (12), 235 (51), 169 (46), 105 (100), 83 (26), 77 (43), 43 (45); ^{1}H NMR: 1.15–1.99 (10 H, m, 5 CH_2), 1.36 (3 H, d, ^3J 6.9 Hz, Me), 1.38 (6 H, s, 2 Me), 3.73–3.82 (1 H, m, CH), 4.58 (1 H, quintet, ^3J 6.9 Hz, CH), 6.03 (1 H, d, ^3J 7.9 Hz, NH), 7.33–7.84 (10 H, m, CH-Ar), 8.90 (1 H, s, NH), 10.95 (1 H, d, ^3J 6.9 Hz, NH); ^{13}C NMR ($CDCl_3$): 17.8 (Me), 25.4 (Me), 25.5 (Me), 25.6 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 33.3 (2 CH_2), 49.2 (CH), 54.0 (CH), 63.9 (C), 119.3 (2 CH), 120.3 (C), 127.8 (2 CH), 129.5 (2 CH), 130.6 (2 CH), 131.0 (C), 132.2 (CH), 133.8 (C), 166.8 (C = O), 171.4 (C = O), 173.8 (C = O), 179.4 (C =

S). Anal. Calcd. for $C_{27}H_{34}N_4O_3S$ (494.65): C, 65.56; H, 6.93; N, 11.33%. Found: C, 66.01; H, 6.98; N, 11.37%.

_N_-(1-(Benzyl(1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)amino)-1-oxopropan-2-ylcarbamothioyl) benzamide (5b)

Pale yellow powder; m.p.: 180–182°C; yield: 0.38 g (75%); IR: ν = 3417, 3331, 3236, 1731, 1656, 1507, 1361, 1204, 1138; EI-MS: m/z = 508 (M^+, 1), 273 (10), 235 (44), 169 (41), 105 (100), 91 (75), 83 (34), 77 (37), 43 (49). ^{1}H NMR: δ 0.91–1.90 (10 H, m, 5 CH_2), 1.36 (3 H, d, ^3J 6.7 Hz, Me), 1.50 (3 H, s, Me), 1.53 (3 H, s, Me), 3.71–3.80 (1 H, m, CH), 4.94 (2 H, ABq, ^2J 18.2 Hz, $\Delta\nu$ 127.0, CH_2), 5.12 (1 H, quintet, ^3J 6.7 Hz, CH), 5.65 (1 H, d, ^3J 8.0 Hz, NH), 7.30–7.84 (10 H, m, CH-Ar), 8.92 (1 H, s, NH), 11.06 (1 H, d, ^3J 6.7 Hz, NH). ^{13}C NMR: δ 18.4 (Me), 24.3 (CH_2), 25.3 (Me), 25.4 (Me), 26.0 (CH_2), 26.1 (CH_2), 33.3 (CH_2), 33.4 (CH_2), 48.3 (CH), 48.9 (CH_2), 53.4 (CH), 63.7 (C), 126.9 (2 CH), 127.8 (2 CH), 129.3 (2 CH), 129.5 (2 CH), 131.1 (C),132.2 (CH), 133.9 (CH), 138.8 (C), 166.8 (C = O), 173.0 (C = O), 173.9 (C = O), 179.2 (C = S). Anal. Calcd for $C_{28}H_{36}N_4O_3S$ (508.68): C, 66.11; H, 7.13; N, 11.01%. Found: C, 66.43; H, 7.15; N, 11.05%.

_N_-(1-(Benzyl(1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl-carbamothioyl) benzamide (5c)

Cream powder; m.p.: 172–174°C; yield: 0.39 g (73%); IR: ν = 3426, 3290, 3208, 1732, 1666, 1511, 1421, 1202, 1160; EI-MS: m/z = 536 (M^+, 2), 273 (9), 263 (39), 169 (43), 105 (100), 91 (77), 83 (31), 77 (36), 43 (59). ^{1}H NMR: δ 0.80 (3 H, d, ^3J 6.8 Hz, Me), 1.02 (3 H, d, ^3J 6.8 Hz, Me), 0.90–1.91 (10 H, m, 5 CH_2), 1.48 (3 H, s, Me), 1.54 (3 H, s, Me), 2.00–2.11 (1 H, m, CH), 3.70–3.72 (1 H, m, CH), 4.93 (2 H, ABq, ^2J 18.0 Hz, $\Delta\nu$ 109.1, CH_2), 5.14–5.18 (1 H, m, CH), 5.62 (1 H, d, ^3J 7.8 Hz, NH), 7.30–7.87 (10 H, m, CH-Ar), 8.96 (1 H, s, NH), 11.09 (1 H, d, ^3J 7.9 Hz, NH). ^{13}C NMR: δ 17.4 (Me), 20.4 (Me), 24.2 (CH_2), 25.3 (Me), 25.4 (Me), 25.6 (CH_2), 26.1 (CH_2), 31.8 (CH), 33.1 (CH_2), 33.3 (CH_2), 48.3 (CH), 49.0 (CH_2), 62.0 (CH), 63.7 (C), 127.3 (2 CH), 127.8 (2 CH), 129.2 (2 CH), 129.5 (2 CH), 133.7 (CH), 133.9 (C), 139.1 (CH), 144.0 (C), 166.8 (C = O), 172.1 (C = O), 174.0 (C = O), 180.4 (C = S). Anal. Calcd for $C_{30}H_{40}N_4O_3S$ (536.73): C, 67.13; H, 7.51; N, 10.44%. Found: C, 67.49; H, 7.55; N, 10.49%.

_N_-(1-((1-(Cyclohexylamino)-2-methyl-1-oxopropan-2-yl)(ethyl)amino)-1-oxopropan-2-ylcarbamothioyl) benzamide (5d)

Cream powder; m.p.: 152–153°C; yield: 0.31 g (70%); IR: ν = 3414, 3321, 3249, 1679, 1588, 1511, 1452, 1242, 1093; EI-MS: m/z = 446 (M^+, 2), 235 (47), 211 (12), 169 (39), 105 (100), 83 (42), 77 (32), 29 (27). ^{1}H NMR: δ 0.91–1.91 (10 H, m, 5 CH_2), 1.10 (3 H, t, ^3J 10.5 Hz, Me), 1.53 (3 H, d, ^3J 9.6 Hz, Me), 1.56 (6 H, s, 2 Me), 3.46–3.55 (1 H, m, CH_2), 3.72–3.76 (1 H, m, CH_2), 3.75–3.83 (1 H, m, CH), 5.24–5.27 (1 H, m, CH), 5.63 (1 H, d, ^3J 7.7 Hz, NH), 7.52 (2 H, t, ^3J 7.3 Hz, 2 CH), 7.63 (1 H, t, ^3J 7.3 Hz, 2 CH), 7.84 (2 H, d, ^3J 7.3 Hz, 2 CH), 8.98 (1 H, s, NH), 11.13 (1 H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 17.5 (Me), 19.0 (Me), 24.9 (CH_2), 25.2 (Me), 25.3 (Me), 26.1 (2 CH_2), 33.2 (CH_2), 33.3 (CH_2), 39.2 (CH_2), 47.4 (CH), 61.7 (CH), 62.9 (C), 128.0 (2 CH), 129.2 (2 CH), 132.7 (CH), 133.4 (C), 167.9 (C = O), 172.8 (C = O), 174.0 (C = O), 179.2 (C = S). Anal. Calcd for $C_{23}H_{34}N_4O_3S$ (446.61): C, 61.85; H, 7.67; N, 12.55%. Found: C, 61.57; H, 7.63; N, 12.63%.

_N_-(1-((1-(Cyclohexylamino)-2-methyl-1-oxopropan-2-yl)(ethyl)amino)-3-methyl-1-oxobutan-2-ylcarbamothioyl) benzamide (5e)

Cream powder; m.p: 146–148°C; yield: 0.31 g (65%); IR: ν = 3402, 3299, 3218, 1721, 1686, 1501, 1376, 1210, 1180; EI-MS: m/z = 474 (M^+, 3), 263 (53), 211 (8), 169 (43), 105 (100), 83 (28), 77 (34), 43 (54), 29 (17). ^{1}H NMR: δ 0.91–1.93 (10 H, m, 5 CH_2), 1.11 (3 H, d, ^3J 3.9 Hz, Me), 1.13 (3 H, d, ^3J 3.9 Hz, Me), 1.46 (3 H, t, ^3J 7.1 Hz, Me), 1.53 (3 H, s, Me), 1.54 (3 H, s, Me), 2.25–2.31 (1 H, m, CH), 3.55–3.77 (2 H, m, CH_2), 3.78–3.86 (1 H, m, CH), 5.23 (1 H, dd, ^3J 8.0, ^3J 5.4 Hz, CH), 5.63 (1 H, d, ^3J 6.3 Hz, NH), 7.53 (2 H, t, ^3J 7.5 Hz, 2 CH), 7.64 (1 H, t, ^3J 7.5 Hz, CH), 7.64 (2 H, d, ^3J 7.5 Hz, 2 CH), 8.98 (1 H, s, NH), 11.10 (1 H, d, ^3J 5.4 Hz, NH). ^{13}C NMR: δ 17.7 (Me), 17.9 (Me), 20.6 (Me), 24.9 (CH_2), 25.3 (Me), 25.4 (Me), 26.1 (2 CH_2), 32.1 (CH), 33.1 (CH_2), 33.3 (CH_2), 39.6 (CH_2), 48.8 (CH), 62.0 (CH), 63.3 (C), 127.8 (2 CH), 129.5 (2 CH), 132.1 (CH), 133.9 (C), 166.8 (C = O), 170.8 (C = O), 173.9 (C = O), 180.4 (C = S). Anal. Calcd for $C_{25}H_{38}N_4O_3S$ (474.66): C, 63.26; H, 8.07; N, 11.80%. Found: C, 63.48; H, 8.15; N, 11.86%.

_N_-(1-(Benzyl(3-(cyclohexylcarbamoyl)pentan-3-yl) amino)-1-oxopropan-2-ylcarbamothioyl)benzamide (5f)

Cream powder; m.p.: 170–172°C; yield: 0.33 g (62%); IR: ν = 3413, 3318, 3209, 1736, 1653, 1549, 1381, 1226, 1119; EI-MS: m/z = 536 (M^+, 0.8), 301 (13), 235 (47), 197 (41), 105 (100), 91 (68), 83 (29), 77 (33), 29 (17). ^{1}H NMR: δ 0.79–1.99 (10 H, m, 5 CH_2), 0.87 (3 H, t, ^3J 7.5 Hz, Me), 0.92 (3 H, t, ^3J 7.5 Hz, Me), 1.62 (3 H, d, ^3J 7.0 Hz, Me), 2.04–2.15 (2 H, m, CH_2), 2.33–2.39 (2 H, m, CH_2), 3.77–3.84 (1 H, m, CH), 4.96 (2 H, ABq, ^2J 18.2 Hz, $\Delta\nu$ 157.5, CH_2), 5.01–5.06 (1 H, m, CH), 5.61 (1 H, d, ^3J 7.6 Hz, NH), 7.29–7.87 (10 H, m, CH-Ar), 8.93 (1 H, s, NH), 10.97 (1 H, d, ^3J 7.9 Hz, NH). ^{13}C NMR: δ 8.7 (Me), 9.0 (Me), 17.5 (Me), 18.0 (CH_2), 18.5 (CH_2), 25.4 (CH_2), 26.1 (2 CH_2), 33.4 (CH_2), 33.6 (CH_2), 49.0 (CH_2), 53.6 (CH), 55.4 (CH), 69.6 (C), 127.9(2 CH), 128.1 (2 CH), 129.1 (2 CH), 129.4 (2 CH), 131.9 (CH), 132.2 (C), 133.8 (CH), 134.0 (C), 167.0 (C = O), 170.9 (C = O), 172.7 (C = O), 180.1 (C = S). Anal. Calcd for $C_{30}H_{40}N_4O_3S$ (536.73): C, 67.13; H, 7.51; N, 10.44%. Found: C, 67.50; H, 7.56; N, 10.49%.

_N_-(1-(Benzyl(1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)amino)-1-oxopropan-2-ylcarbamothioyl)-4-nitrobenzamide (5g).

Cream powder; m.p.: 171–175°C; yield: 0.35 g (64%); IR: ν = 3420, 3342, 3243, 1732, 1676, 1562, 1349, 1210, 1153; EI-MS: m/z = 553 (M^+, 1.5), 280 (52), 273 (10), 169 (43), 150 (100), 122 (24), 91 (73), 83 (31). ^{1}H NMR: δ 0.89–1.95 (10 H, m, 5 CH_2), 1.37 (3 H, d, ^3J 6.7 Hz, Me), 1.49 (3 H, s, Me), 1.51 (3 H, s, Me), 3.69–3.79 (1 H, m, CH), 4.87 (2 H, ABq, ^2J 18.2 Hz, $\Delta\nu$ 95.5, CH_2), 5.12 (1 H, quintet, ^3J 6.7 Hz, CH), 5.61 (1 H, d, ^3J 8.0 Hz, NH), 7.29 (1 H, t, ^3J 7.4 Hz, CH), 7.40 (2 H, t, ^3J 7.4 Hz, 2 CH), 7.51 (2 H, d, ^3J 7.4 Hz, 2 CH), 8.04 (2 H, t, ^3J 8.7 Hz, 2 CH), 8.35 (2 H, d, ^3J 8.7 Hz, 2 CH), 9.28 (1 H, br s, NH), 10.96 (1 H, d, ^3J 6.7 Hz, NH). ^{13}C NMR: δ 18.3 (Me), 24.2 (CH_2), 25.3 (Me), 26.0 (Me), 29.7 (CH_2), 31.3 (CH_2), 33.3 (CH_2), 33.4 (CH_2), 48.2 (CH), 48.9 (CH_2), 53.5 (CH), 63.7 (C), 124.6 (2 CH), 126.9 (2 CH), 128.0 (2 CH), 129.3 (2 CH), 129.4 (CH), 137.8 (C), 138.5 (C), 151.0 (C), 165.0 (C = O), 172.8 (C = O), 173.8 (C = O), 178.7 (C = S). Anal. Calcd for $C_{28}H_{35}N_4O_3S$ (553.67): C, 60.74; H, 6.37; N, 12.65%. Found: C, 60.86; H, 6.41; N, 12.71%.

***N*-(1-((1-(Cyclohexylamino)-2-methyl-1-oxopropan-2-yl)(4-methoxybenzyl)am-ino)-1-oxopropan-2-yl-carbamothioyl)-4-methylbenzamide (5h)**.

Pale yellow powder; m.p.: 160–163°C; yield: 0.40 g (72%); IR: ν = 3411, 3352, 3235, 1668, 1580, 1512, 1455, 1248, 1168; EI-MS: m/z = 552 (M^+, 1.3), 303 (21), 249 (48), 169 (40), 121 (78), 119 (100), 91 (23), 83 (36), 43 (24).^{1}H NMR: δ 1.01–1.97 (10 H, m, 5 CH_2), 1.36 (3 H, d, ^3J 6.8 Hz, Me), 1.48 (3 H, s, Me), 1.52 (3 H, s, Me), 2.44 (3 H, s, Me), 3.69–3.76 (1 H, m, CH), 3.80 (3 H, s, OMe), 4.85 (2 H, ABq, ^2J 18.0 Hz, $\Delta\nu$ 113.0, CH_2), 5.16 (1 H, quintet, ^3J 6.8 Hz, CH), 5.64 (1 H, d, ^3J 8.0 Hz, NH), 6.93 (2 H, d, ^3J 8.6 Hz, 2 CH), 7.31 (2 H, d, ^3J 8.1 Hz, 2 CH), 7.43 (2 H, d, ^3J 8.6 Hz, 2 CH), 7.73 (2 H, d, ^3J 8.1 Hz, 2 CH), 8.93 (1 H, s, NH), 11.10 (1 H, d, ^3J 6.8 Hz, NH). ^{13}C NMR: δ 18.4 (Me), 22.0 (Me), 24.4 (CH_2), 25.3 (Me), 25,4 (Me), 26.1 (CH_2), 31.3 (CH_2), 33.2 (CH_2), 33.4 (CH_2), 47.7 (CH), 48.9 (CH_2), 53.4 (CH), 55.7 (OMe), 63.6 (C), 114.7 (2 CH), 127.9 (2 CH), 128.1 (2 CH), 129.3 (C), 130.2 (2 CH), 130.7 (C), 144.9 (C), 159.3 (C), 166.6 (C = O), 172.9 (C = O), 174.9 (C = O), 179.3 (C = S). Anal. Calcd for $C_{30}H_{40}N_4O_3S$ (552.73): C, 65.19; H, 7.29; N, 10.14%. Found: C, 65.06; H, 7.27; N, 10.21%.

***N*-(1-(Benzyl(1-(*tert*-butylamino)-2-methyl-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl-carbamothioyl) benzamide (5i)**

Pale yellow powder; m.p.: 184–85°C; yield: 0.37 g (77%); IR: ν = 3423, 3295, 3210, 1679, 1569, 1515, 1350, 1220, 1080; EI-MS: m/z = 482 (M^+, 1.8), 247 (15), 235 (42), 143 (38), 105 (100), 91 (66), 77 (38), 58 (26). ^{1}H NMR: δ 1.36 (9 H, s, CMe_3), 1.40 (3 H, d, ^3J 6.8 Hz, Me), 1.46 (3 H, s, Me), 1.49 (3 H, s, Me), 4.88 (2 H, ABq, ^2J 17.9 Hz, $\Delta\nu$ 101.8, CH_2), 5.16 (1 H, quintet, ^3J 6.8 Hz, CH), 5.58 (1 H, s, NH), 7.31 (1 H, t, ^3J 7.2 Hz, CH), 7.41 (2 H, t, ^3J 7.2 Hz, 2 CH), 7.49 (2 H, d, ^3J 7.2 Hz, 2 CH), 7.52 (2 H, t, ^3J 7.5 Hz, 2 CH), 7.63 (1 H, t, ^3J 7.5 Hz, CH), 7.84 (2 H, t, ^3J 7.5 Hz, 2 CH), 8.94 (1 H, s, NH), 11.11 (1 H, d, ^3J 6.8 Hz, NH). ^{13}C NMR: δ 18.4 (Me), 24.3 (Me), 25.3 (Me), 28.9 (CMe_3), 48.3 (CH_2), 51.4 (C), 53.4 (CH), 64.1 (C), 126.9 (2 CH), 127.8 (2 CH), 127.9 (CH), 129.3 (2 CH), 129.5 (2 CH), 132.2 (C), 133.9 (CH), 138.7 (C), 166.7 (C = O), 172.9 (C = O), 173.9 (C = O), 179.2 (C = S). Anal. Calcd for $C_{26}H_{34}N_4O_3S$ (482.64): C, 64.70; H, 7.10; N, 11.61%. Found: C, 64.85; H, 7.14; N, 11.68%.

***N*-(1-(Benzyl(1-(*tert*-butylcarbamoyl)cyclopentyl)amino)-3-methyl-1-oxobutan-2-ylcarbamothioyl)benzamide (5j)**

Pale yellow powder; m.p.: 180–185°C; yield: 0.35 g (65%); IR: ν = 3431, 3292, 3206, 1729, 1681, 1520, 1413, 1209, 1087; EI-MS: m/z = 536 (M^+, 1.2), 263 (41), 235 (45), 169 (33), 105 (100), 91 (72), 58 (23). ^{1}H NMR: δ 0.79 (3 H, d, ^3J 6.8 Hz, Me), 1.02 (3 H, d, ^3J 6.8 Hz, Me), 1.33 (9 H, s, CMe_3), 1.68–2.10 (8 H, m, 4 CH_2), 2.55–2.59 (1 H, m, CH), 4.94 (2 H, ABq, ^2J 18.0 Hz, $\Delta\nu$ 135.5, CH_2), 5.07 (1 H, dd, ^3J 8.1 Hz, ^3J 4.6 Hz, CH), 6.39 (1 H, s, NH), 7.32–7.87 (10 H, m, CH-Ar), 8.96 (1 H, s, NH), 11.12 (1 H, d, ^3J 4.6 Hz, NH). ^{13}C NMR: δ 17.3 (Me), 20.4 (Me), 24.0 (CH_2), 24.3 (CH_2), 28.9 (CMe_3), 29.9 (CH), 36.3 (CH_2), 37.0 (CH_2), 50.7 (C), 51.3 (CH_2), 62.2 (CH), 75.0 (C), 127.0 (2 CH), 127.8 (2 CH), 128.0 (CH), 129.3 (2 CH), 129.5 (2 CH), 132.1 (C), 133.9 (CH), 138.9 (C), 166.9 (C = O), 173.1 (C = O), 173.7 (C = O), 180.5 (C = S). Anal. Calcd for $C_{30}H_{40}N_4O_3S$ (536.73): C, 67.13; H, 7.51; N, 10.44%. Found: C, 67.52; H, 7.56; N, 10.51%.

***N*-(1-(Benzyl(1-(*tert*-butylcarbamoyl)cyclopentyl)amino)-1-oxopropan-2-ylcarbamothioyl)benzamide (5k)**

White powder; m.p.: 188–190°C; yield: 0.41 g (80%); IR: ν = 3441, 3309, 3198, 1669, 1581, 1509, 1443, 1208, 1112; EI-MS: m/z = 508 (M^+, 1.3), 273 (11), 235 (47), 169 (31), 105 (100), 91 (74), 77 (32), 58 (26). ^{1}H NMR: δ 1.55–2.60 (8 H, m, 4 CH_2), 1.34 (9 H, s, CMe_3), 1.36 (3 H, d, ^3J 6.6 Hz, Me), 4.91 (2 H, ABq, ^2J 18.1 Hz, $\Delta\nu$ 135.0, CH_2), 5.05–5.10 (1 H, m, CH), 6.50 (1 H, br s, NH), 7.31–7.85 (10 H, m, CH-Ar), 8.93 (1 H, s, NH), 11.10 (1 H, d, ^3J 6.6 Hz, NH). ^{13}C NMR: δ 18.4 (Me), 23.9 (CH_2), 24.0 (CH_2), 29.0 (CMe_3), 36.5 (CH_2), 36.6 (CH_2), 50.9 (C), 51.3 (CH_2), 53.7 (CH), 75.1 (C), 126.5 (2 CH), 127.8 (2 CH), 127.9 (CH), 129.4 (2 CH), 129.5 (2 CH), 132.2 (C),133.9 (CH), 138.7 (C), 166.8 (C = O), 172.9 (C = O), 174.7 (C = O), 179.2 (C = S). Anal. Calcd for $C_{28}H_{36}N_4O_3S$ (508.68): C, 66.11; H, 7.13; N, 11.01%. Found: C, 66.53; H, 7.16; N, 11.09%.

***N*-(1-(Benzyl(1-(*tert*-butylcarbamoyl)cyclohexyl)amino)-1-oxopropan-2-ylcarbamothioyl)benzamide (5l)**

Pale yellow powder; m.p: 177–179°C; yield: 0.41 g (78%); IR: ν = 3395, 3303, 3225, 1658, 1586, 1519, 1450, 1132; EI-MS: m/z = 522 (M^+, 1.8), 287 (9), 235 (45), 183 (28), 105 (100), 91 (71), 77 (34), 58 (22). ^{1}H NMR: δ 1.19–2.48 (10 H, m, 5 CH_2), 1.35 (9 H, s, CMe_3), 1.42 (3 H, d, ^3J 6.7 Hz, Me), 4.84 (2 H, ABq, ^2J 18.1 Hz, $\Delta\nu$ 80.1, CH_2), 5.22 (1 H, quintet, ^3J 6.7 Hz, CH), 6.23 (1 H, s, NH), 7.27–7.40 (5 H, m, CH-Ar), 7.52 (2 H, t, ^3J 8.1 Hz, 2 CH), 7.63 (1 H, t, ^3J 8.1 Hz, CH), 7.85 (2 H, d, ^3J 8.1 Hz, 2 CH), 8.94 (1 H, s, NH), 11.18 (1 H, d, ^3J 6.7 Hz, NH). ^{13}C NMR: δ 18.6 (Me), 23.2 (CH_2), 23.4 (CH_2), 25.8 (CH_2), 29.0 (CMe_3), 33.1 (CH_2), 33.7 (CH_2), 48.3 (C), 51.4 (CH_2), 54.2 (CH), 67.9 (C), 126.8 (2 CH), 127.8 (2 CH), 127.9 (CH), 129.3 (2 CH), 129.5 (2 CH), 132.2 (C),133.9 (CH), 138.7 (C), 166.7 (C = O), 172.1 (C = O), 174.1 (C = O), 179.0 (C = S). Anal. Calcd for $C_{29}H_{38}N_4O_3S$ (522.70): C, 66.64; H, 7.33; N, 10.72%. Found: C, 66.85; H, 7.39; N, 10.80%.

***N*-(1-(Benzyl(1-(*tert*-butylamino)-2-methyl-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-ylcarbamothioyl) benzamide (5m)**

White powder; m.p.: 179–181°C; yield: 0.42 g (82%); IR: ν = 3440, 3302, 3261, 1683, 1592, 1560, 1369, 1205, 1170; EI-MS: m/z = 510 (M^+, 0.9), 263 (38), 235 (40), 143 (47), 105 (100), 91 (53), 77 (28), 58 (32), 43 (49). ^{1}H NMR: δ 0.84 (3 H, d, ^3J 6.8 Hz, Me), 1.04 (3 H, d, ^3J 6.8 Hz, Me), 1.35 (9 H, s, CMe_3), 1.44 (3 H, s, Me), 1.49 (3 H, s, Me), 2.10–2.15 (1 H, m, CH), 4.89 (2 H, ABq, ^2J 17.9 Hz, $\Delta\nu$ 82.0, CH_2), 5.19 (1 H, dd, ^3J 8.0 Hz, ^3J 4.0 Hz, CH), 5.57 (1 H, s, NH), 7.31–7.87 (10 H, m, CH-Ar), 8.99 (1 H, s, NH), 11.12 (1 H, d, ^3J 4.0 Hz, NH). ^{13}C NMR: δ 17.2 (Me), 20.4 (Me), 23.9 (Me), 25.6 (Me), 28.9 (CMe_3), 31.3 (CH), 48.3 (C), 51.3 (CH_2), 62.0 (CH), 64.0 (C), 127.3 (2 CH), 127.9 (2 CH), 129.2 (2 CH), 129.5 (2 CH), 130.8 (CH), 132.2 (C), 133.9 (CH), 139.0 (C), 166.9 (C = O), 172.1 (C = O), 174.1 (C = O), 180.5 (C = S). Anal. Calcd for $C_{28}H_{38}N_4O_3S$ (510.69): C, 65.85; H, 7.50; N, 10.97%. Found: C, 65.98; H, 7.53; N, 11.06%.

***N*-(1-((1-(*tert*-Butylamino)-2-methyl-1-oxopropan-2-yl)(ethyl)amino)-1-oxopropan-2-ylcarbamothioyl) benzamide (5n)**

White powder; m.p.: 132–135°C; yield: 0.28 g (68%); IR: ν = 3415, 3311, 3215, 1680, 1593, 1510, 1421, 1231, 1087; EI-MS: m/z = 420 (M^+, 2.2), 235 (69), 185 (21), 143 (52), 105 (100), 77 (35), 58 (26), 29 (17). ^{1}H NMR: δ 1.32 (9 H, s, CMe_3), 1.41 (3 H, d, ^3J 7.0 Hz, Me), 1.49 (3 H, s, Me), 1.54 (3 H, s, Me), 1.56 (3 H, d, ^3J 6.8 Hz, Me), 3.48–3.52 (1 H, m, CH_2), 3.71–3.75 (1 H,

m, CH_2), 5.25 (1 H, quintet, ^3J 6.8 Hz, CH), 5.53 (1 H, s, NH), 7.52 (2 H, t, ^3J 7.4 Hz, 2 CH), 7.63 (1 H, t, ^3J 7.4 Hz, CH), 7.84 (2 H, d, ^3J 7.4 Hz, 2 CH), 8.95 (1 H, s, NH), 11.14 (1 H, d, ^3J 6.8 Hz, NH). ^{13}C NMR: δ 17.5 (Me), 18.6 (Me), 24.9 (Me), 25.0 (Me), 28.9 (CMe_3), 39.3 (CH_2), 51.2 (C), 53.2 (CH), 63.6 (C), 127.8 (2 CH), 129.5 (2 CH), 132.2 (CH), 133.9 (C), 166.7 (C = O), 171.8 (C = O), 173.9 (C = O), 179.3 (C = S). Anal. Calcd for $C_{21}H_{32}N_4O_3S$ (420.57): C, 59.97; H, 7.67; N, 13.32%. Found: C, 60.23; H, 7.70; N, 13.40%.

_N_-(2-(Benzyl(1-(*tert*-butylamino)-2-methyl-1-oxobutan-2-yl)amino)-2-oxoethylcarbamothioyl)benzamide (5o)

Pale yellow powder; m.p.: 192–194°C; yield: 0.35 g (72%); IR: ν = 3410, 3236, 3063, 1658, 1585, 1512, 1408, 1244, 1163; EI-MS: m/z = 482 (M^+, 2.1), 261 (14), 221 (39), 157 (43), 105 (100), 91 (78), 77 (34), 57 (53). ^{1}H NMR: δ 0.89 (3 H, t, ^3J 7.4 Hz, Me), 1.38 (9 H, s, CMe_3), 1.45 (3 H, s, Me), 1.78–1.87 (1 H, m, CH_2), 2.02–2.09 (1 H, m, CH_2), 4.48 (2 H, ABX, $^2J_{AB}$ 18.5 Hz, $^3J_{AX}$ = $^3J_{BX}$ 4.4 Hz, $\Delta\nu$ 5.3, CH_2NH), 4.69 (2 H, ABq, ^2J 18.5 Hz, $\Delta\nu$ 15.7, CH_2N), 5.64 (1 H, s,NH), 7.28–7.87 (10 H, m, CH-Ar), 9.01 (1 H, s, NH), 11.20 (1 H, br s, NH). ^{13}C NMR: δ 9.06 (Me), 20.8 (Me), 29.05 (CMe_3), 29.7 (CH_2), 48.0 (C), 49.2 (CH_2), 51.6 (CH_2), 67.3 (C), 126.5 (2 CH), 127.9 (2 CH), 128.0 (CH), 129.4 (2 CH), 129.6 (2 CH), 132.3 (C),133.8 (CH), 138.3 (C), 166.6 (C = O), 168.2 (C = O), 172.9 (C = O), 179.8 (C = S). Anal. Calcd. for $C_{26}H_{34}N_4O_3S$ (482.64): C, 64.70; H, 7.10; N, 11.61%. Found: C, 64.82; H, 7.14; N, 11.67%.

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