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One-pot four-component synthesis of novel isothiourea-ethylene-tethered-piperazine derivatives†

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An efficient metal-free four-component approach for the synthesis of piperazine derivatives tethered to an isothiourea group through an ethylene link was developed. 1,4-Diazabicyclo[2.2.2]octane (DABCO) salts, generated *in situ* through the reactions of DABCO with various alkyl bromides, reacted with phenylisothiocyanate (PITC) and amines in a one-pot manner to give the target products. Initially, through two parallel nucleophilic paths, DABCO and the secondary amine adds to the alkyl bromide and PITC, respectively. The process is followed by the combination of the two respective intermediates to produce the final products by forming a new C–S bond with the expense of a C–N bond cleavage. Consequently, various DABCO salts and secondary amines were tolerated well in this protocol to afford the isothiourea-ethylene-tethered-piperazine compounds in good to high yields.

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Introduction

Multicomponent reactions (MCRs) have emerged as a promising synthetic strategy in organic chemistry in recent decades, since they furnish one-pot routes to convert commercially available reactants to complex structures.^{1,2} In addition, MCRs are attractive from economical, operational simplicity, and green chemistry points of view.^{3,4} Consequently, MCRs are widely employed in the synthesis of various natural products,⁵ heterocyclic systems,⁶ and other molecules of interest.^{7–9} However, earlier MCRs often involved the use of limited starting materials, higher reaction temperatures, and toxic reagents. Thus, there is an ongoing demand for further improvement of MCRs by designing new processes with lower overall costs, better selectivity, higher efficiency, enhanced environmental aspects, and improved atom-economy.

Molecules containing isothiourea moieties constitute important structures in medicinal,^{10,11} biological,^{12,13} and agricultural chemistry.^{14,15} In addition, they are also employed as catalysts^{16,17} or reactive intermediates¹⁸ in other synthetic procedures. Illustrative related structures are highlighted in Fig. 1. Various methods are reported so far for the synthesis of these molecules. The majority of these reports are carried out using conventional stepwise approaches,^{19,20} while a few recent studies deal with three-component procedures. For instance, Sun *et al.* developed a three-component synthesis of isothiureas *via* the combination of isocyanides and amines with

disulfides, where the latter component was initially activated by *N*-halogen succinimides using (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO).²¹ Alternatively, Maes devised a copper(i) catalyzed three-component reaction between thiosulfonates, amines, and isocyanides, resulting in the synthesis of isothiurea derivatives.²² Other important related reports include a tandem process by Wu,²³ a three-component reaction by Mishra,²⁴ and a binuclear aluminium complex mediated synthesis of carbodiimides by Panda.²⁵

Despite all the studies carried out on isothiureas, many traditional methods suffer from the use of complicated steps, toxic reagents or additives, and poor reactivity of the starting materials. Therefore, there is a need for further development of efficient and sustainable synthetic methods involving isothiurea chemistry. In the framework of our program on MCRs^{26,27} and heterocyclic chemistry,^{28,29} we would like to report a novel four-component procedure for the synthesis of a new series of isothiurea containing piperazines, as exemplified in Scheme 1 for the reaction of diethylamine (Et₂NH), phenyl isothiocyanate (PITC), 1,4-diazabicyclo[2.2.2]octane (DABCO), and 1-bromo-2-methylpropane.

Although the use of DABCO bond cleavage for the synthesis of various piperazine derivatives has precedence,^{30–32} the current work is the first application of DABCO salts in the synthesis of the isothiurea functional group. For this purpose, we planned to use two very reactive species, the electrophilic isothiocyanate (PITC) moiety and the sterically hindered tertiary amine (DABCO), whose reactive natures can trigger parallel nucleophilic combinations of the reactants, which is a useful tool for launching multicomponent reactions. Consequently, this leads to a concurrent C–N bond cleavage and C–S bond formation reactions to produce the target products, in which

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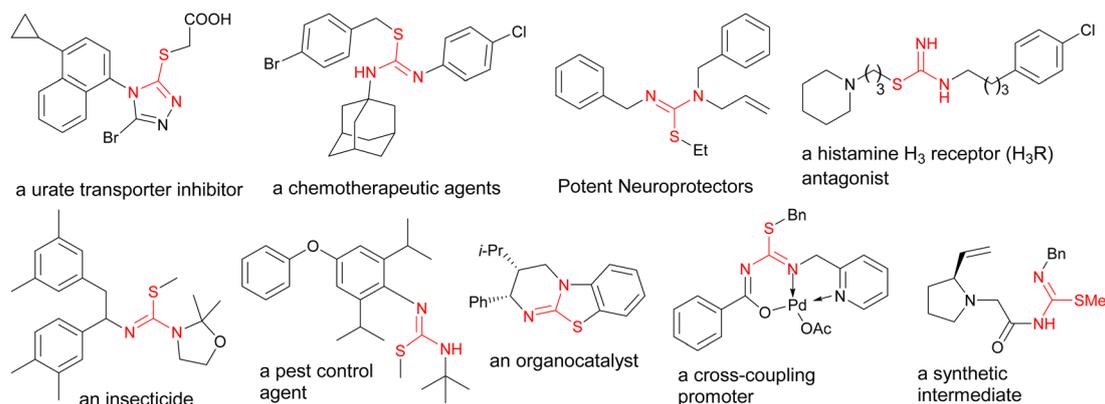
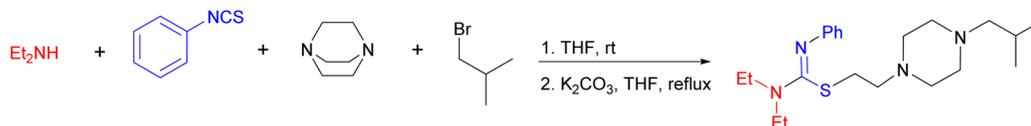


Fig. 1 Important molecules containing the isothiurea functional group.



Scheme 1 One-pot four-component approach for the synthesis of isothiurea-ethylene-tethered piperazine derivatives.

the isothiurea and piperazine functional groups are placed in vicinity and would be interesting candidates for further biological studies.

Results and discussion

For simplicity, we first synthesized the DABCO salts **2** separately to start the study with a three-component process. Thus, to optimize the reaction, we subjected Et_2NH **1a** and PITC to combine with **2a** under various conditions (Table 1). Treatment of a 1.0 : 1.0 : 1.0 mixture of the three reactants and K_2CO_3 at refluxing temperature in THF after 5 h led to the formation of **3a** in 93% yield (entry 1). In the absence of the base (entry 2) or at lower temperatures (entries 3–4), the yield was diminished even at a longer reaction time. Similarly, use of other inorganic bases (entries 5–8) did not lead to higher conversion of the reactants to **3a**. Alternatively, no better results were achieved for conducting the reaction in other protic (entries 9–11) or aprotic (entries 12–16) solvents, conveying that $\text{K}_2\text{CO}_3/\text{THF}/\text{reflux}$ conditions would provide the highest conversion of the reactants to the desired product.

With these results in hand, next we extended the process into a four-component combination by primarily subjecting DABCO to react with various alkyl bromides to provide the required salts **2** for the following steps (Table 2). Consequently, when DABCO, $\text{Me}_2\text{CHCH}_2\text{Br}$, Et_2NH , and PITC were reacted in this manner, **3a** was produced after 12 h in 91% yield (entry 1). By using this approach, Et_2NH and PITC reacted with other *in situ* generated derivatives of **2** to give **3b–e** efficiently (entries 2–5). Similarly, products **3f–j** were obtained in the same manner to emphasize the generality of the process (entries 6–10).

Based on these results, a mechanism would be proposed for this process. Initially, DABCO is alkylated *via* a nucleophilic

attack on the alkyl bromide moiety to produce **2**, while in a parallel reaction, Et_2NH adds to PITC. The two resulting intermediates of the initial steps then would combine through K_2CO_3 -activated attack of the diethyl-phenylthiourea species to the DABCO salt to access to the final products. The stereochemistry of the isothiurea functional group was assigned as *Z* (as seen in Fig. 2 (top) for the product with $\text{R} = \text{Et}$ and $\text{R}' =$

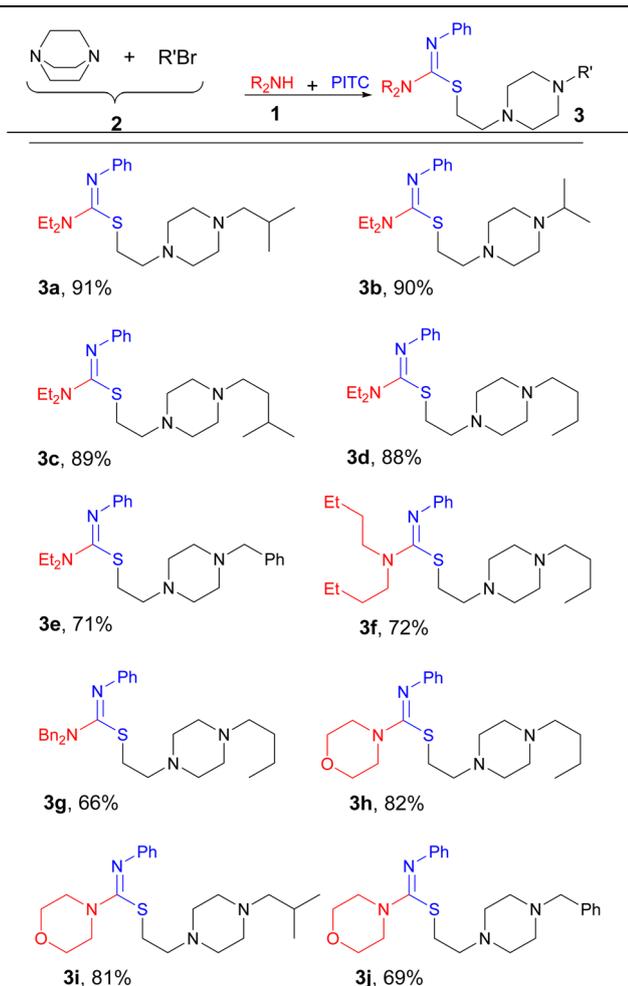
Table 1 Three-component optimization of the synthesis of **3a**

Entry	Base	Solvent	<i>T</i> (°C)	Time (h)	Yield ^a (%)
1	K_2CO_3	THF	Reflux	5	93
2	—	THF	Reflux	24	28
3	K_2CO_3	THF	50	24	49
4	K_2CO_3	THF	25	24	20
5	Na_2CO_3	THF	Reflux	24	59
6	K_3PO_4	THF	Reflux	24	54
7	KOH	THF	Reflux	24	39
8	NaOH	THF	Reflux	24	37
9	K_2CO_3	EtOH	Reflux	24	64
10	K_2CO_3	MeOH	Reflux	24	70
11	K_2CO_3	H_2O	Reflux	24	16
12	K_2CO_3	DMF	Reflux	24	37
13	K_2CO_3	DMSO	Reflux	24	<5
14	K_2CO_3	CHCl_3	Reflux	24	26
15	K_2CO_3	CH_2Cl_2	Reflux	24	<5
16	K_2CO_3	<i>n</i> -Hexane	Reflux	24	18

^a Isolated yields.



Table 2 Diversity scope of the process by 4-component synthesis of derivatives of **3**^{a,b}



^a Reaction conditions: DABCO (10.0 mmol), THF (30 mL) $R'Br$ (10.0 mmol), rt, 10–12 h. Then added to this mixture R_2NH (10.0 mmol), PITC (10.0 mmol), K_2CO_3 (10.0 mmol), THF (10 mL) reflux 4–6 h.
^b Isolated yields.

CH_2Ph). Such assignment for similar molecules resulting from the same chemistry is reported before in the literature.^{15,33} To further support the assignment, we engaged molecular mechanics calculations to verify the proposed stereochemistry. The results arising from molecular mechanics (MM2) calculations using ChemSoft's ChemOffice Pro (version 20) clearly show that the *Z* configuration (Fig. 2, bottom-left) is more stable than the *E* counterpart (Fig. 2, bottom-right).

Experimental

General

FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 spectrometer. NMR spectra were obtained on a Bruker AMX (300 MHz for ¹H and 75 MHz for ¹³C) as $CDCl_3$ solutions using TMS as internal standard reference. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument.

MS spectra were obtained on a Fisons 8000 Trio instrument at ionization potential of 70 eV. TLC experiments were carried out on pre-coated silica gel plates using petroleum ether/EtOAc as the eluent. Starting materials and reagents were purchased from commercial sources.

Synthesis of ammonium salts **2a** from DABCO

To a solution of DABCO (1.12 g, 10.0 mmol) in THF (20 mL) was added Me_2CHCH_2Br (10.0 mmol), and the solution was stirred at room temperature for 12 h. A precipitate was formed, which was filtered, washed with ethyl acetate (10 mL) and dried under vacuum to get **2a**.

Typical procedure for three-component synthesis of functionalized piperazines **3a**

A mixture of **2a** (0.11 g, 0.5 mmol), Et_2NH (57.0 μ L, 0.55 mmol), PITC (0.07 g, 0.5 mmol), and K_2CO_3 (0.069 g, 0.5 mmol) in THF (5 mL) was stirred at refluxing temperature for 5 h. After completion of the reaction, the solvent was evaporated under vacuum and the concentrated crude mixture was fractionated by column chromatography on silica gel (EtOAc/petroleum ether; 60/40) to afford the pure product. The isolated product was fully characterized by various spectroscopic methods.

Typical procedure for four-component synthesis of functionalized piperazines **3a**

To a solution of DABCO (1.12 g, 10.0 mmol) in THF (30 mL) was added Me_2CHCH_2Br (10.0 mmol), and the solution was stirred at room temperature for 12 h to get **2a**. To this was added Et_2NH (1140 μ L, 10.0 mmol), PITC (1.4 g, 10.0 mmol), and K_2CO_3 (1.4 g, 10.0 mmol) in THF (10 mL) and the mixture was stirred at refluxing temperature for 5 h. After completion of the reaction, the solvent was evaporated under vacuum and the concentrated crude mixture was fractionated by column chromatography on silica gel (EtOAc/petroleum ether; 60/40) to afford the pure product. The isolated product was fully characterized by various spectroscopic methods.

2-(4-Isobutylpiperazin-1-yl)ethyl (Z)-N,N-diethyl-N'-phenylcarbamiimidiothioate **3a**

¹H NMR (300 MHz, $CDCl_3$) δ 7.21–7.16 (m, 2H), 6.92–6.86 (m, 3H), 3.54 (q, $J = 7.0$ Hz, 4H), 2.47–2.41 (m, 2H), 2.38–2.29 (m, 10H), 2.04 (d, $J = 7.0$ Hz, 2H), 1.70 (t, septet, $J = 7.0$, 6.5 Hz, 1H), 1.17 (t, $J = 7.0$ Hz, 6H), 0.85 (d, $J = 6.5$ Hz, 6H) ppm; ¹³C NMR (75 MHz, $CDCl_3$) δ 152.3, 149.8, 128.3, 121.4, 121.2, 66.5, 57.4, 53.1, 52.4, 44.0, 28.6, 25.0, 20.7, 20.6, 13.5 ppm; IR (KBr) $\nu = 2953$, 2807, 1568, 1227, 1112 cm^{-1} ; MS (70 eV) m/z 376 [M^+], 235, 168, 125; anal. calcd for $C_{21}H_{36}N_4S$: C, 66.97; H, 9.64; N, 14.88; S, 8.51. Found: C, 66.76; H, 9.80; N, 14.97; S, 8.67.

2-(4-Isopropylpiperazin-1-yl)ethyl (Z)-N,N-diethyl-N'-phenylcarbamiimidiothioate **3b**

¹H NMR (300 MHz, $CDCl_3$) δ 7.29–7.23 (m, 2H), 6.97–6.91 (m, 3H), 3.53 (q, $J = 7.0$ Hz, 4H), 2.78 (septet, $J = 6.5$ Hz, 1H), 1.69–1.58 (m, 4H), 1.43–1.36 (m, 8H), 1.10 (d, $J = 6.5$ Hz, 6H), 0.99 (t, J



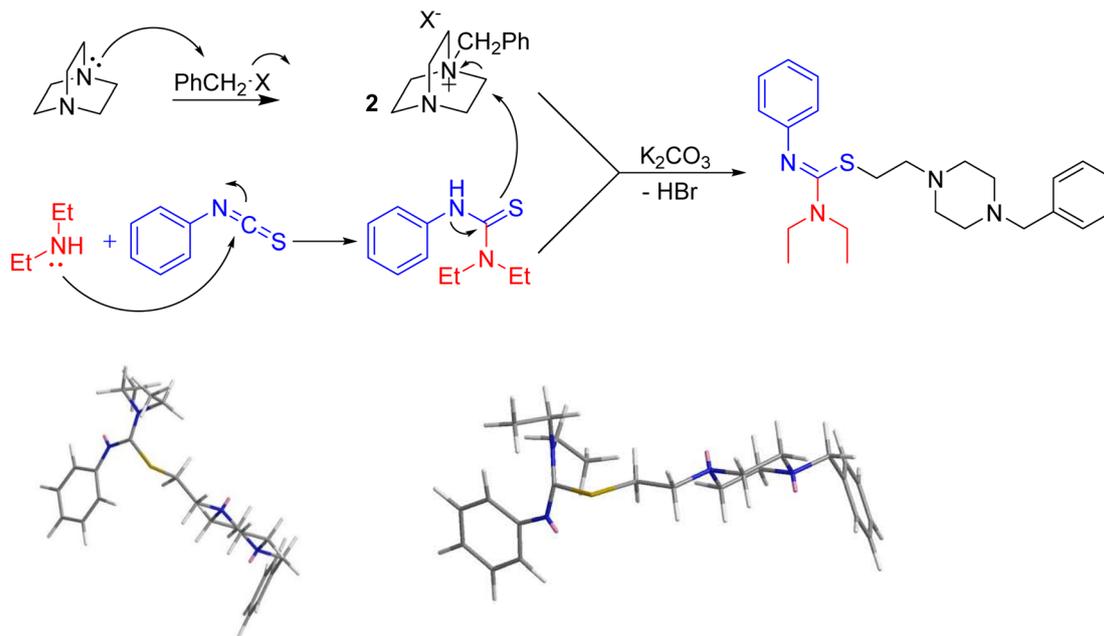


Fig. 2 Proposed mechanism for the synthesis of the products (top) and configurational projection of MM2-energy-minimised **3e** (bottom) obtained from ChemDraw Pro.

= 7.0 Hz, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 153.2, 150.3, 128.6, 121.5, 121.1, 68.1, 49.8, 48.7, 30.7, 29.7, 29.6, 20.1, 14.0 ppm; IR (KBr) ν = 2954, 2809, 1577, 1227 cm⁻¹; MS (70 eV) *m/z* 362 [M⁺], 279, 248, 192; anal. calcd for C₂₀H₃₄N₄S: C, 66.25; H, 9.45; N, 15.45; S, 8.84. Found: C, 66.14; H, 9.23; N, 15.60; S, 9.05.

2-(4-Isopentylpiperazin-1-yl)ethyl (Z)-N,N-diethyl-N'-phenylcarbamimidothioate **3c**

¹H NMR (300 MHz, CDCl₃) δ 7.21–7.15 (m, 2H), 6.94–6.84 (m, 3H), 3.53 (q, *J* = 7.0 Hz, 4H), 2.45–2.40 (m, 4H), 2.38–2.33 (m, 4H), 2.31–2.24 (m, 6H), 1.53 (t, septet, *J* = 7.0, 6.5 Hz, 1H), 1.36–1.29 (m, 2H), 1.16 (t, *J* = 7.0 Hz, 6H), 0.86 (d, *J* = 6.5 Hz, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 152.5, 149.9, 128.4, 121.4, 121.1, 57.4, 56.7, 53.0, 52.4, 44.1, 35.6, 28.7, 26.5, 22.6, 13.7 ppm; IR (KBr) ν = 2953, 2808, 1578, 1227, 1112 cm⁻¹; MS (70 eV) *m/z* 390 [M⁺], 350, 318, 214, 182; anal. calcd for C₂₂H₃₈N₄S: C, 67.64; H, 9.81; N, 14.34; S, 8.21. Found: C, 67.82; H, 10.08; N, 14.58; S, 8.05.

2-(4-Butylpiperazin-1-yl)ethyl (Z)-N,N-diethyl-N'-phenylcarbamimidothioate **3d**

¹H NMR (300 MHz, CDCl₃) δ 7.21–7.15 (m, 2H), 6.92–6.86 (m, 3H), 3.54 (q, *J* = 7.0 Hz, 4H), 2.48–2.36 (m, 4H), 2.36–2.19 (m, 10H), 1.47–1.37 (m, 2H), 1.33–1.27 (m, 2H), 1.17 (t, *J* = 7.0 Hz, 6H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 152.6, 149.9, 128.4, 121.5, 121.3, 58.3, 57.4, 52.9, 52.4, 44.1, 28.8, 28.7, 20.6, 13.8, 13.6 ppm; IR (KBr) ν = 2957, 2808, 1577, 1227 cm⁻¹; MS (70 eV) *m/z* 376 [M⁺], 264, 168, 125; anal. calcd for C₂₁H₃₆N₄S: C, 66.97; H, 9.64; N, 14.88; S, 8.51. Found: C, 66.77; H, 9.83; N, 14.99; S, 8.43.

2-(4-Benzylpiperazin-1-yl)ethyl (Z)-N,N-diethyl-N'-phenylcarbamimidothioate **3e**

¹H NMR (300 MHz, CDCl₃) δ 7.36–7.30 (m, 5H), 7.25–7.20 (m, 2H), 6.95–6.93 (m, 3H), 3.58 (q, *J* = 7.0 Hz, 4H), 3.52 (s, 2H), 2.57–2.37 (m, 12H), 1.21 (t, *J* = 7.0 Hz, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 152.8, 150.0, 129.3, 128.7, 128.2, 127.1, 121.7, 121.5, 121.3, 62.9, 57.5, 52.7, 52.4, 44.3, 28.8, 13.7 ppm; IR (KBr) ν = 2931, 2807, 1578, 1227 cm⁻¹; MS (70 eV) *m/z* 410 [M⁺], 264, 202, 175, 146; anal. calcd for C₂₄H₃₄N₄S: C, 70.20; H, 8.35; N, 13.64; S, 7.81. Found: C, 70.41; H, 8.57; N, 13.49; S, 7.95.

2-(4-Butylpiperazin-1-yl)ethyl (Z)-N,N-dibutyl-N'-phenylcarbamimidothioate **3f**

¹H NMR (300 MHz, CDCl₃) δ 7.22–7.17 (m, 2H), 6.91–6.87 (m, 3H), 3.48 (t, *J* = 7.5 Hz, 4H), 2.46–2.41 (m, 4H), 2.36–2.35 (m, 10H), 1.62–1.52 (m, 4H), 1.48–1.36 (m, 2H), 1.34–1.22 (m, 6H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 153.1, 150.0, 128.5, 121.5, 121.2, 58.3, 57.4, 53.0, 52.4, 49.7, 30.5, 28.8, 28.7, 20.6, 19.9, 13.9, 13.8 ppm; IR (KBr) ν = 2930, 1578, 1376, 1161 cm⁻¹; MS (70 eV) *m/z* 432 [M⁺], 261, 207, 168, 125; anal. calcd for C₂₅H₄₄N₄S: C, 69.39; H, 10.25; N, 12.95; S, 7.41. Found: C, 69.19; H, 10.41; N, 13.08; S, 7.57.

2-(4-Benzylpiperazin-1-yl)ethyl (Z)-N,N-dibutyl-N'-phenylcarbamimidothioate **3g**

¹H NMR (300 MHz, CDCl₃) δ 7.34–7.30 (m, 5H), 7.25–7.19 (m, 3H), 6.95–6.89 (m, 3H), 3.52 (s, 2H), 3.51 (t, *J* = 7.5 Hz, 3H), 2.53–2.45 (m, 2H), 2.45–2.35 (m, 10H), 1.60 (t, *J* = 7.5, 7.5 Hz, 4H), 1.32 (t, q, *J* = 7.0, 7.5 Hz, 4H), 0.95 (t, *J* = 7.0 Hz, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 153.3, 150.1, 134.0, 129.3, 128.6, 128.2, 127.1, 121.6, 121.4, 62.9, 57.5, 52.7, 52.4, 49.9, 30.7, 20.1,



14.0 ppm; IR (KBr) ν = 2941, 2808, 1578, 1159 cm^{-1} ; MS (70 eV) m/z 466 [M^+], 320, 265, 202, 146; anal. calcd for $\text{C}_{28}\text{H}_{42}\text{N}_4\text{S}$: C, 72.06; H, 9.07; N, 12.00; S, 6.87. Found: C, 71.90; H, 9.15; N, 12.11; S, 6.97.

2-(4-Butylpiperazin-1-yl)ethyl (Z)-N-phenylmorpholine-4-carbimidothioate 3h

^1H NMR (300 MHz, CDCl_3) δ 7.21 (d, t, J = 7.5, 2.0 Hz, 2H), 6.94 (t, t, J = 7.5, 2.0 Hz, 1H), 6.87–6.84 (m, 2H), 3.69 (t, J = 4.5 Hz, 4H), 3.59 (t, J = 4.5 Hz, 4H), 2.53–2.47 (m, 4H), 2.38–2.34 (m, 6H), 2.28–2.24 (m, 4H), 1.46–1.36 (m, 2H), 1.27 (t, q, J = 7.0, 7.5 Hz, 2H), 0.87 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 154.9, 149.2, 128.4, 121.3, 121.0, 66.4, 58.2, 57.6, 52.8, 52.4, 48.5, 28.9, 28.7, 20.5, 13.9 ppm; IR (KBr) ν = 2955, 2807, 1582, 1158 cm^{-1} ; MS (70 eV) m/z 390 [M^+], 336, 281, 168, 125; anal. calcd for $\text{C}_{21}\text{H}_{34}\text{N}_4\text{OS}$: C, 64.58; H, 8.77; N, 14.34; S, 8.21. Found: C, 64.62; H, 8.91; N, 14.27; S, 8.40.

2-(4-Isobutylpiperazin-1-yl)ethyl (Z)-N-phenylmorpholine-4-carbimidothioate 3i

^1H NMR (300 MHz, CDCl_3) δ 7.24 (d, t, 7.5, 1.5 Hz, 2H), 7.25 (d, t, 7.5, 1.5 Hz, 1H), 6.81–6.88 (m, 2H), 3.71 (t, 4.5 Hz, 4H), 3.63 (t, 4.5 Hz, 4H), 2.56–2.51 (m, 2H), 2.52–2.34 (m, 10H), 2.05 (d, J = 7.0 Hz, 2H), 1.77 (t, septet, J = 7.0, 6.5 Hz, 1H), 0.88 (d, J = 6.5 Hz, 6H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 154.8, 149.2, 128.3, 121.9, 121.0, 66.5, 66.3, 57.6, 53.0, 52.5, 48.4, 28.9, 25.0, 20.6 ppm; IR (KBr) ν = 2953, 2807, 1583, 1159 cm^{-1} ; MS (70 eV) m/z 390 [M^+], 249, 189, 168, 125; anal. calcd for $\text{C}_{21}\text{H}_{34}\text{N}_4\text{OS}$: C, 67.58; H, 8.77; N, 14.34; S, 8.21. Found: C, 67.65; H, 8.89; N, 14.47; S, 8.39.

2-(4-Benzylpiperazin-1-yl)ethyl (Z)-N-phenylmorpholine-4-carbimidothioate 3j

^1H NMR (300 MHz, CDCl_3) δ 7.35–7.31 (m, 5H), 7.29–7.24 (m, 2H), 7.02 (dd, J = 7.0, 1.5 Hz, 1H), 6.92–6.90 (m, 2H), 3.76 (t, J = 4.5 Hz, 4H), 3.65 (t, J = 4.5 Hz, 4H), 3.53 (s, 2H), 2.59–2.54 (m, 2H), 2.49–2.40 (m, 10H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 155.2, 149.5, 129.3, 128.7, 128.2, 127.1, 122.3, 121.5, 121.3, 66.7, 62.9, 57.8, 52.7, 52.5, 48.7, 29.1 ppm; IR (KBr) ν = 2934, 2807, 1581, 1156 cm^{-1} ; MS (70 eV) m/z 424 [M^+], 278, 202, 146; anal. calcd for $\text{C}_{24}\text{H}_{32}\text{N}_4\text{OS}$: C, 67.89; H, 7.60; N, 13.20; S, 7.55. Found: C, 67.70; H, 7.81; N, 13.32; S, 7.74.

Conclusions

In summary, we developed a method for the synthesis of a novel series of isothiourethane-ethylene-tethered piperazine derivatives. The process can be performed in the same vessel using all the four required reactants in a one-pot manner. The operation is convenient, the process is multicomponent and atom economy, no expensive reagent is required, and each reaction gives a sole product in good yields. The products are expected to exhibit biological properties and would be assessed accordingly in due course.

Author contributions

Conceptualization, study design, data validation, supervision, project administration, and funding acquisition: Mohammed M. Mojtahedi; methodology; investigation, resources, software, formal analysis, and data curation: Fatima Hajizadeh; writing, original draft preparation, review and editing: M. Saeed Abaee. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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