RSC Advances

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

A non-isothiocyanate route to synthesize trisubstituted thioureas of arylamines using *in situ* generated dithiocarbamates†

Cite this: *RSC Advances*, 2013, **3**, 3079

Begur Vasanthkumar Varun and Kandikere Ramaiah Prabhu*

Received 14th September 2012,
Accepted 12th December 2012

DOI: 10.1039/c2ra23257j

www.rsc.org/advances

A novel, user-friendly, and convenient method for the synthesis of trisubstituted thioureas of arylamines is presented, for the first time, using *in situ* generated dithiocarbamates of secondary amines. This strategy provides an excellent opportunity to access thioureas containing primary aryl amines. A non-isothiocyanate route to obtain thioureas is the advantage of this strategy, which may provide a useful route to synthesize a variety of biologically active derivatives of thioureas.

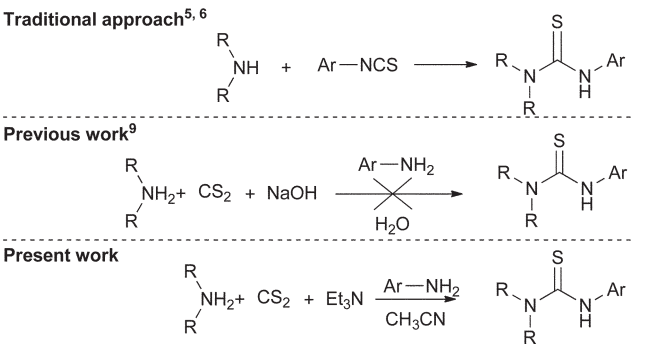
Introduction

Thioureas are a potentially useful class of molecules which are biologically active[1] and serve as precursors for a variety of biologically active heterocyclic compounds.[2] Their utility as organocatalysts, for asymmetric transformations, has led to a variety of synthetic protocols to accomplish a large number of thioureas.[2] Di-substituted thioureas are useful as catalysts for asymmetric reactions through their hydrogen bonding capabilities.[3] Whereas, trisubstituted thioureas find their applications in medicinal chemistry as they are biologically active compounds[4] as well as precursors (especially trisubstituted thioureas of aryl amines) for useful biologically active molecules such as 2-aminobenzothiazole derivatives, amidines *etc*.[5] As trisubstituted thioureas are synthesized using isothiocyanates, it is important to develop methods to access these useful compounds by employing non-isothiocyanate routes. In this context, even today thioureas are synthesized using hazardous precursors such as thiophosgene and isothiocyanates.[5,6] Therefore, there are few attempts to develop safer protocols to access thioureas.[7] In this direction, we have developed strategies to synthesize thioureas by reacting amines with molybdenum dithiocarbamate[8] or dithiocarbamates.[9] But the aryl amines were unreacted under these conditions. Therefore, these methods[9] were useful in synthesizing alkyl substituted thioureas, but were not successful for the synthesis of aryl trisubstituted thioureas. In view of the importance of aryl substituted trisubstituted thioureas, and continuation of our expedition in developing user-friendly methods to access thioureas, herein we report a detailed study on developing a strategy to synthesize trisubstituted thioureas of arylamines using *in situ* generated dithiocarbamates of secondary amines.

Results and discussion

Earlier, we have reported the synthesis of trisubstituted thioureas by reaction of secondary amines with molybdenum xanthate.[8] Further, we reported an improved method to access thioureas using sodium dialkyldithiocarbamates and secondary amines in water.[9] In these methods the aryl amines were unreacted, but it was noticed that solubility of dithiocarbamates and amines in water are limiting factors in obtaining the thioureas. However the reactions with aryl amines or alkyl amines in organic solvents resulted in the formation of a mixture of thioureas or no reactions were observed with aryl amines in water (Scheme 1; previous work).

Unreactivity of aromatic amines under the reaction conditions may be attributed to the poor nucleophilicity and insolubility of aromatic amines in water. Further, dithiocarba-



Scheme 1 Methods to synthesise trisubstituted thioureas.

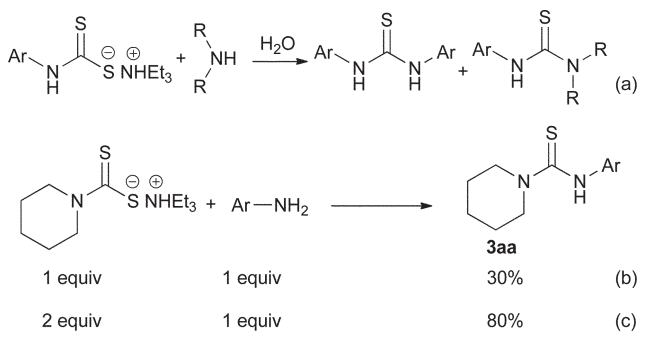
Department of Organic chemistry, Indian Institute of Science, Bangalore, 560 012, Karnataka, India. E-mail: prabhu@orgchem.iisc.ernet.in; Fax: +91-80-23600529; Tel: +91-80-22932887

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ra23257j

mates being poor electrophiles makes it difficult to force the reaction between them and aromatic amines. To overcome this problem, it is essential to modify the counter ion of dithiocarbamate to make it compatible with organic solvents. However, the reaction of dithiocarbamate of aromatic amines with secondary amines in H_2O or CH_3CN led to the formation of a mixture of aromatic symmetrical thioureas and unsymmetrical thioureas (Scheme 2a, also see ESI-Scheme 1, ESI†). Nevertheless, the reaction of 1 equiv. dithiocarbamate of **1a** with 1 equiv. of **2a** in CH_3CN furnished 30% of **3aa** and the formation of aromatic symmetrical thiourea was not observed (Scheme 2b). Whereas, the reaction of 2 equiv. dithiocarbamate of **1a** with 1 equiv. of arylamine (**2a**) in CH_3CN furnished 80% of **3aa** (Scheme 2c). Then, we thought it would be appropriate to design an *in situ* method to synthesize trisubstituted thioureas of aryl amines such as **3aa**.

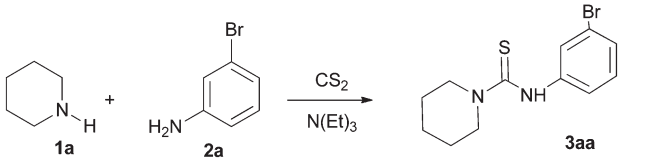
To optimize the reaction conditions, piperidine (**1a**) and 3-bromoaniline (**2a**) were used as the secondary amine and aromatic amine (Table 1).[10] Reaction of equimolar amounts of **2a** with *in situ* generated dithiocarbamate of **1a** (using CS_2 and triethylamine) in CH_3CN at room temperature did not furnish the expected thiourea (entry 1). Whereas the reactions at elevated temperature (80 °C) resulted in the formation of the corresponding unsymmetrical thiourea **3aa** in 31% yield (entry 2, Table 1). Extending the reaction time to 12 h resulted in better yields (67%, entry 3, Table 1). Further extension of the reaction time did not result in any improvements of the yield. However, increasing the amount of amine **1a** (1.5 equiv.) and performing the reaction for 6 h was not very useful as the product **3aa** was obtained in 51% (entry 4, Table 1). The reaction of 2 equiv. of **1a** with 1 equiv. of **2a** at 80 °C was pleasing as it resulted in the formation of **3aa** exclusively in quantitative yield (entry 5, Table 1). Using K_2CO_3 as a base or different solvents such as dioxane, EtOH, EtOAc, toluene or water resulted in lower yield of the product (entries 6–11, Table 1).[10] Therefore, it was decided to use 2 equiv. of secondary amine, 2.2 equiv. of triethylamine, and 2.4 equiv. of CS_2 and carry out the further reactions in CH_3CN at 80 °C.[11]

The scope and limitation of the reaction was further established by carrying out reactions of a variety of secondary amines with substituted anilines and the results are presented in Table 2. Halosubstituted anilines such as, 4-bromoaniline,



Scheme 2 Reactions of aryl dithiocarbamates and dialkyl dithiocarbamates.

Table 1 Screening studies

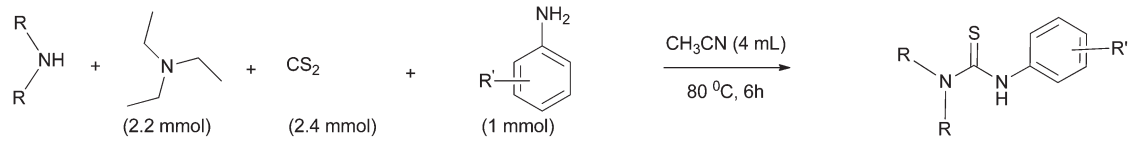


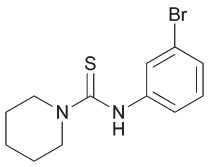
Entry	**1a** (equiv.)[a]	Solvent	T (°C)	Time (h)	**3aa** Conversion[b]
1	1	CH_3CN	RT	24	nd
2	1	CH_3CN	80	6	31
3	1	CH_3CN	80	12	67
4	1.5	CH_3CN	80	6	51
5	2	CH_3CN	80	6	>98
6	2	CH_3CN	80	6	48[c]
7	2	Dioxane	80	6	48
8	2	EtOH	80	6	47
9	2	EtOAc	80	6	26
10	2	Toluene	80	6	51
11	2	H_2O	80	24	nd

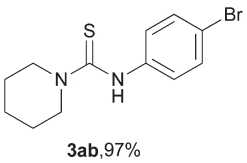
[a] CS_2 and triethylamine are used 1.2 equiv. and 1.1 equiv. with respect to **1a**. [b] Determined by ^1H NMR. [c] Base is K_2CO_3. nd = Not detected

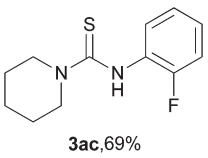
3-bromoaniline, 2-fluoroaniline reacted with piperidine to yield corresponding thioureas **3aa**, **3ab**, and **3ac** in 97%, 81% and 69% respectively (Table 2). 3,5-Bis(trifluoromethyl)aniline under the optimal conditions reacted well with piperidine to furnish the corresponding thiourea **3ad** in 61% yield. Alkoxy substituted anilines such as 3-methoxyaniline, 4-methoxyaniline, and 2-methoxyaniline reacted well with piperidine to afford their corresponding thioureas **3ae**, **3af** and **3ag** in excellent yields (93%, 82%, 82%, respectively, Table 2). The reaction of aniline with piperidine under the optimal conditions resulted in the formation of **3ah** in good yield (83%, Table 2). Piperidine underwent a smooth reaction with a variety of substituted anilines such as *p*-toluidine, *o*-toluidine, 2,6-dimethylaniline, 3,5-dimethylaniline to furnish corresponding thioureas **3ai**, **3aj**, **3ak**, and **3al** in excellent yields (Table 2). Acetyl, amide and sulfonamide substituted arylamines are good substrates for this reaction as 1-(4-aminophenyl)ethanone, 4-aminobenzamide, 4-aminobenzenesulfonamide reacted with piperidine to produce the corresponding thioureas **3am**, **3an** and **3ao** in 61%, 76% and 76% respectively (Table 2). The versatility of this methodology to access a variety of trisubstituted thiourea was examined with a variety of dialkylamines and substituted anilines. As seen in Table 2, morpholine reacted well with a variety of aromatic amines such as aniline, 2,6-dimethylaniline, 3,5-dimethylaniline, and 2,6-diisopropylaniline to furnish the corresponding thioureas **3bh**, **3bk**, **3bl**, and **3bp** in good to excellent yields (Table 2). As noticed earlier with piperidine, morpholine also reacted well with aromatic amines containing carboxylic acid, carbonyl and nitro functionalities to furnish the corresponding thioureas **3bm**, **3bq**, and **3br** in 63%, 85%, and 72% respectively (Table 2). Similarly, thiomorpholine reacted well with 3-methoxy aniline and 4-bromoaniline to furnish corresponding thioureas **3ce** and **3cb** in excellent yields

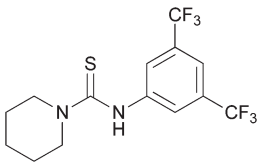
Table 2 Scope of the reaction

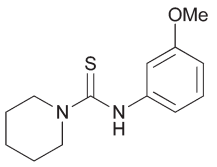


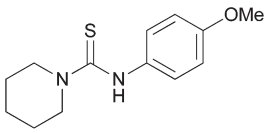

3aa,81%

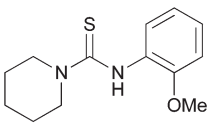

3ab,97%

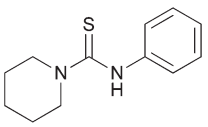

3ac,69%

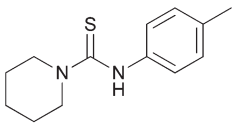

3ad, 61%

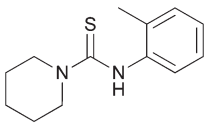

3ae, 93%

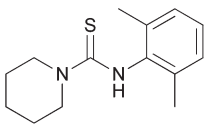

3af, 82%

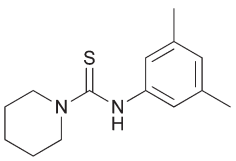

3ag, 82%

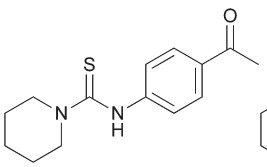

3ah, 83%

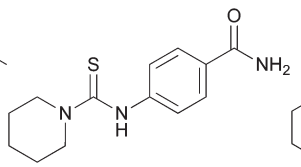

3ai,90%

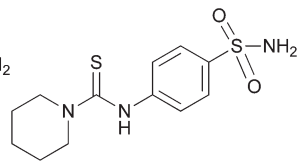

3aj,88%

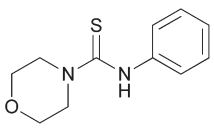

3ak,95%

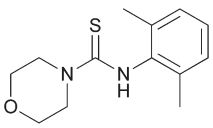

3al,89%

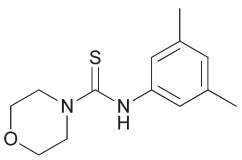

3am,81%[b,c]

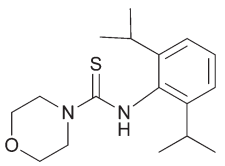

3an,76%

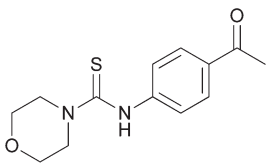

3ao,76%[b,c]

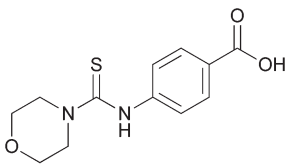

3bh,79%

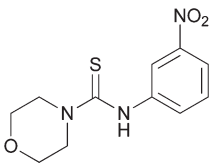

3bk,93%

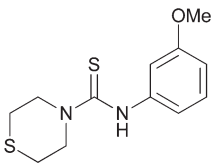

3bl,88%

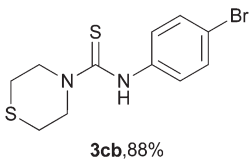

3bp,72%

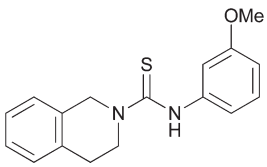

3bm ,63%[b,c]

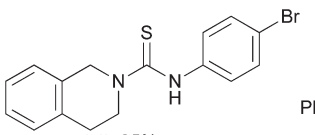

3bq,85%[b]

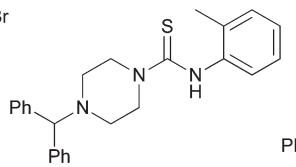

3br,72%

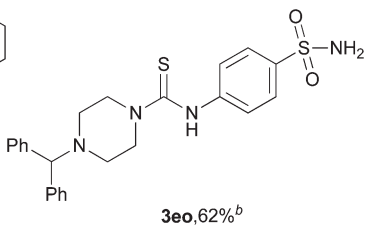

3ce,90%

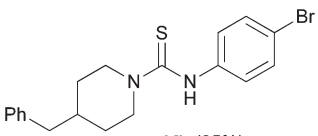

3cb,88%

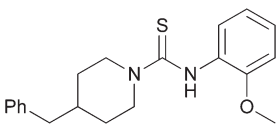

3de, 91%

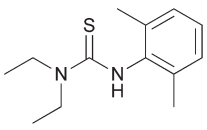

3db,85%

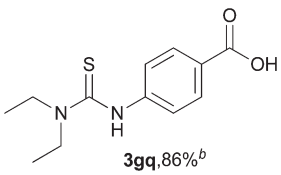

3ej,93%

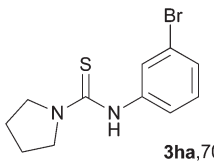

3eo,62%[b]


3fb,(85%)


3fg,(81%)


3gk,91%


3gq,86%[b]


3ha,70%

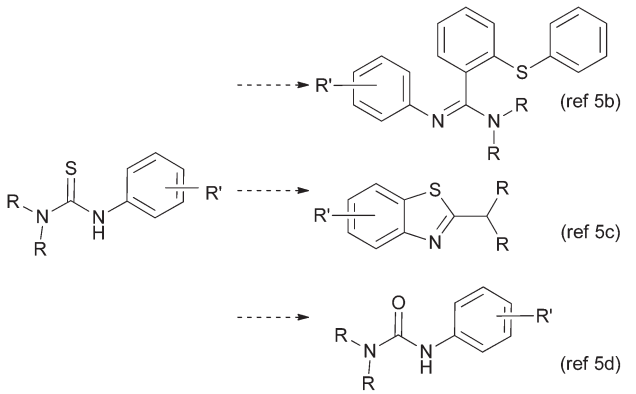
[a] Isolated yields. [b] Heated at 80 °C for 12 h. [c] Used 3 equiv. of secondary amine.

(90% and 88%, Table 2). Tetrahydroisoquinoline reacted well with amines such as 4-methoxy aniline and 4-bromoaniline under the optimal conditions to provide the corresponding thioureas **3de** and **3db** in excellent yields 91% and 85%, Table 2). 1-Benzhydrylpiperazine reacted well with 2-methylaniline and 4-aminobenzenesulfonamide to yield the corresponding trisubstituted thioureas **3ej** and **3eo** in good yields (93% and 62%, Table 2). 4-Benzylpiperidine reacted well with 4-bromoaniline and 2-methoxyaniline to furnish their corresponding thioureas **3fb** and **3fg** in good yields. *N*,*N*-Diethylamine reacted smoothly with 2,6-dimethylaniline and 4-aminobenzoic acid to afford the corresponding thioureas **3gk** and **3gq** in 91% and 86% respectively. Similarly, tetrahydropyrrole reacted well with 3-bromoxyaniline to afford the corresponding thioureas **3ha** in 70% (Table 2). Looking at the wide spectrum of the reactivity presented here, this reaction appeared to be versatile as electron withdrawing or electron donating substituents on phenyl ring has no effect on the outcome of the reaction. Additionally, the reaction tolerates a variety of functionality such as acid, ketone, halide, amide, nitro, and sulfonamide. The wide scope of this reaction is established using a number of secondary amines such as piperidine, morpholine, thiomorpholine, substituted piperidines, pyrrolidine *etc*. Apart from this, many of the products presented in the Table 2 have features of biologically active molecules. Therefore, this method may pave way for a new avenue to access a wide variety of useful thioureas.

To examine the application of this methodology, the scaling up experiments of 3-bromoaniline or 4-bromoaniline (20 mmol) with piperidine under the optimal conditions were performed. As can be seen in the Scheme 3, these reaction proceeded well to afford the expected thioureas **3aa** and **3ab** in good yields (Scheme 3).[12]

Trisubstituted thioureas can be transformed in to amidines, 2-aminobenzothiazole derivatives, guanidines and ureas (in one step), which are useful as biologically active molecules (Scheme 4).[5] Therefore, we believe that this non-isothiocyanate route is important in small scale (academia) and large scale (industry) preparations as it avoids phosgene and thiophosgene.

The formation of trisubstituted thioureas of arylamines can be explained based on our earlier observation and reports,[8,9] which is presented in Scheme 5.



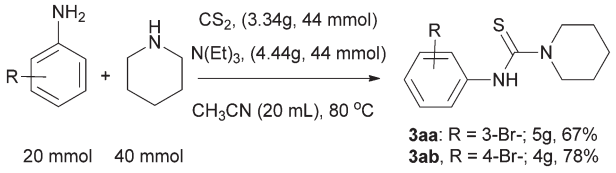
Scheme 4 Possible applications of trisubstituted thioureas.

Conclusion

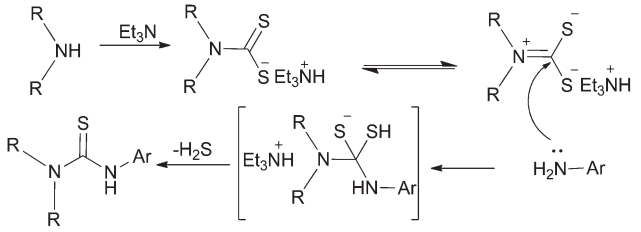
In summary, we have demonstrated a facile and convenient method to access trisubstituted thioureas by reacting *in situ* generated dithiocarbamate of secondary amines with aryl amines. To the best of our knowledge, this is the first report of the reaction of *in situ* generated dithiocarbamate of secondary amines with aryl amines to accomplish trisubstituted thioureas of aryl amines. One of the salient features of this method is that it does not employ isothiocyanate. Apart from these advantages, it has been shown that the reaction is versatile and works with a variety of substrates.

Experimental

NMR spectra were recorded on a JEOL LA-300, BRUKER-AV400 spectrometer in $CDCl_3$, Tetramethylsilane (TMS; δ = 0.00 ppm) served as internal standards for ^{1}H NMR. The corresponding residual non-deuterated solvent signal ($CDCl_3$: δ = 77.00 ppm) was used as internal standards for ^{13}C NMR. IR spectra were measured using a JASCO FT/IR-410 spectrometer, and Perkin-Elmer FT/IR Spectrum BX, GX. Mass spectra were measured with Micromass Q-Tof (ESI-HRMS). Column chromatography was conducted on Silica gel 230–400 mesh (Merck) and preparative thin-layer chromatography was carried out using SILICA GEL GF-254.



Scheme 3 Scaling up experiment.



Scheme 5 Tentative mechanism.

Typical experimental procedure

To a well stirred solution of dialkyl amine (2 mmol) and triethylamine (222 mg, 2.2 mmol) in CH_3CN (3 mL) was added CS_2 (182 mg, 2.4 mmol) drop-wise during 5 min at 0 °C, and the stirring was continued for 10 min at 0 °C. After allowing the reaction mixture to warm to room temperature, the stirring was continued for additional 10 min (to expel the excess CS_2). Then was added aryl amine (1 mmol), and the reaction mixture was heated at 80 °C until the completion of the reaction (monitored by TLC). The evaporation of the solvent under vacuum, followed by the addition of 2 N HCl (5 mL) resulted in the precipitation of brown solid, which was filtered, washed with hexane (10 mL) and dried to furnish a pale brown solid. For the compounds **3ej** and **3eo** the work up procedure is as follows: after the completion of the reaction, the crude material was partitioned between EtOAc (10 mL)/water (30 mL). The aqueous layer was extracted with EtOAc (10 mL × 3), the combined organic layer was dried over anhydrous Na_2SO_4, purified on a silica gel column.

Preparation of triethylammonium dithiocarbamate of piperidine and aniline

Triethylammonium dithiocarbamate of piperidine. To a well-stirred solution of piperidine (2 mmol), and triethylamine (2 mmol) in diethyl ether (3 mL) was added CS_2 (2.2 mmol) drop-wise over 2 mins at room temperature and stirred for 10 mins. The white solid precipitated was filtered, dried and used (yield: quantitative, 524 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 917–8.97 (1H, br, m), 4.38 (4H, m), 7.23 (1H, d, J = 8 Hz), 3.15 (6H, q, J = 7.3 Hz), 1.64 (6H, s), 1.33 (9H, t, J = 7.3 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 208.8, 51.6, 45.6, 25.8, 24.3, 9.04 (a small amount of disulfirum was observed as impurity)

Triethylammonium dithiocarbamate of aniline. To a well-stirred solution of aniline (2 mmol), and triethyl amine (2 mmol) in diethyl ether (3 mL) was added CS_2 (2.2 mmol) drop-wise over 2 mins at room temperature and stirred for 1 h. The yellow solid precipitated was filtered, dried and used (yield; 90%, 486 mg). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 9.36 (1H, bs), 7.65 (2H, d, J = 9.2 Hz), 7.30 (2H, *t*, J = 7.8 Hz), 7.11 (1H, t, J = 7.3 Hz), 3.21 (6H, q, J = 8.0 Hz), 1.35 (9H, t, J = 8.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 214.2, 140.8, 128.1, 124.5, 123.5, 45.7, 8.7.

Characterization data

N*-(3-Bromophenyl)piperidine-1-carbothioamide (3aa).** Prepared as described in the general experimental procedure; Pale brown solid; Yield 81% (242 mg); ***mp: 129–131 °C (recrystallized from EtOAc/hot hexane 1 : 20); R_f (10% EtOAc/hexane) 0.1; **IR** (KBr, cm^{-1}): 3442, 3190, 2935, 2919, 2853, 1585, 1591, 1537, 1438, 1315, 1232, 772, 712. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.36 (1H, bs), 7.27 (1H, s), 7.23 (1H, d, J = 8 Hz), 7.16 (1H, t, J = 7.92 Hz), 7.06 (1H, d, J = 7.92 Hz), 3.78–3.77 (4H, m), 1.66 (6H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 182.0, 141.5, 130.1, 127.5, 125.5, 122.3, 121.3, 50.8, 25.4, 24.0. **HRMS (ESI)** (m/z): Calculated for $C_{12}H_{15}BrN_2S$ (M+Na): 321.0037, found (M+Na): 321.0036.

N*-(4-Bromophenyl)piperidine-1-carbothioamide (3ab).** Prepared as described in the general experimental procedure; Pale brown solid; yield 97% (290 mg); ***mp: 165–167 °C; (lit.[13] 166 °C); R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3449, 3249, 2946, 2922, 2854, 1583, 1534, 1487, 1420, 1282, 1326, 1236, 1009, 827, 716; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.41 (2H, d, J = 8.2 Hz), 7.18 (1H, bs), 7.01 (2H, d, J = 8.16 Hz) (3.77 (4H, s), 1.66 (6H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 182.2, 139.3, 131.9, 124.6, 117.8, 50.65, 25.5, 24.0; **HRMS (ESI)** (m/z): Calculated for $C_{12}H_{15}N_2SBr$ (M+Na): 321.0037, found (M+Na): 321.0039.

***N*-(2-Fluorophenyl)piperidine-1-carbothioamide (3ac).** Prepared as described in the general experimental procedure and purified on a silica gel column (EtOAc/hexane 5 : 95–10 : 90): Brown semi-solid; Yield 69% (164 mg); R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3233, 2935, 2855, 1638, 1522, 1406, 1315, 1261, 1237, 1125, 1102, 1018, 853, 756; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.55–7.50 (1H, m), 7.13–7.05 (4H, m), 3.84–3.83 (4H, m), 1.68 (6H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 181.6, 154.8 (d, ^1J (CF) = 243.8 Hz), 128.0 (d, ^3J (CF) = 11.1 Hz), 125.9 (d, ^3J (CF) = 7.7 Hz), 125.7, 123.9 (d, ^4J (CF) = 3.8 Hz), 115.5 (^2J (CF) = 19.4 Hz); **HRMS (ESI)** (m/z): Calculated for $C_{12}H_{15}N_2SF$ (M+H): 239.1018, found (M+H): 239.1018.

N*-(3,5-Bis(trifluoromethyl)phenyl)piperidine-1-carbothioamide (3ad).** Prepared as described in the general experimental procedure: Pale brown solid; Yield 61% (217 mg); ***mp: 176–178 °C (lit.[14] 182–184 °C); (recrystallized from EtOAc/hot hexane 1 : 20), R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3442, 3141, 2936, 1540, 1379, 1280, 1238, 1188, 1129, 887; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.65 (2H, s), 7.59 (1H, s), 7.29 (1H, br) 3.86–3.85 (4H, m), 1.72 (6H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 181.3, 141.6, 131.9 ($^2J_{3,5}$ (CF) = 33.3 Hz), 123.0 (q, ^1J (CF) = 271.1 Hz), 122.6 ($^3J_4$ (CF) = 3.4 Hz) , 117.6 ($^3J_2$ (CF) = 4 Hz) 50.6, 25.5, 24.0; **HRMS (ESI)** (m/z): Calculated for $C_{14}H_{14}N_2SF_6$ (M+H): 357.0860, found (M+H): 357.0850.

N*-(3-Methoxyphenyl)piperidine-1-carbothioamide (3ae).** Prepared as described in the general experimental procedure: The crude compound was extracted with EtOAc (10 mL × 3) and washed with 1N HCl (30 mL), the combined organic fractions were evaporated under reduced pressure and then crystalized from EtOAc/hot hexane 1 : 20 to give white solid; Yield 93% (232 mg); ***mp: 88–90 °C; R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3645, 3182, 2939, 2853, 1605, 1597, 1493, 1537, 1531, 1434, 1327, 1319, 1238, 1011 ,778, 713; **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.15 (1H, bs), 7.17 (1H, t, J = 8.04), 6.88–6.84 (2H, m), 6.66–6.64 (1H m), 3.85–3.84 (4H, m) 3.72 (3H, s), 1.63–1.55 (6H, m); **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) 180.7, 159.0, 142.4, 128.6, 116.9, 110.3, 109.4, 55.0, 49.3, 25.4, 23.9; **HRMS (ESI)** (m/z): Calculated for $C_{13}H_{18}N_2OS$ (M+Na): 273.1038, found (M+Na): 273.1038.

N*-(4-Methoxyphenyl)piperidine-1-carbothioamide (3af)[15].** Prepared as shown in the general experimental procedure; Pale yellow solid. Yield 82% (205 mg); ***mp: 145–148 °C; (lit.[16] 141–144 °C); R_f (50% EtOAc/hexane) 0.4; **IR** (KBr, cm^{-1}): 3444, 3201, 2935, 2853, 1627, 1528, 1425, 1320, 1242, 1035, 1010, 837, 729. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.15 (1H, br), 7.08 (2H, d, J = 8.8 Hz), 6.85 (2H, d, J = 8.8 Hz), 3.79–3.78 (7H, m), 1.65 (6H s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 182.6, 157.2, 133.2, 125.9, 114.1, 55.4, 50.3, 25.4, 24.1; **HRMS (ESI)**

(*m*/*z*): Calculated for $C_{13}H_{18}N_2OS$ (M+Na): 273.1038, found (M+Na): 273.1039.

***N*-(2-Methoxyphenyl)piperidine-1-carbothioamide (3ag).** Prepared as shown in the general experimental procedure and purified on a silica gel column (EtOAc/hexane 5 : 95–10 : 90). Yellow liquid: Yield 82% (206 mg); R_f (20% EtOAc/hexane) 0.3; **IR** (neat): 3398, 2936, 2853, 1601, 1522, 1399, 1352, 1286, 1328, 1227, 1128, 1115, 1108, 1022, 852, 746; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.72 (1H, d, J = 7.9 Hz), 7.39 (1H, bs), 7.05 (1H, t J = 8 Hz), 6.93 (1H, t, J = 7.7 Hz), 6.87 (1H, d J = 8.2 Hz), 3.84–3.82 (7H, m), 1.67 (6H s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 181.1, 149.4, 128.9, 124.1, 122.1, 120.1, 110.3, 55.5, 50.1, 25.3, 24.0. **HRMS (ESI)** (*m*/*z*): Calculated for $C_{13}H_{18}N_2OS$ (M+Na): 273.1038, found (M+Na): 273.1036.

N*-Phenylpiperidine-1-carbothioamide (3ah)[17].** Prepared as described in the general experimental procedure and purified on silica gel column (EtOAc/hexane 5 : 95-10 : 90): White crystalline solid : Yield 83% (182 mg); ***mp: 98–100 °C (lit.[16] 99–101 °C); R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3480, 3259, 3119, 3045, 2931, 2913, 2847, 2884, 2949, 1593, 1534, 1499, 1411, 1324, 1313, 1228, 1133, 1004, 753, 691; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.33–7.27 (3H, m), 7.14–7.09 (3H, m), 3.77–3.75 (4H, m), 1.65 (6H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 182.5, 140.3, 129.0, 124.7, 122.7, 50.8, 25.4, 24.0; **HRMS (ESI)** (*m*/*z*): Calculated for $C_{12}H_{16}N_2S$ (M+Na): 243.0932, found (M+Na): 243.0933.

***N*-(4-Methylphenyl)piperidine-1-carbothioamide (3ai)[18].** Prepared as shown in the general experimental procedure: Pale yellow solid: Yield 90% (210 mg); 130–132 °C (lit.[18] 132–133 °C) (recrystallized from EtOAc/hot hexane 1 : 20); R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3208, 2923, 2855, 2022, 1519, 1324, 1233, 818, 701; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.25 (1H, br), 7.10 (2H, d, J = 8 Hz), 6.99 (2H, d, J = 8.1 Hz), 3.76–3.74 (4H, m), 2.31 (3H, s), 1.64 (6H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 182.5, 137.6, 134.7, 129.4, 123.3, 50.5, 25.4, 24.0, 20.8. **HRMS (ESI)** (*m*/*z*): Calculated for $C_{12}H_{16}N_2S$ (M+Na 257.1088), found (M+Na): 257.1084.

N*-(2-Methylphenyl)piperidine-1-carbothioamide (3aj).** Prepared as shown in the general experimental procedure; Pale yellow needle like crystals; Yield 88% (205 mg); ***mp: 97–99 °C (lit.[13] 98 °C) (recrystallized from EtOAc/hot hexane 1 : 20); R_f (20% EtOAc/hexane) 0.5; **IR** (KBr, cm^{-1}): 3219, 2949, 2936, 1524, 1409, 1332, 1324, 1253, 1235, 1005, 762, 722; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.20–7.15 (2H, m), 7.12–7.05 (2H, m), 6.90 (1H, bs), 3.74–3.73 (4H, m), 2.25 (3H, s), 1.63–1.61 (6H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 182.9, 138.8, 132.3, 130.7, 126.5, 125.9, 124.9, 50.6, 25.34, 24.0, 17.9. **HRMS (ESI)** (*m*/*z*): Calculated for $C_{13}H_{18}N_2S$ (M+Na): 257.1088, found (M+Na): 257.1089.

N*-(2,6-Dimethylphenyl)piperidine-1-carbothioamide (3ak).** Prepared as described in the general experimental procedure: The brown solid was dissolved in 0.5 mL of DMSO, followed by the addition of cold water (20 mL) furnished white precipitate, which was filtered and dried. Yield 95% (235 mg); ***mp: 159–161 °C; R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3448, 3231, 2938, 2855, 1638, 1518, 1330,1320, 1243, 1225, 1131, 1007, 854, 781; **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 8.77 (1H, broad), 7.05 (3H, s), 3.91–3.89 (4H, m), 2.14 (6H, s) 1.67–1.55 (6H, m); **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) 180.1, 138.6, 136.2, 127.5, 126.3, 49.0, 25.5, 24.0, 18.0; **HRMS (ESI)** (*m*/*z*): Calculated for $C_{14}H_{20}N_2S$ (M+Na): 271.1245, found (M+Na): 271.1244.

N*-(3,5-Dimethylphenyl)piperidine-1-carbothioamide (3al).** Prepared as described in the general experimental procedure: Pale brown solid; Yield 89% (220 mg); ***mp: 133–135 °C; R_f (20% EtOAc/hexane) 0.4; **IR** (KBr, cm^{-1}): 3188, 2929, 2848, 1604, 1534, 1474, 1433, 1326,S 1233, 1126,847, 721, 603; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.14 (1H, bs), 6.76 (1H, s), 6.70 (2H, s), 3.75–3.74 (m, 4H), 2.28 (6H, s), 1.64 (6H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): 182.8, 140.2, 138.7, 126.5, 120.2, 50.9, 25.4, 24.1, 21.2; **HRMS (ESI)** (*m*/*z*): Calculated for $C_{14}H_{20}N_2S$ (M+Na): 271.1245 found (M+Na): 271.1242.

N*-(4-Acetylphenyl)piperidine-1-carbothioamide (3am).** Prepared as described in the general experimental procedure: Pale brown solid: Yield 81% (212 mg); ***mp: 157–159 °C; R_f (30% EtOAc/hexane) 0.2; **IR** (KBr, cm^{-1}): 3448, 3158, 2999, 2918, 2846, 1677, 1602, 1524, 1508, 1432, 1360, 1303, 1264, 1238, 1176, 1133, 1004, 960, 854, 835, 747, 705, 599; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.88 (2H, d, J = 8.6 Hz), 7.65 (1H, br), 7.16 (2H, d, J = 8.5 Hz), 3.79 (4H, s) 2.56 (3H s) 1.68 (6H s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 197.1, 182.0, 144.8, 132.7, 129.8, 120.8, 51.3, 26.6, 25.7, 24.2; **HRMS (ESI)** (*m*/*z*): Calculated for $C_{14}H_{18}N_2SO$ (M+Na): 285.1038, found (M+Na): 285.1041.

4-(Piperidine-1-carbothioamido)benzamide (3an). Prepared as shown in the general experimental procedure; Pale brown solid: Yield 76% (200 mg); ***mp***: 188–190 °C; R_f (100% EtOAC) 0.3; **IR** (KBr, cm^{-1}): 3798, 3611, 3396, 3177, 2938, 2840, 1695, 1604, 1517, 1418, 1300, 1231, 1131, 1031, 844, 718, 515; **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.35 (1H, br), 7.86 (1H, br), 7.78 (2H, d, J = 8.5 Hz), 7.34 (2H, d, J = 8.5 Hz), 7.23 (1H, br), 3.87–3.86 (4H, m), 1.64–1.56 (6H m); **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) 180.5, 167.5, 144.0, 129.1, 127.4, 123.2, 49.4, 25.5, 23.8; **HRMS (ESI)** (*m*/*z*): Calculated for $C_{13}H_{17}N_3OS$ (M+Na): 286.0990, found (M+Na): 286.0991.

N*-(4-Sulfamoylphenyl)piperidine-1-carbothioamide (3ao).** Prepared as described in the general experimental procedure; Pale brown solid: Yield 76% (227 mg); ***mp: 196–199 °C; R_f (50% EtOAc/hexane) 0.2; **IR** (KBr, cm^{-1}): 3796, 3721, 3557, 3333, 3244, 3158, 2932, 2849, 2244, 1598, 1531, 1428, 1285, 1242, 1302, 1156, 1133, 1009, 897, 729, 541; **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.44 (1H, br), 7.70 (2H, d, J = 8.5 Hz), 7.44 (2H, d, J = 8.5 Hz), 3.87 (4H, s), 1.64–1.57 (6H, m); **^{13}C NMR** (100 MHz, DMSO): δ (ppm) 180.4, 144.5, 138.5, 125.7, 123.6, 49.5, 25.5, 23.8; **HRMS (ESI)** (*m*/*z*): Calculated for $C_{12}H_{17}N_3O_2S_2$ (M+Na): 322.0660, found (M+Na): 322.0662.

N*-Phenylmorpholine-4-carbothioamide (3bh)[19].** Prepared as described in the general experimental procedure and purified on silica gel column (EtOAc/hexane 5 : 95–10 : 90); White solid: Yield 79% (175 mg); ***mp: 132–134 °C; (lit.[19] 136–137); R_f (20% EtOAc/hexane) 0.1; **IR** (KBr, cm^{-1}): 3196, 2935, 2875, 1612, 1533, 1446, 1324, 1219, 1115, 1002, 845, 715. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.47 (1H, bs), 7.35–7.31 (2H, m), 7.18–7.12 (3H, m), 3.80–3.78 (4H, m), 3.72–3.69 (4H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 183.5, 139.8, 129.1, 125.3,

123.1, 66.0, 49.5; **HRMS (ESI)** (*m*/*z*): Calculated for $C_{11}H_{14}N_2OS$ (M+H): 223.0905, found (M+H): 223.0906.

N*-(2,6-Dimethylphenyl)morpholine-4-carbothioamide (3bk).** Prepared as described in the general experimental procedure; Pale brown solid; Yield 94% (235 mg); ***mp: 138–140 °C; R_f (30% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3210, 2923, 2860, 1671, 1517, 1399, 1339, 1275, 1235, 1119, 1029, 942, 781; **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 8.95 (1H, bs), 7.07 (3H, s), 3.92–3.90 (4H, m), 3.66–3.64 (4H, m), 2.14 (6H, s); **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) 181.3, 138.2, 136.1, 127.6, 126.5, 65.9, 48.2, 17.9 **HRMS (ESI)** (*m*/*z*): Calculated for $C_{13}H_{18}N_2OS$ (M+Na): 273.1038, found (M+Na): 273.1035.

N*-(3,5-Dimethylphenyl)morpholine-4-carbothioamide (3bl)[20].** Prepared as described in the general experimental procedure; White solid; Yield 88% (220 mg); ***mp: 155–157°; (lit.[20] 153–154 °C); R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3451, 3216, 2966, 2854, 2917, 1612, 1542, 1535, 1332, 1230, 1212, 1115, 1025, 843, 722; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.27 (1H, broad), 6.80 (1H, s), 6.72 (2H, s), 3.80–3.78 (4H, m), 3.72–3.71 (4H, m), 2.3 (6H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 183.8, 139.6, 139.0, 127.1, 120.4, 66.1, 49.8, 21.3 **HRMS (ESI)** (*m*/*z*): Calculated for $C_{13}H_{18}N_2OS$ (M+Na): 273.1038, found (M+Na): 273.1037.

N*-(2,6-Diisopropylphenyl)morpholine-4-carbothioamide (3bp).** Prepared as described in the general experimental procedure; pale yellow solid; Yield 72% (220 mg); ***mp: 175–177 °C; R_f (20% EtOAc/hexane) 0.2; **IR** (KBr, cm^{-1}): 3271, 2926, 2962, 2865, 1513, 1302, 1339, 1322, 1273, 1229, 1120, 1028, 802, 678. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 8.83 (1H, bs), 7.23 (1H, t, J = 7.46), 7.13 (2H, t, J = 7.36 Hz), 3.94 (4H, s), 3.66 (4H, s), 3.02–3.2.95 (2H, m), 1.44 (6H, d, J = 6.64 Hz), 1.13 (6H, d, J = 6.6 Hz); **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) 182.7, 146.2, 135.6, 127.3, 122.9, 65.9, 48.4, 27.9, 23.4, 23.2. **HRMS (ESI)** (*m*/*z*): Calculated for $C_{17}H_{26}N_2OS$ (M+Na): 329.1664, found (M+Na): 329.1660.

N*-(4-Acetylphenyl)morpholine-4-carbothioamide (3bm).** Prepared as described in the general experimental procedure; Pale yellow solid: Yield 63% (166 mg); ***mp: 87–89 °C; R_f (50% EtOAc/hexane) 0.1; **IR** (KBr, cm^{-1}): 3448, 3151, 3091, 2977, 2894, 2856, 1682, 1672, 1603, 1587, 1525, 1421, 1358, 1316, 1302, 1219, 1178, 1066, 1028, 861, 834, 742, 589; **^{1}H NMR** (400 MHz, $CDCl_3$); δ (ppm) 7.90 (2H, d, J = 8.5 Hz), 7.75 (1H, br), 7.22 (2H, d, J = 8.5 Hz), 3.87–3.85 (4H, m), 3.76–3.74 (4H, m), 2.56 (3H s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 197.0, 182.8, 144.1, 133.0, 129.5, 121.3, 66.0, 49.8, 26.4; **HRMS (ESI)** (*m*/*z*): Calculated for $C_{13}H_{16}N_2O_2S$ (M+Na): 287.0830, found (M+Na): 287.0841.

4-(Morpholine-4-carbothioamido)benzoic acid (3bq). Prepared as described in the general experimental procedure; pale brown solid: Yield 85% (226 mg); ***mp***: 193–195 °C; (the crude compound was recrystallized from EtOAc/hexane 1 : 15). R_f (5% MeOH/DCM) 0.2; **IR** (KBr, cm^{-1}): 3427, 3152, 2963, 2865, 2534, 1702, 1609, 1522, 1420, 1291, 1265, 124, 1170, 1120, 1029, 864, 771, 722; **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 12.71 (1H, br), 9.58 (1H, br), 7.86 (2H, d, J = 8 Hz), 7.45 (2H, d, J = 8 Hz), 3.89 (4H, s), 3.65 (4H, s); **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) 181.3, 167.0, 145.3, 129.5, 125.5, 123.2, 65.8, 48.8; **HRMS (ESI)** (*m*/*z*): Calculated for $C_{12}H_{14}N_2O_3S$ (M+H): 267.0803, found (M+H) 267.0808.

N*-(3-Nitrophenyl)morpholine-4-carbothioamide (3br).** Prepared as described in the general experimental procedure; pale brown solid; Yield 73% (195 mg); ***mp: 200–202 °C; (the crude compound was recrystallized from EtOAc/hexane 1 : 20). R_f (50% EtOAc/hexane) 0.25; **IR** (KBr, cm^{-1}): 3440, 3149, 2982, 2849, 1589, 1560, 1524, 1474, 1347, 1314, 1301, 1229, 1119, 1030, 811, 723; **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.7 (1H, br), 8.27 (1H, s), 7.93 (1H, d, J = 8.12 Hz), 7.81 (1H, d, J = 8 Hz), 7.57 (1H, t, J = 8 Hz), 3.92–3.91 (4H, m), 3.66 (4H, m); **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) 180.7, 146.8, 141.8, 130.3, 128.6, 118.3, 118.0, 65.2, 48.1. **HRMS (ESI)** (*m*/*z*): Calculated for $C_{11}H_{13}N_3O_3S$ (M+Na): 290.0575, found (M+ Na): 290.0579.

N*-(4-Bromophenyl)thiomorpholine-4-carbothioamide (3cb).** Prepared as described in the general experimental procedure and purified on silica gel column (EtOAc/hexane 5 : 95–10 : 90); White crystalline solid: Yield 86% (273 mg); ***mp: 188–190 °C (lit.[21] 189.5–190.5 °C); R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3436, 3179, 3150, 3084, 3003, 2909, 1586, 1525, 1486, 1423, 1308, 1290, 1186, 1164, 957, 823, 729; **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.35 (1H, bs), 7.46 (2H, d, J = 8.6 Hz), 7.23 (2H, d, J = 8.6 Hz), 4.17 (4H, s), 2.67 (4H, s); **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) 180.7, 140.0, 130.5, 127.4, 116.5, 50.7, 26.0; **HRMS (ESI)** (*m*/*z*): Calculated for $C_{16}H_{15}N_2SBr$ (M+Na): $C_{11}H_{13}N_2S_2Br$ (M+Na): 338.9601, found (M+Na): 338.9602.

N*-(3-Methoxyphenyl)thiomorpholine-4-carbothioamide (3ce).** Prepared as shown in the general experimental procedure and purified on silica gel column (EtOAc/hexane 5 : 95–10 : 90); White solid; Yield 90% (241 mg); ***mp: 126–128 °C; R_f (20% EtOAc/hexane) 0.5; **IR** (KBr, cm^{-1}): 3443.9, 3193, 2915, 1598, 1528, 1490, 1417, 1336, 1231, 1155, 1181, 1043, 967, 952, 861, 782, 710; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.36 (1H, br), 7.22 (1H, t, J = 8.4 Hz), 6.70–6.65 (3H, m), 4.08–4.06 (4H, m), 3.79 (3H, s), 2.71–2.68 (4H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 183.6, 160.2, 141.0, 129.9, 114.8, 110.5, 108.6, 55.3, 52.5, 26.9. **HRMS (ESI)** (*m*/*z*): Calculated for $C_{12}H_{16}N_2OS_2$ (M+Na): 291.0602, found (M+Na): 291.0605.

N*-(4-Bromophenyl)-3,4-dihydroisoquinoline-2(1H)-carbothioamide (3db).** Prepared as described in the general experimental procedure and purified on silica gel column (EtOAc/hexane 5 : 95–10 : 90); White solid: Yield 85% (298 mg); ***mp: 168–170 °C; R_f (20% EtOAc/hexane) 0.5; **IR** (KBr, cm^{-1}): 3448, 3200, 3031, 2967, 2906, 1584, 1528, 1489, 1451, 1425, 1316, 1305, 1211, 1176, 748, 722; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.40 (2H, d, J = 8.6 Hz), 7.26–7.18 (4H, m), 7.12–7.10 (3H, m), 4.92 (2H, s) 3.98 (2H, t, J = 5.8 Hz), 2.96 (2H, t, J = 5.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 181.8, 138.8, 134.7, 132.4, 131.8, 127.9, 127.3, 126.8, 126.4, 126.2, 118.6, 50.7, 46.9, 28.6. **HRMS (ESI)** (*m*/*z*): Calculated for $C_{16}H_{15}N_2SBr$ (M+Na): 369.0037, found (M+Na): 369.0039.

N*-(3-Methoxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carbothioamide (3de).** Prepared as described in the general experimental procedure and purified on silica gel column (EtOAc/hexane 5 : 95–10 : 90); White solid: Yield 91% (271 mg); ***mp: 104–106 °C; R_f (20% EtOAc/hexane) 0.2; **IR** (KBr, cm^{-1}): 3271, 2923, 2852, 1605, 1557, 1525, 1494, 1455, 1435,

1318, 1198, 1043, 1018, 749, 707; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.29 (1H, bs), 7.26–7.16 (4H, m), 7.11–7.09 (1H, m), 6.79–6.70 (2H, m), 6.68 (1H, d , J = 1.76), 4.89 (2H, s), 3.99 (2H, t, J = 5.8), 3.75 (3H s), 2.96 (2H, t, J = 5.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 182.4, 160.0, 141.0, 134.7, 132.6, 129.6, 128.0, 127.1, 126.6, 126.3, 115.9, 110.9, 109.6, 55.3, 51.1, 47.3, 28.6; **HRMS (ESI)** (m/z): Calculated for $C_{17}H_{18}N_2OS$ (M+Na): 321.1038, found (M+Na): 321.1036.

4-Benzhydryl-*N*-(*o*-tolyl)piperazine-1-carbothioamide (3ej). Prepared as described in the general experimental procedure and purified on silica gel column (EtOAc/hexane 5 : 95–10 : 90); White solid: Yield 93% (372 mg); ***mp***: 216–218 °C; R_f (20% EtOAc/hexane) 0.5; purified on silica gel. **IR** (KBr, cm^{-1}): 3449, 3219, 3024, 2812, 1582, 1451, 1519, 1399, 1333, 1231, 1145, 1028, 997, 722, 704; **^{1}H NMR** (400 MHz, CDCl3): δ (ppm) 7.39 (4H, d, J = 7.4 Hz), 7.28–7.24 (4H, m), 7.19–7.14 (4H, m), 7.09 (1H ,d, J = 7.36 Hz), 7.06–704 (1H, m), 6.91 (1H, br), 4.22 (1H, s), 3.76–3.74 (4H, m), 2.41 (4H, t, J = 5.0 Hz), 2.2 (3H, s); **^{13}C NMR** (100 MHz, CDCl3): δ (ppm) 183.7, 141.9, 138.7, 131.9, 130.9, 128.6, 127.8, 127.2, 126.7, 126.0, 124.6, 75.7, 51.2, 49.6, 17.9; **HRMS (ESI)** (m/z): Calculated for $C_{25}H_{27}N_3S$ (M +H): 402.2004, found (M+H): 402.2006.

4-Benzhydryl-*N*-(4-sulfamoylphenyl)piperazine-1-carbothioamide (3eo). Prepared as described in the general experimental procedure and purified on silica gel column (EtOAc/hexane 5 : 95–10 : 90); White solid: Yield 62% (289 mg); ***mp***: 210–212; R_f (50% EtOAc/hexane) 0.4; **IR** (KBr, cm^{-1}): 3794, 3387, 3136, 2896, 2801, 2349, 1760, 1529, 1431, 1327, 1300, 1239, 1225, 1161, 1150, 1006, 923, 747, 708; **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.51 (1H, br), 7.71 (2H, d, J = 8.4 Hz), 7.46–7.44 (6H, m), 7.31 (4H, t, J = 7.4 Hz), 7.23 (2H, br), 7.21 (2H, t, J = 7.08 Hz), 4.40 (1H, s), 3.92 (4H, s), 2.39 (4H, s); **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) 190.0, 144.2, 142.3, 138.8, 128.6, 127.7, 127.0, 125.7, 123.8, 74.4, 51.2, 48.2; **HRMS (ESI)** (m/z): Calculated for $C_{24}H_{26}N_4O_2S_2$ (M+Na): 489.1395, found (M+Na): 489.1392.

4-Benzyl-*N*-(4-bromophenyl)piperidine-1-carbothioamide (3fb). Prepared as described in the general experimental procedure and purified on silica gel column (EtOAc/hexane 5 : 95–10 : 90); White solid: Yield 86% (334 mg); ***mp***: 174–176 °C; R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3754, 3438, 3200, 2939, 2913, 2872, 2847, 1523, 1321, 1277, 1212, 747, 716, 702; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.40 (2H, d, J = 8.4 Hz), 7.30–7.26 (2H, m), 7.22–7.18 (2H, m), 7.13 (2H, d, J = 7.4 Hz), 7.00 (2H, d, J = 8.4 Hz), 4.54 (2H, d, J = 12.8 Hz), 2.93 (2H, t, J = 12.2 Hz), 2.56 (2H, d, J = 7.08 Hz), 1.84–1.79 (1H m), 1.70 (2H, d, J = 13.1 Hz), 1.37–1.25 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 182.1, 139.6, 139.2, 131.9, 129.0, 128.3, 126.1, 124.7, 117.9, 49.9, 42.5, 37.8, 31.6; **HRMS (ESI)** (m/z): Calculated for $C_{19}H_{21}BrN_2S$ (M+Na): 411.0507, found (M+Na): 411.0506.

4-Benzyl-*N*-(2-methoxyphenyl)piperidine-1-carbothioamide (3fg). Prepared as described in the general experimental procedure and purified on silica gel column (EtOAc/hexane 5 : 95–10 : 90); yellow liquid: Yield —81% (275 mg); R_f (20% EtOAc/hexane) 0.4; **IR** (neat): 3501, 3208, 2926, 2656, 2255, 1994, 1910, 1618, 1600, 1495, 1411, 1320, 1227, 1194, 1022, 769, 751; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.71 (1H, d, J = 8 Hz), 7.39 (1H, br), 7.30–7.25 (2H, m), 7.19 (1H , t, J = 7.1 Hz), 7.13 (2H, d, J = 7.4 Hz), 7.04 (1H, t, J = 78 Hz), 6.92 (1H, t, J = 7.7 Hz), 6.86 (1H, d, J = 8.2 Hz), 4.61 (2H, d, J = 13.2 Hz), 3.83 (3H, s), 3.03–2.97 (2H, m), 2.56 (2H, d, J = 7.2 Hz), 1.87–1.79 (1H, m), 1.71 (2H, d, J = 13.3 Hz), 1.41–1.31 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 181.4, 149.4, 139.7, 129.0, 128.9, 128.2, 126.0, 124.3, 122.1, 120.3, 110.4, 55.6, 49.5, 42.6, 37.9, 31.6; **HRMS (ESI)** (m/z): Calculated for $C_{20}H_{24}N_2OS$ (M+Na): 363.1507, found (M+Na): 363.1506.

3-(2,6-Dimethylphenyl)-1,1-diethylthiourea (3gk). Prepared as described in the general experimental procedure: pale brown solid. Yield 91% (215 mg); ***mp***: 124–126 °C (the crude black solid obtained by filtration was dissolved in 1 mL of DMSO followed by the addition of cold water (20 mL) resulted in the pale brown solid precipitate). R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3195, 2923, 1514, 1257, 905. **^{1}H NMR** (400 MHz, $CDCl_3$) 7.14–7.04 (3H, m), 6.58 (1H, br), 3.77 (4H, q, J = 6.8 Hz), 2.24 (6H, s), 1.31 (6H, t, J = 7.1 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 180.2, 137.1, 136.6, 128.1, 127.4, 45.4, 18.43, 12.8; **HRMS (ESI)** (m/z): Calculated for $C_{13}H_{20}N_2S$ (M+Na) 259.1245, found (M+Na): 259.1249.

4-(3,3-Diethylthioureido)benzoic acid (3gq). Prepared as described in the general experimental procedure: pale brown solid; Yield 86% (216 mg); 155–157 °C; (the crude compound was recrystallized from EtOAc/hexane 1 : 15), R_f (20% EtOAc/hexane) 0.07; Yield 86%; ***mp***: 135–138; R_f (5% MeOH/CH_2Cl_2) 0.05; **IR** (KBr, cm^{-1}): 3197, 2979, 2934, 2906, 2543, 1702, 1609, 1523, 1422, 1319, 1281, 1244, 1171, 1137, 905, 792, 723; **^{1}H NMR** (400 MHz, DMSO-d_6) 12.69 (1H, br), 9.08 (1H, s), 7.85 (2H, d, J = 8.4 Hz), 7.46 (2H, d, J = 8.5 Hz), 3.77 (4H, q, J = 6.9 Hz), 1.17 (6H, t, J = 6.9 Hz); **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) 179.4, 167.1, 145.4, 129.1, 125.9, 124.8, 45.04, 12.7; **HRMS (ESI)** (m/z): Calculated for $C_{12}H_{16}N_2O_2S$ (M+Na): 275.0830, found (M+Na): 275.0834.

***N*-(3-Bromophenyl)pyrrolidine-1-carbothioamide (3ha).** Prepared as described in the general experimental procedure and purified on silica gel column (EtOAc/hexane 10 : 90–20 : 80); White solid; Yield 70% (200 mg); 155–157 °C; R_f (20% EtOAc/hexane) 0.07; **IR** (KBr, cm^{-1}): 3255, 2968, 1719, 1526, 1436, 1342, 1298, 864, 701. **^{1}H NMR** (400 MHz, DMSO-d_6) 8.94 (1H, br), 7.66 (1H, s), 7.41 (1H, d, J = 7.4 Hz), 7.79–7.22 (2H, m), 3.61 (4H, br), 1.92 (4H, br); **^{13}C NMR** (100 MHz, DMSO-d_6): δ (ppm) 177.2, 142.3, 129.8, 127.8, 126.8, 124.3, 120.4, 48.7, 24.7. **HRMS (ESI)** (m/z): Calculated for $C_{11}H_{13}N_2SBr$ (M+Na): 306.9881, found (M+Na): 306.9881.

Acknowledgements

The financial assistant from CSIR (No. 01/2415/10-EMR-II) is acknowledged with thanks. Thanks are due to Dr A. R. Ramesha and Prof. S. Chandrasekhar for useful suggestions. BVV thanks CSIR for a fellowship.

Notes and references

1 (*a*) C. Walpole, S. Y. Ko, M. Brown, D. Beattie, E. Campbell, F. Dickenson, S. Ewan, G. A. Hughes, M. Lemaira,

J. Lerpiniere, S. Patel and L. Urban, *J. Med. Chem.*, 1998, **41**, 3159; (*b*) D. C. Schroeder, *Chem. Rev.*, 1955, **55**, 181; (*c*) G. Y. Sarkis and E. D. Faisal, *J. Heterocycl. Chem.*, 1985, **22**, 137.

2 (*a*) H. Suter and H. Zutter, *Helv. Chim. Acta*, 1967, **50**, 1084; (*b*) P. Jimonet, F. Audiau, M. Barreau, J. C. Blanchard, A. Boireau, Y. Bour, M. A. Coleno, A. Doble, G. Doerflinger, C. D. Huu, M. H. Donat, J. M. Duchesne, P. Ganil, C. Gueremy, E. Honore, B. Just, R. Kerphirique, S. Gontier, P. Hubert, P. M. Laduron, J. LeBlevec, M. Meunier, J. M. Miquet, C. Nemecek, M. Pasquet, O. Piot, J. Pratt, J. Rataud, M. Reibaud, J. M. Stutzmann and S. Mignani, *J. Med. Chem.*, 1999, **42**, 2828; (*c*) D. L. Garmaise and C. H. Chrlmbers, *J. Med. Chem.*, 1968, **11**, 1205; (*d*) K. D. Hargrave, F. K. Hess and J. T. Oliver, *J. Med. Chem.*, 1983, **26**, 1158; (*e*) S. N. Sawhney, S. K. Arora, J. V. Singh, O. P. Bansal and S. P. Singh, *Indian J. Chem.*, 1978, **16B**, 605; (*f*) V. G. Shirke, K. Bobade, R. P. Bhamaria, B. G. Khadse and S. R. Sengupta, *Indian Drugs*, 1990, **27**, 350; (*g*) C. Levallet, J. Lerpiniere and S. Y. Ko, *Tetrahedron*, 1997, **53**, 5291.

3 For reviews of H-bonding organocatalysis, see: (*a*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520; (*b*) S. J. Connon, *Chem.–Eur. J.*, 2006, **12**, 5418; (*c*) Y. Takemoto, *Org. Biomol. Chem.*, 2005, **3**, 4299; (*d*) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289; (*e*) S. H. McCooey and S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367; (*f*) J. Wang, H. Li, X. Yu, L. Zu and W. Wang, *Org. Lett.*, 2005, **7**, 4293 and references therein; (*g*) Y. Hoashi, T. Okino and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2005, **44**, 4032; (*h*) P. M. Pihko, *Angew. Chem., Int. Ed.*, 2004, **43**, 2062.

4 (*a*) C. S. J. Walpole, S. Bevan, G. Bovermann, J. J. Boelsterli, R. Breckenridge, J. W. Davies, G. A. Hughes, I. James, L. Oberer, W. Janet and R. Wrigglesworth, *J. Med. Chem.*, 1994, **37**, 1942; (*b*) E. Honkanen, A. Pippuri, P. Kairisalo, P. Nore, H. Karppanen and Ilari. Paakkari, *J. Med. Chem.*, 1983, **26**, 1433.

5 (*a*) A. D. Jordan, C. Luo and A. B. Reitz, *J. Org. Chem.*, 2003, **68**, 8693; (*b*) K. Biswas and M. F. Greaney, *Org. Lett.*, 2011, **13**, 4946; (*c*) L. L. Joyce and R. A. Batey, *Org. Lett.*, 2009, **11**, 2792 and references therein; (*d*) L. Jamir, N. Khatun and B. K. Patel, *RSC Adv.*, 2011, **1**, 447.

6 (*a*) A. R. Katritzky, S. Ledoux, R. M. Witek and S. K. Nair, *J. Org. Chem.*, 2004, **69**, 2976; (*b*) For a review see: S. Sharma, *Synthesis*, 1978, 803; (*c*) H. A. Staab, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 351.

7 (*a*) K. Ramadas and N. Janarthanan, *J. Chem. Res. (S)*, 1998, 228; (*b*) A. Dirksen, P. J. Nieuwenhuizen, M. Hoogenraad, J. G. Haasnoot and J. Reedijk, *J. Appl. Polym. Sci.*, 2000, **79**, 1074–1083.

8 M. Maddani and K. R. Prabhu, *Tetrahedron Lett.*, 2007, **48**, 7151.

9 M. R. Maddani and K. R. Prabhu, *J. Org. Chem.*, 2010, **75**, 2327.

10 A broad screening study conducted using aniline, methoxy substituted anilines, and bromo-substituted anilines are presented in the ESI (see ESI-Table 1†).

11 It was observed that the reaction of dithiocarbamate of secondary amines with arylamines produced a small amount of the disulfirum of **2a** (8-10%). This impurity was easily removed by washing the product with hexane during the work up.

12 In the scaling up experiments, there is reduction in the yields of **3aa** and **3ab** by almost 10–15%. We believe that this can be addressed separately, when scaling up is needed.

13 M. Tisler, *Croatica chemica Acta*, 1957, **29**, 409.

14 K. Nagarajan, J. David, S. Rajappa and S. Talwalker, *Ind. J. Chem.*, 1985, **B24**, 934.

15 Z. Halimehjani, Y. Pourshojaei and M. R. Saidi, *Tetrahedron Lett.*, 2009, **50**, 32.

16 S. Rajappa, T. G. Rajagopalan, R. Sreenivasan and S. Kanal, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2001.

17 M. Dai, C. Wang, G. Dong, J. Xiang, T. Luo, B. Liang, J. Chen and Z. Yang, *Eur. J. Org. Chem.*, 2003, **68**, 4346.

18 H. Lee and K. Kim, *J. Org. Chem.*, 1993, **58**, 7001.

19 K. Inamoto, C. Hasegawa, J. Kawasaki, K. Hiroya and T. Doi, *Adv. Synth. Catal.*, 2010, **352**, 2643.

20 L. L. Joyce and R. A. Batey, *Org. Lett.*, 2009, **11**, 2792.

21 N. B. Galstukhova, M. N. Shchukina and Z. Budesynsky, *Khimiko-Farmatsevticheskii Zhurnal*, 1968, **2**, 14.