Synthesis and Characterization of Novel *N*-Alkylamine- and *N*-Cycloalkylamine-Derived 2-Benzoyl-*N*-aminohydrazinecarbothioamides, 1,3,4-Thiadiazoles and 1,2,4-Triazole-5(4*H*)thiones

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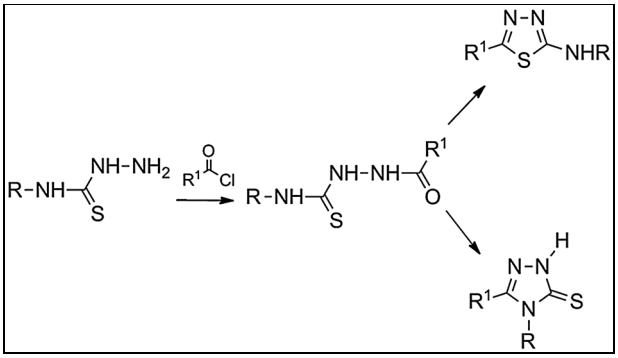

4-Aminomorpholine, 1-aminopiperidine, and 1,1-dimethylhydrazine were carried out in the corresponding methyl dithiocarbamates and those in turn in aminohydrazinethioamides, which under the influence of acid chlorides (benzoyl, 4-chlorobenzoyl, 4-fluorobenzoyl, 4-methoxybenzoyl and 2-furoyl) gave arylcarbonyl derivatives. Those compounds were cyclized in concentrated H_2SO_4 to 2-(*N*-cycloalkylamino- and *N*-dimethylamino)-amino-5-phenyl-1,3,4-thiadiazole derivatives and in 10% NaOH aqueous solution to 4-cycloalkylamino- and 4-dimethylamino-3-phenyl-1,2,4-triazole-5(4*H*)-thiones.

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INTRODUCTION

In recent years, the interest in thiadiazole derivatives as a group of biologically active compounds increased. Turkish scientists obtained encouraging results by testing 2-amino-5-aryl-1,3,4-thiadiazoles against *Mycobacterium tuberculosis* [1]. 2-Hydrazine derivatives were tested for antihypertensive and anti-epileptic activities [2,3], whereas carbazones and dithiocarbazones for antimicrobial properties [4]. Among those derivatives, new classes of compounds with analgesic and anti-inflammatory activity [5], lowering blood sugar levels [6], urease inhibitors, and agents of antioxidant activity were sought [7]. For derivatives of 5-amino-1,3,4-thiadiazole-2-sulfonamide antiglaucoma activity was found [8], Scheme 1.

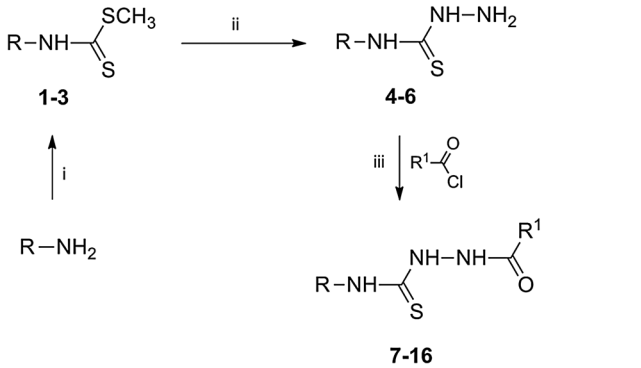
Among 1,2,4-triazole derivatives, compounds with antimicrobial activity against *Bacillus subtilis*, *Bacillus cereus*, *Escherichia coli*, *Pilina solarium* [9], and with antimycobacterial activity against *M. tuberculosis* were synthesized [10,11]. Antiproliferative and anticancer activities of 1,2,4-triazoles were also reported [12,13]. 4-Amino-5-aryl-1,2,4-triazole-3-thioles were found to exhibit fungitoxic properties [14–16]. 1,2,4-Triazoles and 1,3,4-thiadiazoles are a group of heterocyclic compounds, which focus the interest of researchers because of the multidirectional biological activity. Previously, our research team also reported synthesis of that group of compounds [17–19].

CHEMISTRY

Continuing our research for new antibacterial agents, we undertook synthesis of 2-benzoyl-*N*-amino-hydrazinecarbothioamide derivatives, which cyclized to 2-(*N*-cycloalkylamino- and *N*-dimethylamino)-amino-5-phenyl-1,3,4-thiadiazoles and 4-cycloalkylamino- and 4-dimethyloamino-3-phenyl-1,2,4-triazole-5(4*H*)-thiones.

Substrates for syntheses were 4-aminomorpholine, 4-aminopiperidine, and 1,1-dimethylaminohydrazine, which underwent carbon disulfide addition in the presence of triethylamine (TEN) to yield the corresponding salts of carbamodithioic acids. Salts were not isolated but transformed in corresponding methyl esters acting with methyl iodide (**1–3**). Compounds (**1**, **2**) have been already described by Podgornaya and co-workers [20,21], whereas methyl 2,2-dimethylhydrazinecarbodithioate by Johnston and Gallagher [22]. In the reaction of methyl carbamodithioates with hydrazine hydrate, the appropriate aminohydrazinecarbothioamides (**4–6**) were obtained [18,23]. Then, synthesized aminohydrazinecarbothioamides (**4–6**) were treated with the following acid chlorides: benzoyl, 4-chlorobenzoyl, 4-fluorobenzoyl, 4-methoxubenzoyl, and 2-furoyl. The reactions were carried out in anhydrous dioxane to TEN at room temperature for 24 h to give most of the products in excellent yields (**7–16**). The exception was 2-(4-fluorobenzoyl)-*N*-morpholino hydrazinecarbothioamide

Scheme 1. Reactions conditions and yields: (i) TEA (1.2 molar equiv.), CS_2 (1 molar equiv.), MeI (1 molar equiv.), EtOH, rt, 34–63%; (ii) 100% $H_2NNH_2 \times H_2O$ (1.5 molar equiv.), EtOH, reflux, 76–96%; (iii) TEA (1 molar equiv.), benzoyl chloride (1 molar equiv.), anhydrous dioxane, rt, 23–98%; (iv) conc. H_2SO_4,G 90°C, 26–77%; (v) 10% NaOH, reflux, 20–98%.



No	1, 4	2, 5	3, 6	7, 17, 25	8, 18, 26	9, 19, 27	10, 20, 28	11, 29	12, 21, 30	13, 31	14, 22, 32	15, 23, 33	16, 24, 34
R	–N O	–N	$-N(CH_3)_2$	–N O	–N O	–N O	–N O	–N O	–N	–N	$-N(CH_3)_2$	$-N(CH_3)_2$	$-N(CH_3)_2$
R^1	-	-	-	Ph	4-F-Ph	4-Cl-Ph	4-MeO-Ph	O	4-Cl-Ph	O	Ph	4-Cl-Ph	4-F-Ph

(**8**), which was managed to obtain in 23% yield only. Previously, we reported the synthesis of 2-(4-chlorobenzoyl)-*N*-morpholinohydrazinecarbothioamide (**9**) as an intermediate in the reaction of methyl morhpholine-4-carbodithioate with 4-chlorobenzhydrazide, but the yield of that reaction was much lower (30%) [19]. Currently described method allows to obtain derivative (**9**) in 95% yield.

Obtained hydrazinecarbothioamide derivatives (**7–10**, **12, 14–16**) were cyclized to 2-(*N*-morpholino, *N*-piperidino, and *N*-dimethylamino)-amino-5-phenylo-1,3,4-thiadiazoles (**17–24**). Reactions were carried out in concentrated sulfuric acid at 90°C. The cyclization of thiosemicarbazide derivatives in boiling 10% NaOH aqueous solution led to 1,2,4-triazole-5(4*H*)-thiones (**25–33**) substituted at *N*-4 position with *N*,*N*-dimethylamine, morpholine, or piperidine. This method seems to be a convenient way to obtain novel 1,2,4-triazoles possessing cyclic amines at *N*-4 position. Derivatives of this type cannot be obtained in another way. It should be noted that there are two chiral nitrogen atoms in the molecule of 1,2,4-triazole-5 (4*H*)-thione. Because of the newness of this type of structures and X-ray crystallography interesting results, we plan to devote a separate article on this topic.

Cyclization reactions proceeded with different yields. The dependence of the reaction yield on the structure of the substituent at the carbonyl carbon atom has been observed. Generally, the lowest yields were recorded for the reactions of 4-fluorophenyl, possessing highly electronegative fluorine atom as in the case of intermediate **8** synthesis. The cyclization reactions to 1,3,4-thiadiazoles (**18**, **24**) and 1,2,4-triazole-5(4*H*)-thiones (**26**, **34**) proceeded with 22–52% yields. Also, the cyclization from intermediate **10**, possessing 4-methoxyphenyl, to 1,3,4-thiadiazole **20** occurred with low yield (20%). Similar results were obtained for the synthesis of 1,2,4-triazole-5(4*H*)-thione substituted with 2-furyl (**29**, **31**) at C-3 position. The synthesis of 1,3,4-thiadiazoles from 2-(furan-carbonyl)-*N*-cycloaminohydrazinecarbothiamides **11**, **13** was impossible because of the reaction conditions. In fact, furan decomposes under the action of concentrated sulfuric acid or strong Lewis acids, such as aluminum chloride [24]. In all cases mentioned, we have seen in the TLC experiment a series of products, which could be the result of decomposition of the reaction substrate or product.

All newly synthesized compounds were characterized by IR and ^{1}H NMR spectra as well as the elemental

analysis listed in the experimental section. The spectral analyses were in accordance with the assigned structures.

CONCLUSION

Novel 2-amino-1,3,4-thiadiazoles and 4-amino-1,2,4-triazole-5(4*H*)-thiones have been synthesized successfully *via* cyclization of 2-benzoyl-*N*-aminohydrazinecarbothioamides, which are the perfect starting compounds for the synthesis of heterocyclic componds such as 1,3,4-thiadiazole and 1,2,4-triazole with substituents in the system inaccessible or impossible to obtain in no other way. However, we have found that substituent type determines if and how efficiently desired products can be obtained. All newly synthesized compounds were characterized by IR and ^{1}H NMR spectra as well as the elemental analysis.

EXPERIMENTAL

All materials and solvents were of analytical reagent grade. TLC was performed on Merck silica gel $60F_{254}$ plates and visualized with UV lamp (Spectroline, Westbury, NY). The results of elemental analyses (%C, H, N) for all of obtained compounds were in agreement with the calculated values within $\pm$ 0.3% range. ^{1}H NMR spectra in $CDCl_3$ or DMSO-d_6 were recorded on Varian Unity Plus (500 MHz) and Varian Gemini (200 MHz) instruments (Varian, Palo Alto, CA). IR spectra (KBr) were determined as KBr pellets of the solids on a Satellite FT-IR spectrophotometer (Mattson Instruments, Madison, WI). Melting points were determined with Reichert apparatus (Reichert Technologies, Depew, NY) and were uncorrected.

General method for the synthesis of methyl aminocarbamodithioates (1–3). 4-Aminomorpholine, 1-aminopiperidine, or 1,1-dimethylhydrazine (0.1 mole) was dissolved in 20 mL of ethanol and 17 mL (0.12 mole) of TEN and 6 mL (0.1 mole) of CS_2 were added. The mixture was stirred at room temperature for 15 min, and 6 mL (0.1 mole) of methyl iodide was added. The solution was stirred for another 30 min. Then, the mixture was cooled and precipitate was filtered off, dried, and recrystallized from methanol. Reaction yields and compounds' characteristics were found to be identical with those described earlier [20–22].

General method for the synthesis of *N*-aminohydrazinecarbothioamides (4–6). Appropriate methyl aminocarbamodithioate (**1–3**) (30 mmole) was dissolved in 20 mL of ethanol, and 2 mL (45 mmole) of 100% hydrazine monohydrate was added. The mixture was refluxed for 2 h. Then, the solution was cooled, and the precipitate was filtered off, washed with ice-cold water, dried, and recrystallized from water (**4**) or methanol (**5**, **6**). Reaction yields and compounds' characteristics were found to be identical with those described earlier [18,23].

General method for the synthesis of 2-benzoyl-*N*-aminohydrazincarbothioamides (7–16). Appropriate *N*-aminohydrazinecarbothioamide (**4–6**) (5 mmole) was suspended in 15 mL of anhydrous dioxane, and 0.7 mL (5 mmole) of TEN was added. The mixture was heated to dissolve, and then, the solution of an equimolar amount of appropriate benzoyl chloride in 5 mL of anhydrous dioxane was added. The mixture was stirred at room temperature for 24 h. Then, the solvent was evaporated to dryness, and 20 mL of ice-cold water was added to the residue. The precipitate was filtered off, dried, and recrystallized from suitable solvent.

2-Benzoyl-N-morpholinohydrazinecarbothiamide (7). The crude product was recrystallized from ethanol. Yield 64%, mp 219–221°C; IR (KBr): 3195 (ν N-H), 2962, 2919, 2833 (ν C-H), 1692 (ν C=O), 1530 (δ N-H), 1301 (ν C-N), 1256 (ν C=S), 1111 (ν C-O), 866 (γ C-H) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.68–3.19 (m, 4H, $2NCH_2$), 3.62–4.05 (m, 4H, $2OCH_2$), 7.54–7.62 (m, 3H, Ph), 7.85–7.90 (m, 2H, Ph), 6.85 (brs, 1H, 1NH), 9.50 (brs, 1H, NH), 9.86 (brs, 1H, NH) ppm; *Anal*. Calcd. for $C_{12}H_{16}N_4O_2S$ (mw 280.35): C, 51.41; H, 5.75; N, 19.98. Found: C, 51.28; H, 5.74; N, 20.02.

2-(4-Fluorobenzoyl)-N-morpholinohydrazinecarbothioamide (8). The crude product was recrystallized from ethanol. Yield 23%, mp 189–191°C; IR (KBr): 3188 (ν N-H), 2960, 2864, 2828 (ν C-H), 1696 (ν C=O), 1514 (δ N-H), 1266 (ν C=S), 1108 (ν C-O), 1006 (δ C-H), 866 (γ C-H) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.60–3.15 (m, 4H, $2NCH_2$), 3.59–3.92 (m, 4H, $2OCH_2$), 7.18–7.22 (m, 2H, Ph), 7.85–7.90 (m, 2H, Ph), 6.74 (brs, 1H, NH), 9.42 (brs, 1H, NH), 9.81 (brs, 1H, NH) ppm; *Anal*. Calcd. for $C_{12}H_{15}N_4O_2S$ (mw 298.34): C, 48.31; H, 5.07; N, 18.78. Found: C, 48.43; H, 5.08; N, 18.81.

2-(4-Chlorobenzoyl)-N-morpholinohydrazinecarbothioamide (9). The crude product was recrystallized from ethanol. Yield 95%. Compound characteristic was found to be identical with that described earlier [19].

2-(4-Methoxybenzoyl)--morpholinohydrazinecarbothioamide (10). The crude product was recrystallized from ethanol. Yield 98%, mp 203–205°C; IR (KBr): 3229 (ν N-H), 3003, 2866 (ν C-H), 1665 (ν C=O), 1523 (δ N-H), 1261 (ν C=S), 1109 (ν C-O), 1020 (δ C-H) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.70–2.85 (m, 4H, $2NCH_2$), 3.58–3.78 (m, 4H, $2OCH_2$), 3.81 (s, 3H, OCH_3), 7.04 (d, 2H, Ph, J = 7.8 Hz), 7.89 (d, 2H, Ph, J = 7.8 Hz), 9.31 (s, 1H, NH), 9.72 (s, 1H, NH), 10.29 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{12}H_{18}N_4O_3S$ (mw 310.37): C, 50.31; H, 5.85; N, 18.05. Found: C, 50.45; H, 5.86; N, 18.00.

2-(Furan-carbonyl)-N-morpholinohydrazinecarbothiamide (11). The crude product was recrystallized from ethanol. Yield 74%, mp 195–197°C; IR (KBr): 3450, 3234 (ν N-H), 3043, 2965, 2839 (ν C-H), 1661 (ν C=O), 1596, 1508, 1476 (ν C=C), 1323 (ν C-N), 1105 (ν C-O), 875 (γ C-H) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): 2.63–2.82 (m, 4H, $2NCH_2$), 3.52–3.80 (m, 4H, $2OCH_2$), 6.66 (dd, 1H, furan-2-yl, H-4, J_1 = 3.6 Hz, J_2 = 1.6 Hz), 7.26 (d, 1H, furan-2-yl, H-3, J = 3.6 Hz), 7.90 (d, 1H, furan-2-yl, H-5, J = 1.6 Hz), 9.36 (s, 1H, NH), 9.76 (s, 1H, NH), 10.33 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{10}H_{14}N_4O_3S$ (mw 270.31): C, 44.43; H, 5.22; N, 20.73. Found: C, 44.32; H, 5.20; N, 20.69.

2-(4-Chlorobenzoyl)-N-(piperidin-1-yl)hydrazinecarbothioamide (12). The crude product was recrystallized from ethanol. Yield 96%, mp 181–183°C; IR (KBr): 3470, 3284, 3204 (ν N-H), 2940 (ν C-H), 1675 (ν C=O), 1530 (δ N-H), 1485 (ν C=C), 1326 (ν C-N), 1095 (δ C-H) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.17–1.61 (m, 6H, $3CH_2$), 2.57–2.92 (m, 4H, $2NCH_2$), 7.62 (d, 2H, Ph, J = 8.1 Hz), 7.94 (d, 2H, Ph, J = 8.5 Hz), 9.31 (s, 1H, NH), 9.62 (s, 1H, NH), 10.53 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{13}H_{17}ClN_4OS$ (mw 312.82): C, 49.91; H, 5.48; N, 17.91. Found: C, 50.02; H, 5.49; N, 17.94.

2-(Furan-2-carbonyl)--(piperidin-1-yl)hydrazinecarbothioamide (13). The crude product was recrystallized from dioxane. Yield 95%, mp 240–242°C; IR (KBr): 3247, 3149 (ν N-H), 2945, 2853 (ν C-H), 1698 (ν C=O), 1568 (ν C=C), 1545 (ν N-H), 1513 (ν C=C), 1318 (ν C-N), 1121 (ν C-O), 871 (γ C-H) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.15–1.92 (m, 6H, $3CH_2$), 2.48–2.97 (m, 4H, $2NCH_2$), 6.58–6.69 (m, 1H, furan-2-yl, H-4),7.22 (d, 1H, furan-2-yl, H-3, $J = 3.5$ Hz), 7.88 (d, 1H, furan-2-yl, H-5, $J = 1.7$ Hz), 9.26 (s, 1H, NH), 9.53 (s, 1H, NH), 10.28 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{11}H_{16}N_4O_2S$ (mw 268.34): C, 49.24; H, 6.01; N, 20.88. Found: C, 49.09; H, 6.02; N, 20.93.

N′-(2,2)-dimethylhydrazinecarbonothioyl)benzohydrazide (14). The crude product was recrystallized from ethanol. Yield 53%, mp 182–183°C; IR (KBr): 3254, 3169 (ν N-H), 2990, 2861 (ν C-H), 1672 (ν C=O), 1540 (δ N-H), 1484 (ν C=C), 1307 (ν C-N), 1259 (ν C=S), 714 (γ N-H) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.64 (s, 6H, $2NCH_3$), 7.48–7.55 (m, 3H, Ph), 7.84–7.93 (m, 2H, Ph), 6.67 (s, 1H, NH), 9.57 (s, 1H, NH), 9.88 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{10}H_{14}N_4OS$ (mw 238.31): C, 50.40; H, 5.92; N, 23.51. Found: C, 50.29; H, 5.91; N, 23.45.

4-Chloro-N′-(2,2)-dimethylhydrazinecarbonothioyl) benzohydrazide (15). The crude product was recrystallized from ethanol. Yield 84%, mp 210–212°C; IR (KBr): 3289, 3148 (ν N-H), 2964, 2861 (ν C-H), 1678 (ν C=O), 1541 (δ N-H), 1495 (ν C=C), 1313 (ν C-N), 1091, 1011 (δ C-H) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.50 (s, 6H, $2NCH_3$), 7.58 (d, 2H, Ph, $J = 7.9$ Hz), 7.90 (d, 2H, Ph, $J = 8.0$ Hz), 9.22 (s, 1H, NH), 9.70 (s, 1H, NH), 10.51 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{10}H_{13}ClN_4OS$ (mw 272.75): C, 44.03; H, 4.80; N, 20.54. Found: C, 44.14; H, 4.78; N, 20.49.

N′-(2,2)-dimethylhydrazinecarbonothioyl)-4-fluorobenzo-hydrazide (16). The crude product was recrystallized from water. Yield 98%, mp 236–237°C; IR (KBr): 3288, 3152 (ν N-H), 2996, 2964, 2863 (ν C-H), 1675 (ν C=O), 1542 (δ N-H), 1487 (ν C=C), 1234 (ν C=S), 1160 (δ C-H), 853 (γ C-H) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.50 (s, 6H, $2NCH_3$), 7.28–7.42 (m, 2H, Ph), 7.90–8.14 (m, 2H, Ph), 9.21 (s, 1H, NH), 9.68 (s, 1H, NH), 10.45 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{10}H_{13}FN_4OS$ (mw 256.30): C, 46.86; H, 5.11; N, 21.86. Found: C, 47.00; H, 5.12; N, 21.91.

General method for the synthesis of 1,3,4-thiadiazoles (17–24). 2-Benzoyl-*N*-aminohydrazincarbothioamide (**7–9**, **12**, **14–16**) (2 mmole) was dissolved in 4 mL of concentrated H_2SO_4. The mixture was heated at 90°C in an oil bath for 1 h. Then, mixture was cooled, poured on 10 g of ice and neutralized with concentrated NH_4OH. The precipitate was filtered off, dried, and recrystallized from suitable solvent.

N-(5-Phenyl-1,3,4-thiadiazol-2-yl)morpholin-4-amine (17). This compound was recrystallized from methanol–water mixture (1:1). Yield 53%, mp 211–212°C; IR (KBr): 3141 (ν N-H), 3045, 2964, 2852 (ν C-H), 1558 (δ N-H), 1424 (ν C=C), 1264 (ν C-C), 1118 (ν C-O), 1066 (δ C-H), 877 (γ C-H) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 2.71–3.03 (m, 4H, $2NCH_2$), 3.49–3.80 (m, 4H, $2OCH_2$), 7.31–7.42 (m, 3H, Ph), 7.75–7.82 (m, 2H, Ph), 9.17 (brs, 1H, NH) ppm; *Anal*. Calcd. for $C_{12}H_{14}N_4OS$ (mw 262.33): C, 54.94; H, 5.38; N, 21.36. Found: C, 54.79; H, 5.37; N, 21.41.

N-(5-(4-Fluorophenyl)-1,3,4-thiadiazol-2-yl)morpholin-4-amine (18). The crude product was recrystallized from ethanol. Yield 31%, mp 206–207°C; IR (KBr): 3171 (ν N-H), 3031, 2922, 2832 (ν C-H), 1596, 1512, 1440 (ν C=C), 1222 (ν C-C), 1111 (ν C-O), 837 (γ C-H) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.77–2.87 (m, 4H, $2NCH_2$), 3.55–3.65 (m, 4H, $2OCH_2$), 7.23–7.29 (m, 2H, Ph), 7.76–7.83 (m, 2H, Ph), 9.32 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{12}H_{13}FN_4OS$ (mw 280.32): C, 51.42; H, 4.67; N, 19.99. Found: C, 51.52; H, 4.66; N, 19.95.

N-(5-(4-Chlorophenyl)-1,3,4-thiadiazol-2-yl)morpholin-4-amine (19). The crude product was recrystallized from ethanol. Yield 63%, mp 228–229°C; IR (KBr): 3169 (ν N-H), 3065, 2921, 2854, 2835 (ν C-H), 1577, 1438 (ν C=C), 1266 (ν C-C), 1113 (ν C-O), 1078 (δ C-H), 871, 830 (γ C-H) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 2.77–2.87 (m, 4H, $2NCH_2$), 3.54–3.64 (m, 4H, $2OCH_2$), 7.46–7.52 (m, 2H, Ph), 7.75–7.81 (m, 2H, Ph), 9.38 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{12}H_{13}ClN_4OS$ (mw 296.78): C, 48.56; H, 4.42; N, 18.88. Found: C, 48.68; H, 4.41; N, 18.83.

N-(5-(4-Methoxyphenyl)-1,3,4-thiadiazol-2-yl)morpholin-4-amine (20). The crude product was recrystallized from methanol. Yield 20%, mp 208–210°C; IR (KBr): 3164 (ν N-H), 2918, 2857, 2830 (ν C-H), 1609, 1579, 1522, 1428 (ν C=C), 1250 (δ C-C), 1174, 1110 (γ C-O), 1070 (δ C-H), 873, 843 (γ C-H), 651 (γ N-H) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): 2.82–2.90 (m, 4H, $2NCH_2$), 3.63–3.72 (m, 4H, $2OCH_2$), 3.79 (s, 3H, OCH_3), 7.01 (d, 2H, Ph, $J = 8.7$ Hz), 7.71 (d, 2H, Ph, $J = 8.7$ Hz), 9.07 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{13}H_{16}N_4O_2S$ (mw 292.36): C, 53.41; H, 5.52; N, 19.16. Found: C, 53.29; H, 5.53; N, 19.19.

5-(4-Chlorophenyl)-N-(piperidin-1-yl)-1,3,4-thiadiazol-2-amine (21). The crude product was recrystallized from dimethylformamid-water mixture (1:1). Yield 77%, mp 194–196°C; IR (KBr): 3166 (ν N-H), 3056, 2934, 2853 (ν C-H), 1581, 1497, 1432 (ν C=C), 1090, 1074 (δ C-H), 982, 830 (γ C-H) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): 1.31–1.36 (m, 2H, CH_2), 1.50–1.59 (m, 4H, $2CH_2$), 2.72–2.81 (m, 4H, $2NCH_2$), 7.52 (d, 2H, Ph, $J = 8.1$ Hz), 7.80 (d, 2H, Ph, $J = 8.2$ Hz), 9.29 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{13}H_{15}ClN_4S$ (mw 294.80): C, 52.96; H, 5.13; N, 19.00. Found: C, 52.83; H, 5.14; N, 19.04.

2-(2,2-Dimethylhydrazinyl)-5-phenyl-1,3,4-thiadiazole (22). The crude product was recrystallized from ethanol-water mixture (1:1). Yield 40%, mp 155–156°C; IR (KBr): 3165 (ν N-H), 3044, 2994, 2828 (ν C-H), 1586, 1455, 1415 (ν C=C), 1104, 879, 759 (γ C-H), 688 (γ N-H) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 2.59 (s, 6H, $2NCH_3$); 7.36–7.43 (m, 3H, Ph); 7.70–7.77 (m, 2H, Ph); 9.12 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{10}H_{12}N_4S$ (mw 220.29): C, 54.52; H, 5.49; N, 25.43. Found: C, 54.37; H, 5.49; N, 25.49.

2-(4-Chlorophenyl)-5-(2,2)-dimethylhydrazinyl)-1,3,4-thiadiazole (23). The crude product was recrystallized from ethanol-water mixture (1:1). Yield 68%, mp 180–182°C; IR (KBr): 3268, 3169 (ν N-H), 3070, 2927, 2864 (ν C-H), 1574, 1455 (ν C=C), 1090 (δ C-H), 826 (γ C-H) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.60 (s, 6H, $2NCH_3$), 7.52 (d, 2H, Ph, $J = 8.2$ Hz), 7.90 (d, 2H, Ph, $J = 8.3$ Hz), 9.20 (s, 1H, NH) ppm; *Anal.* Calcd. for $C_{10}H_{11}ClN_4S$ (mw 254.74): C, 47.15; H, 4.35; N, 21.99. Found: C, 47.21; H, 4.33; N, 21.93.

2-(2,2-Dimethylhydrazinyl)-5-(4-fluorophenyl)-1,3,4-thiadiazole (24). This compound was recrystallized from ethanol-water mixture (1:1). Yield 26%, mp 177–178°C; IR (KBr): 3168 (ν N-H), 2999, 2961, 2834 (ν C-H), 1597, 1518, 1456 (ν C=C), 1221, 838 (γ C-H) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): 2.59 (s, 6H, $2NCH_3$), 7.23–7.30 (m, 2H, Ph), 7.74–7.81 (m, 2H, Ph), 9.13 (s,

1H, NH) ppm; *Anal*. Calcd. for $C_{10}H_{11}FN_4S$ (mw 238.28): C, 50.40; H, 4.65; N, 23.51. Found: C, 50.48; H, 4.66; N, 23.56.

General method for the synthesis of 4-amino-3-phenyl-1*H*-1,2,4-triazole-5(4*H*)-thiones (25–33). 2-Benzoyl-*N*-aminohydrazincarbothioamide (**7–16**) (2 mmole) was suspended in 5 mL of 10% NaOH aqueous solution and refluxed for 2 h. Then, the mixture was cooled, acidified with concentrated HCl, and cooled again. The precipitate was filtered off, dried and recrystallized.

4-Morpholino-3-phenyl-1H-1,2,4-triazole-5(4H)-thione (25). Yield 53%. Compound characteristics were found to be identical with those reported (mp 239–240°C), ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.92–3.01 (m, 2H, NCH_2), 3.61–3.67 (m, 2H, NCH_2), 3.93–4.05 (m, 2H, OCH_2), 4.82–4.88 (m, 2H, OCH_2), 7.51–7.58 (m, 3H, Ph), 8.89–8.94 (m, 2H, Ph), 13.75 (s, 1H, NH) ppm) [19].

3-(4-Fluorophenyl)-4-morpholino-1H-1,2,4-triazole-5(4H)-thione (26). The crude product was recrystallized from ethanol-water mixture (1:1). Yield 52%, mp 236–238°C; IR (KBr): 3238 (ν N-H), 3001, 2978, 2926, 2872, 2849 (ν C-H), 1606, 1508, 1426 (ν C=C), 1308 (ν C-N), 1265 (ν C=S), 1101 (ν C-O), 844 (γ C-H) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.93–2.98 (m, 2H, NCH_2), 3.39–3.44 (m, 2H, NCH_2), 3.77–3.82 (m, 2H, OCH_2), 4.57–4.62 (m, 2H, OCH_2), 7.35–7.41 (m, 2H, Ph), 7.88–7.94 (m, 2H, Ph), 13.91 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{12}H_{13}FN_4OS$ (mw 280.32): C, 51.42; H, 4.67; N, 19.99. Found: C, 51.28; H, 4.68; N, 20.02.

3-(4-Chlorophenyl)-4-morpholino-1H-1,2,4-triazole-5(4H)-thione (27). Yield 81%. Compound characteristics were found to be identical with those reported (mp. 239–240°C), ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.95–3.05 (m, 2H, NCH_2), 3.35–3.44 (m, 2H, NCH_2), 3.76–3.83 (m, 2H, OCH_2), 4.58–4.62 (m, 2H, OCH_2), 7.52 (d, 2H, Ph, *J* = 8.7 Hz), 7.84 (d, 2H, Ph, *J* = 8.7 Hz), 13.94 (s, 1H, NH) ppm) [19].

3-(4-Methoxyphenyl)-4-morpholino-1H-1,2,4-triazole-5(4H)-thione (28). Yield 98%. Compound characteristics were found to be identical with those reported (mp. 287–288°C), ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.88–2.92 (m, 2H, NCH_2), 3.39–3.45 (m, 2H, NCH_2), 3.81, (s, 3H, OCH_3), 3.82–3.87 (m, 2H, OCH_2), 4.62 (t, 2H, OCH_2, *J* = 10 Hz), 7.03 (d, 3H, Ph, *J* = 8.8 Hz), 7.78 (d, 2H, Ph, *J* = 8.8 Hz), 13.79 (s, 1H, NH) ppm) [19].

3-(Furan-2-yl)-4-morpholino-1H-1,2,4-triazole-5(4H)-thione (29). The crude product was recrystallized from ethanol. Yield 20%, mp 274–276°C; IR (KBr): 3163 (ν N-H), 2978, 2938, 2850 (ν C-H), 1628, 1525, 1453, 1432 (ν C=C), 1306 (ν C-N), 1105 (ν C-O) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.86–2.91 (m, 2H, NCH_2), 3.81–3.86 (m, 2H, NCH_2), 3.86–3.91 (m, 2H, OCH_2), 4.53–4.58 (m, 2H, OCH_2), 6.65–6.69 (m, 1H, furan-2-yl, H-4), 7.36–7.40 (m, 1H, furan-2-yl, H-3), 7.88–7.92 (m, 1H, furan-2-yl, H-5), 13.89 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{10}H_{12}N_4O_2S$ (mw 252.29): C, 47.61; H, 4.79; N, 22.21. Found: C, 47.72; H, 4.78; N, 22.25.

3-(4-Chlorophenyl)-4-(piperidin-1-yl)-1H-1,2,4-triazole-5(4H)-thione (30). Yield 32%. Compound characteristics were found to be identical with those reported (mp. 228–229°C), ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.20–1.62 (m, 2H, $3CH_2$), 3.01–3.38 (m, 2H, NCH_2), 4.27–4.51 (m, 2H, NCH_2), 7.61 (d, 2H, Ph, *J* = 8.8 Hz), 7.86 (d, 2H, Ph, *J* = 8.7 Hz), 13.75 (s, 1H, NH) ppm) [19].

3-(Furan-2-yl)-4-(piperidin-1-yl)-1H-1,2,4-triazole-5(4H)-thione (31). The crude product was recrystallized from ethanol-water mixture (1:1). Yield 22%, mp 211–213°C; IR (KBr): 3102 (ν N-H), 2942, 2859 (ν C-H), 1631, 1531, 1503, 1454 (ν C=C), 1312 (ν C-N), 1288 (ν C=S), 969 (γ C-H), 734 (γ N-H) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.58–1.64 (m, 2H, CH_2), 2.93–3.02 (m, 4H, $2CH_2$), 4.16–4.27 (m, 4H, $2NCH_2$), 6.66–6.69 (m, 1H, furan-2-yl, H-4), 7.31–7.34 (m, 1H, furan-2-yl, H-3), 7.88–7.91 (m, 1H, furan-2-yl, H-5), 13.82 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{11}H_{14}N_4OS$ (mw 250.32): C, 52.78; H, 5.64; N, 22.38. Found: C, 52.67; H, 5.65; N, 22.41.

4-(Dimethylamino)-3-phenyl-1H-1,2,4-triazole-5(4H)-thione (32). Yield 54%. Compound characteristics were found to be identical with those reported (mp. 236–237°C), ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.15 (s, 6H, $2NCH_3$), 7.49–7.63 (m, 3H, Ph), 7.80–7.92 (m, 2H, Ph), 13.85 (s, 1H, NH) ppm) [19].

3-(4-Chlorophenyl)-4-(dimethylamino)-1H-1,2,4-triazole-5(4H)-thione (33). Yield 78%. Compound characteristics were found to be identical with those reported (mp. 250–255°C), ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.15 (s, 6H, $2NCH_3$), 7.60 (d, 2H, Ph, *J* = 8.7 Hz), 7.84 (d, 2H, Ph, *J* = 8.8 Hz), 13.89 (s, 1H, NH) ppm) [19].

4-(Dimethylamino)-3-(4-fluorophenyl)-1H-1,2,4-triazole-5(4H)-thione (34). The crude product was recrystallized from ethanol-water mixture (1:1). Yield 22%, mp 220–221°C; IR (KBr): 3093, 3014, 2932 (ν C-H), 1514, 1422 (ν C=C), 1312 (ν C-N), 1235 (ν C=S), 840 (γ C-H) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.14 (s, 6H, $2NCH_3$), 7.31–7.36 (m, 2H, Ph), 7.82–7.86 (m, 2H, Ph), 13.85 (s, 1H, NH) ppm; *Anal*. Calcd. for $C_{10}H_{11}FN_4S$ (mw 238.28): C, 50.40; H, 4.65; N, 23.51. Found: C, 50.36; H, 4.65; N, 23.48.

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