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Synthesis of New *N*-Benzoyl-*N*′-Triazine Thiourea Derivatives and Their Antibacterial Activity

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Abstract—A series of new *N*-benzoyl-*N*'-triazine thiourea derivatives have been synthesized via the reaction of 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one with benzoyl chloride derivatives and ammonium thiocyanate in acetone under reflux conditions. 4-Amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one was prepared from the reaction of two equivalents of hydrazine hydrate with carbon disulfide and sodium pyruvate. The chemical structure of thioureas was confirmed using FT-IR, ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry, and elemental analysis. The synthesized thioureas were assayed for their antibacterial activity against both gram-positive (*Micrococcus luteus* and *Bacillus cereus*) and gram-negative (*Pseudomonas aeruginosa* and *Escherichia coli*) bacteria using the agar well diffusion method.

Keywords: thiourea, triazin, hydrazine hydrate, sodium pyruvate, antibacterial

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INTRODUCTION

Compounds containing carbonyl and thiocarbonyl groups have an important role among organic reagents as potential donor ligands [1–4]. There is significant interest in the chemistry of nitrogen- and sulfur-containing heterocyclic substances due to the fact that they are multifunctional donors with nitrogen or sulfur atoms. Thiourea and its derivatives are nitrogen- and sulfur-containing compounds that display important pharmaceutical and biological activities, therefore they are useful materials in drug research [5, 6]. The potential activities shown by this cores include anticonvulsant [7], antitumor [8], insecticidal [9], fungicidal [10], antimicrobials [11], anti-inflammatory [12], anti-hepatitis C [13], antidepressant [14], phosphodiesterases enzyme inhibitor [15], β-lactamase inhibitor [16], and aromatase inhibitor [17] activities. In addition, some of the thiourea derivatives are highly active in inhibiting formation of micelles, and denature proteins [18, 19]. Most of thioureas that contain heterocyclic cores, such as thiadiazoles, triazoles, oxadiazoles, and pyrazoles, in their structure indicate potent biological activities [20, 21]. A number of thioureas, as fungicides, have attracted widespread attention from researchers for decades [22]. Various studies have shown that these compounds exhibit significant anticancer activity against prostate cancer, lung cancer, breast cancer, liver cancer, etc. [23–27].

In recent decades, there has been notable interest in the studying of Schiff base compounds. Schiff bases, containing various donor atoms, also find use in metal coordination and analytical applications. Since most compounds containing nitrogen and sulfur atoms have biological activity, preparation of the corresponding compounds could be of interest from the opinion of biological activity and chemical reactivity [28–30]. 1,2,4-Triazines are well known as heterocyclic thiones derived from thiocarbohydrazide. A number of their derivatives display biological activity and have been used for different objectives, such as neutral antibiotics, antibacterials, herbicides, etc. 1,2,4-Thiotriazines are well known compounds derived from thiosemicarbazide and thiocarbohydrazide, some of which exhibit biological activity [31–33]. In continuation of our previous research on preparation of catalysts, organic compounds, and heterocycles and study of their biological activity [34–38], herein we report synthesis of several new *N*-benzoyl-*N*'-triazine thiourea derivatives. Products (**Xa–g**) were prepared through reaction of 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**VI**) with benzoyl chloride derivatives (**VIIa–g**) and ammonium thiocyanate (**VIII**) in good yield. In addition, antibacterial activity of *N*-benzoyl-*N*'-triazin thiourea derivatives was evaluated against a set of gram-positive and gram-negative bacteria.

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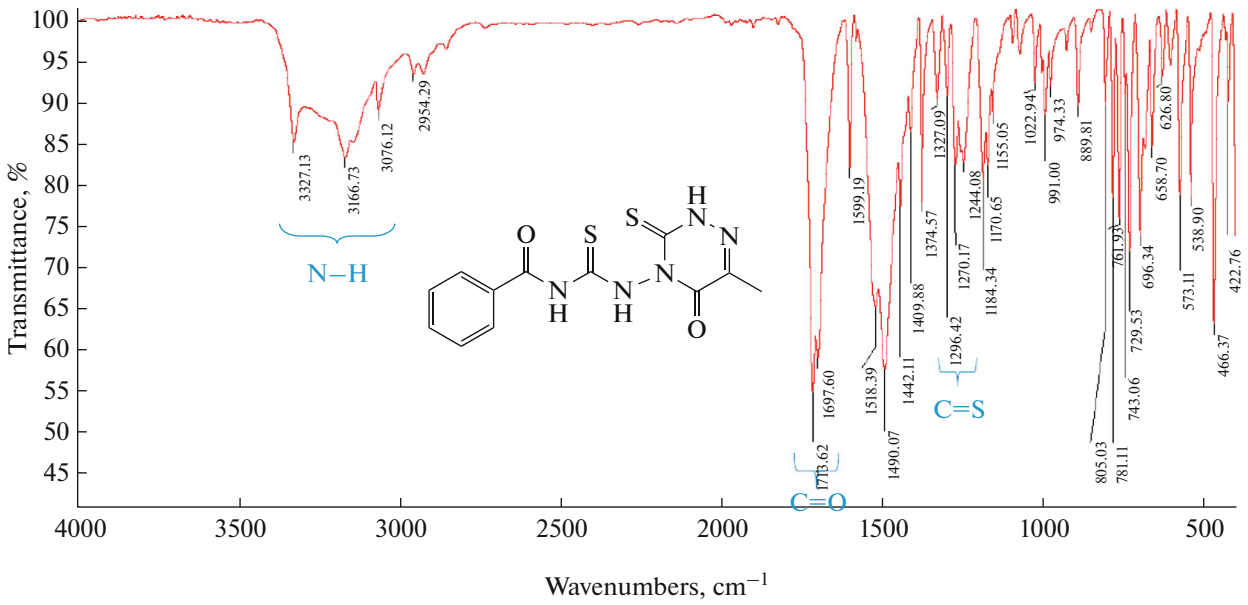


Fig. 1. FT-IR spectrum of thiourea (**Xa**).

RESULTS AND DISCUSSION

Synthesis of several *N*-benzoyl-*N*'-triazine thiourea derivatives was carried out by treating benzoyl chloride (**VII**) with an equivalent of ammonium thiocyanate (**VIII**) in dry acetone followed by reaction with an equivalent of 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**VI**) to furnish the thiourea derivatives (**Xa**–**g**) in good yields and excellent purity. The product structures were confirmed using FT-IR, ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry, and elemental analysis. The Fourier transform infrared (FT-IR) spectra of synthesized compounds showed similar trend of stretching frequency modes. FT-IR spectrum of compound (**Xa**) reveals the presence of three bands at 3327, 3166, and 3076 cm^{-1} for the N–H groups. Also, presence of two peaks at 1713 and 1697 cm^{-1} indicates the existence of C=O moiety and two peaks at 1296 and 1270 cm^{-1} indicate the C=S moiety (Fig. 1).

The ^{1}H NMR spectrum of compound (**Xa**) in DMSO-d_6 showed a singlet for CH_3 (δ 2.18 ppm) and a multiple singlet (δ 7.52–7.66 ppm), along with a doublet (δ 7.9) for the aromatic protons and three characteristic N–H protons at δ 12.11, 12.48, and 13.80 ppm (Fig. 2). The ^{13}C NMR spectrum of compound (**Xa**) showed ten signals in agreement with the proposed structure. In this spectrum, the methyl carbon appeared at 17.0 and two C=O groups resonated at δ 181.6 and 174.3 ppm, while two C=S resonated at δ 168.2 and 141.0 ppm, respectively.

Adhami et al. [39] have synthesized triazine thioureas (**Xa**). The FT-IR spectra of triazine thiourea derivatives (**Xb**–**g**) reveal the presence of three stretching vibration bands at υ 3447–3056 cm^{-1} for N–H, two absorption bands in the regions of υ 1663–1728 cm^{-1} related to C=O and two stretching bands in the regions of υ 1482–1608 cm^{-1} related to C=C bond; peaks in the regions of 1236–1379 cm^{-1} suggest the presence of the C=S group.

The ^{1}H NMR spectra of triazine thioureas (**Xb**–**g**) show a sharp singlet at δ 2.04–2.40 ppm due to the protons of CH_3 triazine rings and multiple signals in the regions of δ 7.31–8.35 ppm due to the aromatic protons. Amino protons appear as three single signals at δ 9.92–13.79 ppm, while for compounds (**Xc**) and (**Xe**), phenyl CH_3 protons appear as a singlet signal at δ 2.36 and 2.49 ppm, respectively. The ^{13}C NMR spectra of triazine thioureas (**Xb**–**g**) show 10 to 13 signals which are in agreement with the proposed structure of compounds. High-resolution mass spectra of all the thioureas showed molecular ion peaks. Also, elemental analysis data match with the theoretical values. Intermediate (**IX**) was prepared from the reaction of one equivalents of NH_4SCN (**VIII**) with one equivalent of benzoyl chloride (**VII**); color of reaction mixture turned pale yellow. Later (**IX**) underwent an addition reaction with 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**VI**) to produce (**Xa**–**g**) with a color change of the reaction to orange.

The novel *N*-benzoyl-*N*'-triazine thiourea derivatives (**Xa**–**g**) were appraised for their in vitro antibacterial activity against two gram-positive (*Micrococcus luteus*, ATCC 9341, and *Bacillus cereus*, ATCC 11778) and two gram-negative (*Pseudomonas aeruginosa*, ATCC 27853, and *Escherichia coli*, ATCC 25922) bacterial strains using the zone inhibition method [40]. Penicillin and DMSO were used as positive and nega-

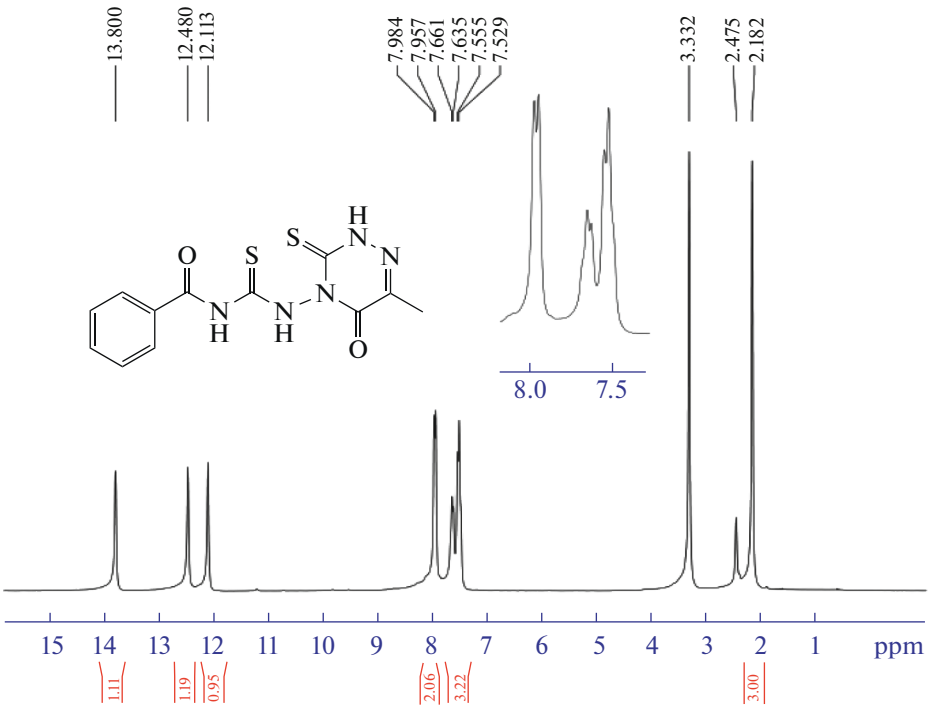


Fig. 2. ^{1}H NMR spectrum of thiourea (**Xa**).

tive controls, respectively. DMSO showed no activity against afore-mentioned bacterial strains, while penicillin showed the highest antibacterial activity against all bacterial strains (Table 1). Antibacterial activity of *N*-benzoyl-*N'*-triazine thiourea derivatives (**Xa–g**) was measured at a concentration of 1000 g/mL in DMSO. Each of the experiments was performed in triplicate. All data are reported as mean ± standard deviation in millimeter and shown in Table 1. All the synthesized thioureas showed reasonable antibacterial activity against gram-negative and gram-positive bacteria.

Thiourea derivatives with the electron withdrawing substituents such as F, Cl, and NO_2 showed better antibacterial activity than the unsubstituted compounds or those with electron donating substituents. Compound (**Xf**) showed excellent activity against *M. luteus*, while compound (**Xg**) showed good activity against *B. cereus*. Lipophilicity is a very important

Table 1. Antimicrobial activity of *N*-benzoyl-*N'*-triazine thiourea derivatives (**Xa–g**)

Entry	Product	Antimicrobial activity (zone of inhibition), mm			
		gram-positive		gram-negative	
		B. cereus	*M. luteus*	*E. coli*	*P. aeruginosa*
1	**(Xa)**	11	12	9	8
2	**(Xb)**	27	15	16	9
3	**(Xc)**	17	14	11	8
4	**(Xd)**	25	19	14	11
5	**(Xe)**	18	13	12	16
6	**(Xf)**	26	32	21	21
7	**(Xg)**	28	21	14	12
8	DMSO	–	–	–	–
9	Penicillin	33	49	21	47

molecular descriptor, which is well suited to biochemical activity, and the behavior of various lipophilic compounds plays an important role in their biological activity mechanisms.

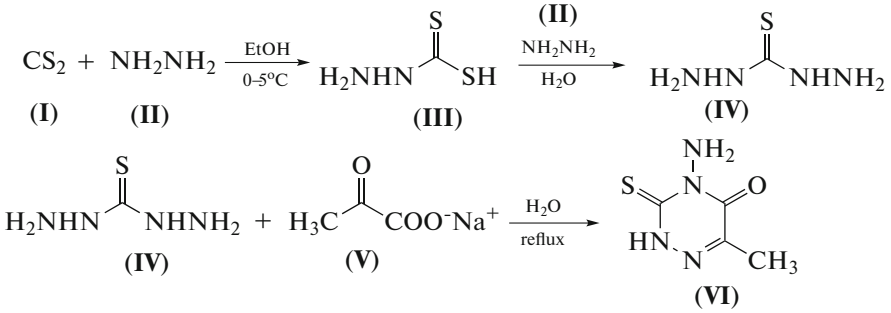
CONCLUSIONS

We report a simple and efficient protocol for synthesis of *N*-benzoyl-*N*'-triazine thiourea derivatives (**Xa**–**g**) in good yields and excellent purity from reaction of 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**VI**) with benzoyl chloride derivatives (**VIIa**–**g**) and ammonium thiocyanate (**VIII**) under reflux conditions in dry acetone. The chemical structure of thioureas was characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry, and elemental analysis. The antibacterial activities of *N*-benzoyl-*N*'-triazine thiourea derivatives were estimated against four bacterial strains, including *M. luteus*, *B. cereus*, *P. aeruginosa*, and *E. coli*. The results show that the thioureas derivatives possess higher activity against gram-positive than gram-negative bacteria.

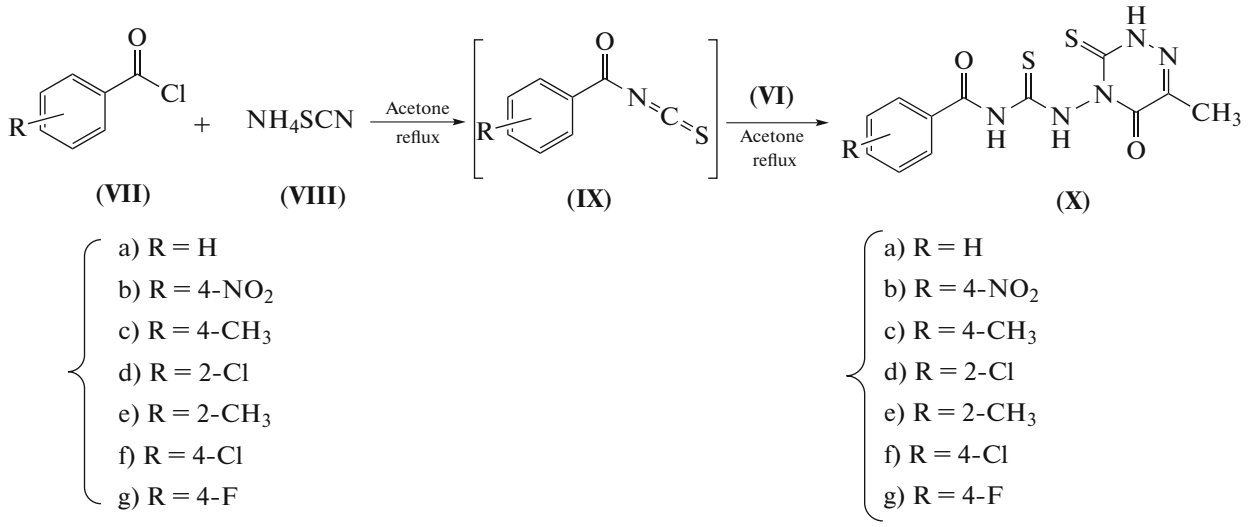
EXPERIMENTAL

Chemicals and Reagents

All chemicals were obtained from Fluka and Merck companies and used without additional purification. Thin-layer chromatography HF254 fluorescent silica gel plates were examined under ultraviolet light at 254 nm. All melting points were recorded on an Electrothermal-type 9100 melting points apparatus and are uncorrected. FT-IR spectra (υ, cm^{-1}) were obtained on a Shimadzu IR-470 spectrophotometer using KBr disks. ^{1}H and ^{13}C NMR spectra (δ, ppm) were recorded using Bruker DRX 250, 300 MHz spectrometer in acetone or DMSO-d_6. High-resolution mass spectra (HRMS) were recorded by Agilent 6520 (QTOF) ESI-HRMS machine. Elemental analyses were carried out on a Carlo-Erba EA1110 CNNO-S analyzer and agreed with calculated values.



Scheme 1. Synthetic route for preparation of 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one.



Scheme 2. Preparation of novel *N*-benzoyl-*N*'-triazine thioureas.

General Procedure for Preparation of 4-Amino-6-Methyl-3-Thioxo-3,4-Dihydro-1,2,4-Triazin-5(2H)One (VI)

4-Amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**VI**) was prepared by reported chemical technique [41]. In a round-bottomed flask, thiocarbohydrazide (**IV**) (1 mmol) was dissolved in 5 mL distilled water at 60°C. To the resulting solution, sodium pyruvate (**V**) (1 mmol) was added, and then the reaction mixture was stirred for 30 min at reflux conditions. The reaction progress was monitored using thin-layer chromatography ($CHCl_3$: MeOH, 4 : 1). After reaction completion, the resulting mixture was cooled and neutralized with 2 N HCl. Finally, the resultant precipitate was filtered, dried, and purified using recrystallization in distilled water (Scheme 1).

*General Procedure for Preparation of N-Benzoyl-N'-Triazine Thioureas (**Xa**–**g**)*

Benzoyl chlorides (5 mmol) were added drop-wise into a rotating solution of ammonium thiocyanate (10 mmol) in dry acetone (10 mL). The reaction mixture was stirred for 1 h under reflux conditions and then cooled in ice bath. At the next step, a solution of 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (1 mmol) in dry acetone (5 mL) was added to the reaction vessel and was stirred under reflux conditions for another 4 h. After cooling, the reaction mixture was poured into ice and water dish. Finally, the resulting solid was filtered, washed with $CHCl_3$, recrystallized from EtOH (96%), and dried to afford pure compounds (**Xa**–**g**) in good yield with high purity (Scheme 2).

***N*-((6-Methyl-5-oxo-3-thioxo-2,5-dihydro-1,2,4-triazin-4(3*H*)-yl)carbamothioyl)benzamide (Xa).** Yellow powder, yield 85%, mp 320–323°C, FT-IR: 3327, 3166, 3076 (N–H), 2954 (C–H_{arom}), 1713, 1697 (C=O), 1518, 1490 (C=C), 1296, 1270 (C=S). ^{1}H NMR (250.13 MHz, DMSO-d_6): 2.18 (3H, s, CH_3), 7.52–7.66 (3H, m, Ar–H), 7.97 (2H, d, J = 6.7 Hz, Ar–H), 12.11 (1H, s, N–H), 12.48 (1H, s, N–H), 13.80 (1H, s, N–H). ^{13}C NMR (62.89 MHz, DMSO-d_6): 181.6 (C=O), 174.3 (C=O), 168.2 (C=S), 151.0 (C=S), 147.6 (C=N), 133.9 (C), 132.0 (C), 129.3 (C), 129.0 (C), 17.0 (CH_3). HRMS ((+)-ESI): m/z = 321.0350 (calcd. 321.0354 for $C_{12}H_{11}N_5O_2S_2$). Anal. Calcd. for: C, 44.85; H, 3.45; N, 21.79. Found: C, 44.81; H, 3.48; N, 21.75.

***N*-((6-Methyl-5-oxo-3-thioxo-2,5-dihydro-1,2,4-triazin-4(3*H*)-yl)carbamothioyl)-4-nitrobenzamide (Xb).** Yellow powder, yield 75%, mp 232–234°C, FT-IR: 3390, 3320, 3265 (N–H), 3156 (C–H_{arom}), 1724, 1691 (C=O), 1600, 1482 (C=C), 1523, 1350 (NO_2), 1322, 1236 (C=S). ^{1}H NMR (250.13 MHz, acetone-d_6): 2.04 (3H, s, CH_3), 8.20 (2H, d, J = 6.7 Hz, Ar–H), 8.35 (2H, d, J = 6.7 Hz, Ar–H), 9.92 (1H, s, N–H), 10.46 (1H, s, N–H), 10.95 (1H, s, N–H). ^{13}C NMR (62.89 MHz, acetone-d_6): 172.0 (C=O), 168.2 (C=O), 166.0 (C=S), 157.4 (C=S), 156.0 (C=N), 150.2 (C), 139.5 (C), 129.8 (C), 123.5 (C), 17.1 (CH_3). HRMS ((+)-ESI): m/z = 366.0202 (calcd. 366.0205 for $C_{12}H_{10}N_6O_4S_2$). Anal. Calcd. for: C, 39.34; H, 2.75; N, 22.94. Found: C, 39.37; H, 2.72; N, 22.91.

4-Methyl-*N*-((6-methyl-5-oxo-3-thioxo-2,5-dihydro-1,2,4-triazin-4(3*H*)-yl)carbamothioyl)benzamide (Xc). Yellow powder, yield 85%, mp 192–194°C, FT-IR: 3321, 3160, 3082 (N–H), 2968 (C–H_{arom}), 1727, 1713 (C=O), 1608, 1571 (C=C), 1378, 1236 (C=S). ^{1}H NMR (250.13 MHz, DMSO-d_6): 2.17 (3H, s, CH_3), 2.36 (3H, s, CH_3), 7.31 (2H, d, J = 7.5 Hz, Ar–H), 7.88 (2H, d, J = 7.5 Hz, Ar–H), 12.01 (1H, s, N–H), 12.50 (1H, s, N–H), 13.79 (1H, s, N–H). ^{13}C NMR (62.89 MHz, DMSO-d_6): 181.7 (C=O), 174.3 (C=O), 168.0 (C=S), 151.0 (C=S), 147.6 (C=N), 143.9 (C), 129.6 (C), 129.4 (C), 129.1 (C), 21.6 (CH_3), 17.0 (CH_3). HRMS ((+)-ESI): m/z = 335.0509 (calcd. 335.0511 for $C_{13}H_{13}N_5O_2S_2$). Anal. Calcd. for: C, 46.55; H, 3.91; N, 20.88. Found: C, 46.51; H, 3.94; N, 20.85.

2-Chloro-*N*-((6-methyl-5-oxo-3-thioxo-2,5-dihydro-1,2,4-triazin-4(3*H*)-yl)carbamothioyl)benzamide (Xd). Pale yellow powder, yield 79%, mp 226–228°C, FT-IR: 3332, 3164, 3089 (N–H), 2972 (C–H_{arom}), 1727, 1687 (C=O), 1515, 1498 (C=C), 1377, 1281 (C=S). ^{1}H NMR (250.13 MHz, acetone-d_6): 2.26 (3H, s, CH_3), 7.49–7.56 (3H, m, Ar–H), 7.73 (1H, d, J = 7.2 Hz, Ar–H), 11.20 (1H, s, N–H), 12.36 (1H, s, N–H), 12.74 (1H, s, N–H). ^{13}C NMR (62.89 MHz, acetone-d_6): 180.9 (C=O), 174.4 (C=O), 167.1 (C=S), 150.6 (C=S), 147.3 (C=N), 133.7 (C), 132.6 (C), 130.8 (C), 130.0 (C) 129.5 (C), 127.2 (C), 16.0 (CH_3). HRMS ((+)-ESI): m/z = 354.9961 (calcd. 354.9964 for $C_{12}H_{10}ClN_5O_2S_2$). Anal. Calcd. for: C, 40.51; H, 2.83; N, 19.68. Found: C, 40.54; H, 2.80; N, 19.65.

2-Methyl-N-((6-methyl-5-oxo-3-thioxo-2,5-dihydro-1,2,4-triazin-4(3H)-yl)carbamothioyl)benzamide (Xe). Yellow powder, yield 87%, mp 212–213°C, FT-IR: 3328, 3138, 3074 (N–H), 2961 (C–H_{arom}), 1711, 1689 (C=O), 1507 (C=C), 1379, 1316 (C=S). ^{1}H NMR (300.13 MHz, acetone-d_6): 2.27 (3H, s, CH_3), 2.49 (3H, s, CH_3), 7.31–7.36 (2H, m, Ar–H), 7.48 (1H, t, J = 7.5 Hz, Ar–H), 7.63 (1H, d, J = 7.5 Hz, Ar–H), 11.05 (1H, s, N–H), 12.54 (1H, s, N–H), 12.81 (1H, s, N–H). ^{13}C NMR (75.56 MHz, acetone-d_6): 181.5 (C=O), 174.6 (C=O), 170.0 (C=S), 150.7 (C=S), 147.3 (C=N), 136.9 (C), 133.4 (C), 131.5 (C), 131.1 (C), 127.8 (C), 125.8 (C), 19.0 (CH_3), 16.0 (CH_3). HRMS ((+)-ESI): m/z = 335.0508 (calcd. 335.0511 for $C_{13}H_{13}N_5O_2S_2$). Anal. Calcd. for: 46.55; H, 3.91; N, 20.88. Found: 46.58; H, 3.88; N, 20.84.

4-Chloro-*N*-((6-methyl-5-oxo-3-thioxo-2,5-dihydro-1,2,4-triazin-4(3*H*)-yl)carbamothioyl)benzamide (Xf).

Yellow powder, yield 81%, mp 183–185°C, FT-IR: 3334, 3254, 3056 (N–H), 2923 (C–H_{arom}), 1726, 1663 (C=O), 1520, 1483 (C=C), 1375, 1255 (C=S). ^{1}H NMR (250.13 MHz, DMSO-d_6): 2.40 (3H, s, CH_3), 7.64 (2H, d, J = 8.0 Hz, Ar–H), 8.11 (2H, d, J = 8.0 Hz, Ar–H), 11.82 (1H, s, N–H), 12.69 (1H, s, N–H), 13.79 (1H, s, N–H). ^{13}C NMR (62.89 MHz, DMSO-d_6): 173.6 (C=O), 166.6 (C=O), 154.2 (C=S), 153.5 (C=S), 148.4 (C=N), 139.1 (C), 130.9 (C), 129.9 (C), 129.4 (C), 17.6 (CH_3). HRMS ((+)-ESI): m/z = 354.9961 (calcd. 354.9964 for $C_{12}H_{10}ClN_5O_2S_2$). Anal. Calcd. for: C, 40.51; H, 2.83; N, 19.68. Found: C, 40.54; H, 2.86; N, 19.65.

4-Fluoro-*N*-((6-methyl-5-oxo-3-thioxo-2,5-dihydro-1,2,4-triazin-4(3*H*)-yl)carbamothioyl)benzamide (Xg). Light yellow powder, yield 76%, mp 220–222°C, FT-IR: 3447, 3356, 3097 (N–H), 2923 (C–H_{arom}), 1728, 1671 (C=O), 1570, 1515 (C=C), 1345, 1296 (C=S). ^{1}H NMR (250.13 MHz, DMSO-d_6): 2.39 (3H, s, CH_3), 7.40 (2H, t, J = 8.5 Hz, Ar–H), 8.18 (2H, t, J = 6.7 Hz, Ar–H), 12.21 (1H, s, N–H), 12.90 (1H, s, N–H), 13.78 (1H, s, N–H). ^{13}C NMR (62.89 MHz, DMSO-d_6): 167.8 (C=O), 166.2 (C=O), 163.8 (C=S), 154.0 (C=S), 153.5 (C=N), 148.4 (C), 132.0 (C, d, $^2J_{C-F}$ = 9.3 Hz), 127.3 (C), 116.3 (C, d, $^1J_{C-F}$ = 21.7 Hz), 17.6 (CH_3). HRMS ((+)-ESI): m/z = 339.0264 (calcd. 339.0260 for $C_{12}H_{10}FN_5O_2S_2$). Anal. Calcd. for: C, 42.47; H, 2.97; N, 20.64. Found: C, 42.45; H, 2.94; N, 20.67.

*General Method for In Vitro Antibacterial Evaluation of Thioureas (**Xa–g**)*

Antibacterial activity of thioureas (**Xa–g**) was measured by the agar well diffusion method. The sterile Mueller–Hinton agar plates were inoculated with the bacteria; 0.001 g of test sample was dissolved in 1 mL DMSO to obtain a stock solution; 0.1 mL of each sample was dropped into each labeled well aseptically. The inoculated plates were then incubated for 24 h at 37°C. Penicillin and DMSO were used as positive and negative control, respectively. After incubation time, antimicrobial activity was evaluated by measuring the zone of inhibition against the test organisms and compared with that of the standard. The results of our tests are reported as the inhibition zones (mm).

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving human participants performed by any of the authors and does not contain any studies involving animals performed by any of the authors.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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