Convenient One Pot Synthesis and Antibacterial Evaluation of Some New Mannich Bases Carrying 1,2,4-Triazolyl Moiety

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A series of Mannich bases were synthesized by a three-component Mannich reaction. The newly synthesized compounds were well characterized by elemental analyses, IR, NMR and mass spectroscopic studies. The potential antibacterial effects of the synthesized compounds were investigated using standard bacterial strains: Gram-positive and Gram-negative bacteria. Interestingly, all the synthesized compounds were observed to be promising leads, possessing moderate to significant inhibitory activity as compared to standard.

Keywords bi-1,2,4-triazoles, Schiff bases, Mannich bases, regioselectivity, antibacterial activity

Introduction

In the past two decades, the incidence of microbial infection has reached on alarming levels over the world as a result of multi-drug resistant microorganisms. For the treatment of microbial infections, the synthesis of new class of antimicrobial compounds effective against pathogenic microorganisms has become an urgent need. For this purpose, several compounds that contain a 1,2,4-triazole possessing antimicrobial activity have been synthesized;[1-5] some of which contains a Schiff base structure,[6-9] piperazine or morpholine moiety as well.[10,11] Also, the thione substituted 1,2,4-triazole ring systems have been synthesized and so far a variety of biological activities have been reported for a large number of their derivatives.[6,7,11]

Multi-component reactions (MCRs) constitute a major part in the organic synthesis with advantages ranging from increasing the reaction rates to higher yield, lowering the reaction times and reproducibility.[12] Mannich reaction is a three component condensation reaction involving active hydrogen containing compound, formaldehyde and a secondary amine.[13] This aminoalkylation of aromatic substrates by Mannich reaction is of considerable importance for the synthesis and modification of biologically active compounds.[14-17]

Prompted by these investigations and in continuation of our research work on the synthesis of novel heterocyclic compounds exhibiting biological activity,[18] hereby we report the synthesis of a new series of 1,2,4-triazole derivatives incorporating Schiff and Mannich bases as hybrid molecules possessing antibacterial activity.

Results and discussions

Chemistry

The reaction sequences employed for synthesis of the title compounds are shown in Schemes 1 and 2. Triazole hydrazide (**1**) was prepared following a previously reported literature procedure.[19] The intermediate **4** was prepared from triazole hydrazide (**1**) according to the literature.[18] The new derivatives **2**, **3**, **8**—**10** have been synthesized by applying the previously reported conditions.[2,20,21] The structural assignments of the new compounds were based on their elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR and Mass).

In methanolic solution of potassium hydroxide, carbohydrazide **1** was interacted with carbon disulphide to afford potassium hydrazide dithiocarbazinate (**2**), which underwent ring closure on refluxing with hydrazine hydrate to give bi-1,2,4-triazole **3**. Alternatively, the bi-1,2,4-triazole derivative **3** was also obtained by the reaction of the oxadiazole-2-thione **4** with hydrazine hydrate in ethanol. The IR spectrum of compound **3** showed strong bands at 3310, 3320 cm^{-1} characteristic for NH and NH_2 groups. The observation of C=S stretching band at 1346 cm^{-1} and the absence of an absorption at about 2550—2600 cm^{-1} region cited for SH group have proved that this compound was in the thionic form. Moreover, the signal observed at δ 181.99 in the ^{13}C NMR spectrum of compound **3** was attributed to C=S group. In the ^{1}H NMR spectrum of compound **3**, the signals observed at δ 5.31 and 12.43 (controlled by changing with D_2O) were attributed to NH_2 and NH groups, respectively. The elemental analysis data of compound **3** were found consistent with the assigned structure. Furthermore, stable molecular ion peak was observed in the mass spectrum of compound **3**. The

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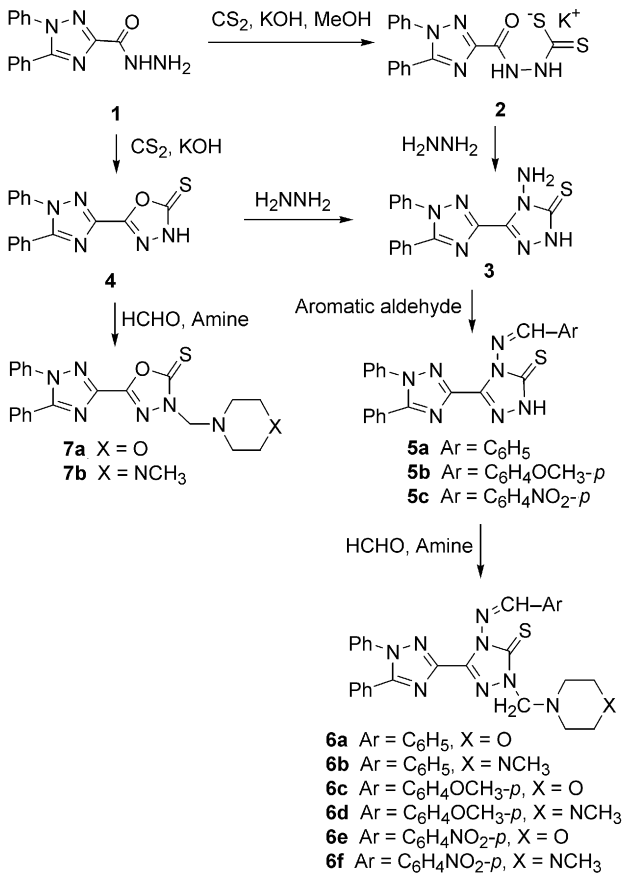
chemical transformation of the amine **3** into Mannich base is possible after the protection of the exocyclic amino group via condensation with aldehydes because compound **3** has two susceptible positions for aminomethylation: NH and NH_2. Thus, the condensation of compound **3** with various aromatic aldehydes in the presence of catalytic amount of H_2SO_4 produced a series of Schiff bases **5a**—**5c**. The ^{1}H NMR spectra of compounds **5a**—**5c** displayed no signals belonging to the NH_2 group; instead, new signals due to N=CH appeared between δ 8.52—8.82 integrated for one proton. This is also supported by recording the ^{13}C NMR spectrum of compound **5a** which showed a signal appeared at δ 153.27 belonging to N=CH. Additionally, mass spectra of compounds **5a**—**5c** showed molecular ion peaks in agreement with their corresponding molecular formula. The Mannich base derivatives **6a**—**6f** were synthesized in one pot multi-component Mannich reaction involving **5a**—**5c**, secondary amines and formaldehyde solution in DMF. The occurrence of the aminomethylation reaction was confirmed by the loss of signal for the proton at the N-1 nitrogen atom of the 1,2,4-triazole ring. Moreover, the ^{1}H NMR spectra of **6a**—**6f** have displayed additional signals originated from methyl piperazine or morpholine residue and methylene linkage. The signal observed at δ 178.16 in the ^{13}C NMR spectrum of **6a** was attributed to C=S group. This group was observed at 1250—1343 cm^{-1} in the IR spectra of compounds **6a**—**6f**. These data confirm that the reaction is highly regioselective and furnishes only *N*-Mannich bases and none of the *S*-Mannich derivatives. The elemental analyses data are consistent with the assigned structures of compounds **6a**—**6f**. Furthermore, derivatives **6a**—**6f** gave stable molecular ion peak in their mass spectra. The resultant 1,3,4-oxadiazol-2-thione (**4**) was further converted into corresponding Mannich bases **7a**, **7b** on aminomethylation with formaldehyde and various secondary amines. The ^{1}H NMR spectra of **7a**, **7b** displayed additional signals originated from methyl piperazine or morpholine residue and methylene linkage, while the NH signal belonging to **4** was disappeared (Scheme 1).

On the other hand, the synthesis of thiosemicarbazides **8a**—**8c** were accomplished by treating the key intermediate **1** with potassium thiocyanate in the presence of diluted hydrochloric acid (for **8a**), ethylisothiocyanate (for **8b**) or benzylisothiocyanate (for **8c**). The structures of compounds **8a**—**8c** were confirmed on the basis of elemental analyses, IR, ^{1}H NMR and mass spectroscopic methods. The ^{1}H NMR spectrum of compound **8b**, for example, displayed three signals belonging to three different NH groups recorded at δ 8.43, 9.10 and 9.67 (controlled by changing with D_2O), respectively. In addition, the stretching bands derived from NH groups were observed in IR spectra of compounds **8a**—**8c**. The elemental analyses and mass spectroscopic data of compounds **8a**—**8c** are found consistent with the assigned structures. Chemical transformation of compounds **8a**—**8c** to **9a**—**9c** was achieved by two different methods. First method involved the treatment of compounds **8a**—**8c** with aqueous sodium hydroxide. While, in the second method, compounds **9a**—**9c** were synthesized by heating the corresponding compounds **8a**—**8c** in an oil bath upon 150 ℃ for 2 h. An interpretation of the reaction may be via the nucleophilic attack of thiosemicarbazide-N-4 to carbonyl group in the side chain of compounds **8a**—**8c**. Noteworthy, compounds **9a**—**9c** are present in thionic form as indicated by their IR spectra (absence of absorption at about 2500—2650 cm^{-1} region cited for SH group and presence of absorption in the region of 1301—1333 cm^{-1} characteristic for C=S group), ^{1}H NMR spectra (presence of one signal belonging to NH group at δ 10.03—10.89 integrating for one proton) and ^{13}C NMR spectrum of compound **9b** (displayed a signal due to C=S group at δ 180.22). In addition, the alkylation of compound **9a** was performed by reacting it with methyl iodide in basic medium, where the *S*-methylated derivative **10** was obtained. The IR spectrum of derivative **10** showed a strong band at 2954 cm^{-1} assigned for aliphatic C—H. The absorption band due to NH group appeared at 3241 cm^{-1}, while the C=S peak disappeared. Also, in the ^{1}H NMR spectrum of compound **10** there is only one signal derived from NH group and a

Scheme 1 Synthetic pathway for the prepareation of compounds **2**—**7**



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new signal due to methyl group appeared at δ 10.24 and 2.61, respectively.

By reacting the *S*-methylated derivative **10** with morpholine in the formaldehyde solution, the 4-(3,3'-bi(1,2,4-triazol)-1-yl)methyl)morpholine derivative (**11a**) was obtained rather than 4-(3,3'-bi(1,2,4-triazol)-4'-yl)methyl)morpholine isomer (**11b**). Compound **11a** shows, in its IR spectrum, the disappearance of NH vibration band. The absorption band at 1100 cm^{-1} is due to the presence of CH_2-O-CH_2 stretch of the morpholine ring system. The ^1H NMR spectrum of compound **11a** displayed new peaks at δ 6.13 and 2.44—2.68 owing to methylene linkage and morpholine moiety, respectively. Since the IR and ^1H NMR spectral data are very similar in isomers **11a** and **11b**, the differentiation between them is not possible. Presence of **11a** or **11b** could be explained by mass spectrum. It was reported that, the presence of the peak derived from the loss of a N_2 molecule was characteristic of thiazolo[2,3-*c*][1,2,4]triazole.[22-24] In the mass spectrum of compound **11a** the signal corresponding to N_2 loss is not present which indicates the formation of 4-(3,3'-bi(1,2,4-triazol)-1-yl)methyl)morpholine isomer **11a**.

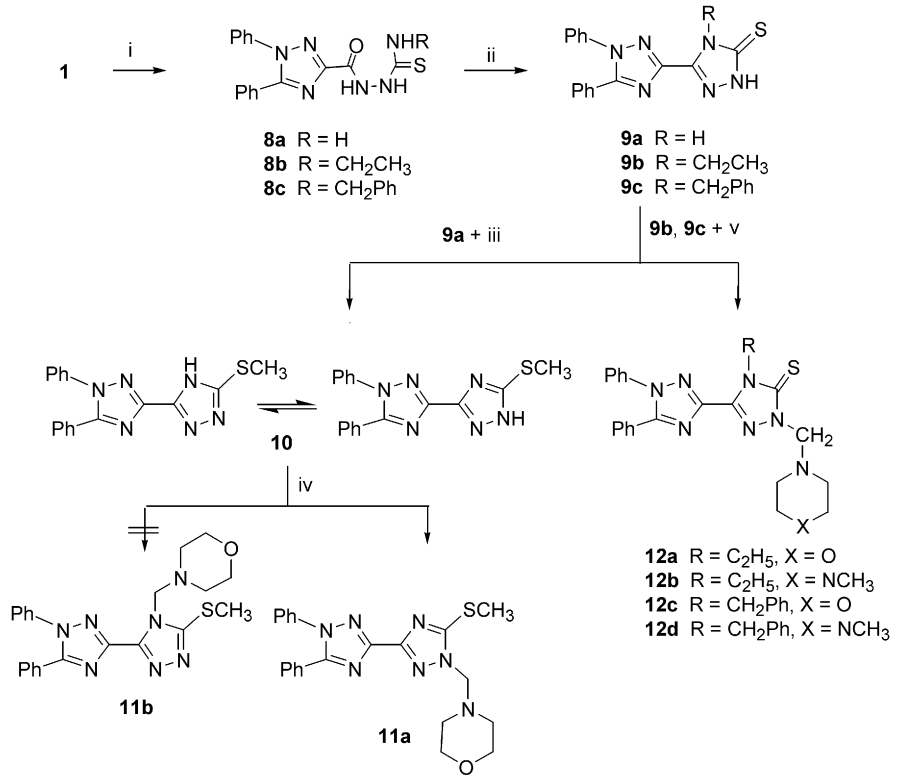
Similarly, the reaction of compounds **9b** and **9c** with several secondary amines in the presence of formaldehyde solution has afforded the corresponding *N*-Mannich bases **12a**—**12d** incorporating piperazine or morpholine ring. The absence of signal due to NH in ^1H NMR spectra of **12a**—**12d** and the presence of a new singlet for N-CH_2-N in the range of δ 5.21—5.57 confirmed that the bi-triazoles **9b** and **9c** were converted into corresponding Mannich bases **12a**—**12d**. Further, the formation of *N*-Mannich **12a**—**12d** rather than the corresponding *S*-Mannich were proved by ^{13}C NMR spectrometry, for example, compound **12a** showed the appearance of a signal corresponding to the thione carbon (C=S) and the absence of a signal corresponding to the C—S carbon. Moreover, **12a**—**12d** gave stable molecular ion peaks in their mass spectra (Scheme 2).

Antibacterial activity

The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good inhibition at 1.56—25 μg/mL in DMSO.

The tested compound **3** exhibited poor activity compared to that of the control drug. Thus, we have considered compound **3** as a lead molecule and subsequent structural modifications were carried out. As a first step towards lead optimization, amino group was protected in corresponding Schiff bases **5a**—**5c**. This modification resulted in a substantial increase in biological activity. Moreover, it is partly in contradiction with the purpose of Ghannoum and co-workers,[25] considering that NH_2 group should be free for antibacterial activity. According to our studies, implication of the

Scheme 2 Synthetic pathway for the preparation of compounds **8**—**12**



Reagents: (i) KSCN, HCl for **8a**, EtNCS for **8b**, $PhCH_2NCS$ for **8c**; (ii) NaOH; (iii) CH_3I; (iv) HCHO, Morpholine; (v) HCHO, Amine

NH_2 group in the azomethine function **5a**—**5c** increases the antibacterial activity comparative with bi-triazole **3**. In this case, the highest activity that was observed for the Schiff base derivatives **5b** and **5c** could also be attributed to the presence biologically active groups like —OMe and —NO_2 substituents, respectively. Mannich bases **6a**—**6f** and **7a**, **7b**, **11a** and **12a**—**12d** showed comparatively good activity against all the bacterial strains (Table 1). The good activity may be attributed to the presence of pharmacologically active —OMe, —NO_2 attached to the phenyl ring and *N*-methyl piperazine or morpholine moiety. Also, it has been observed that the bi-1,2,4-triazole derivatives are found to be more active than 5-(1,2,4-triazol-3-yl)-1,3,4-oxadiazole-2(3*H*)-thione derivatives. Moreover, the cyclization of the linear carbothioamide side chain of **8a**—**8c** into 1,2,4-triazole ring caused an increase in the activity of derivatives **9a**—**9c** against all the tested microorganism except *Escherichia coli*. Also, the tested *S*-methylated derivative **10** exhibited better activity against the used strains compared to the parent thiosemicarbazides **8a**—**8c**. This result confirmed that the presence of —SMe group increased the potency of bitriazole nuclei.

Table 1 Antibacterial activity data of the synthesized compounds[a]

Comp.	MIC in μg/mL and zone of inhibition in mm			
	Bacillus subtitis	*Streptococci*	*Klebsiella pneumoniae*	*Escherichia coli*
3	8 (25)	9 (25)	7 (25)	4 (25)
5a	16 (12.5)	15 (12.5)	16 (12.5)	12 (25)
5b	20 (12.5)	19 (12.5)	17 (12.5)	16 (12.5)
5c	18 (12.5)	19 (12.5)	19 (12.5)	18 (12.5)
6a	19 (12.5)	18 (12.5)	12 (12.5)	15 (12.5)
6b	20 (12.5)	22 (6.25)	15 (12.5)	17 (12.5)
6c	23 (6.25)	27 (1.56)	24 (6.25)	28 (6.25)
6d	23 (6.25)	25 (6.25)	27 (6.25)	25 (6.25)
6e	25 (6.25)	27 (1.5)	24 (6.25)	25 (6.25)
6f	27 (6.25)	27 (6.25)	23 (6.25)	27 (6.25)
7a	15 (12.5)	15 (12.5)	12 (25)	14 (25)
7b	15 (12.5)	15 (12.5)	14 (25)	17 (25)
8a	15 (12.5)	17 (12.5)	12 (12.5)	15 (12.5)
8b	14 (12.5)	18 (12.5)	13 (12.5)	13 (12.5)
8c	14 (12.5)	15 (12.5)	11 (12.5)	14 (12.5)
9a	18 (12.5)	18 (12.5)	17 (12.5)	8 (25)
9b	16 (12.5)	15 (12.5)	15 (12.5)	4 (25)
9c	18 (12.5)	18 (12.5)	19 (12.5)	10 (25)
10	22 (6.25)	25 (6.25)	20 (12.5)	20 (12.5)
11a	23 (6.25)	25 (6.25)	24 (6.25)	26 (6.25)
12a	19 (12.5)	23 (6.25)	26 (6.25)	24 (6.25)
12b	22 (6.25)	21 (12.5)	20 (12.5)	21 (12.5)
12c	20 (12.5)	20 (12.5)	22 (6.25)	19 (12.5)
12d	23 (6.25)	25 (6.25)	24 (6.25)	23 (6.25)
Standard (Ciprofloxacin)	27 (6.25)	29 (1.56)	29(6.25)	33 (6.25)
DMSO	—	—	—	—

[a] The values within the parentheses indicate minimum inhibitory concentration (MIC). The MIC values were evaluated at concentration range, 1.56—25 μg/mL.

Conclusions

The research study reports the successful synthesis and antibacterial activity of some novel Schiff and Mannich base derivatives. The antibacterial activity study revealed that all the compounds tested showed moderate to good antibacterial activities against pathogenic strains. Structure and biological activity relationship of these compounds showed that presence of pharmacologically active groups like —NO_2, —OMe and —SMe groups attached to phenyl ring and *N*-methyl piperazine or morpholine moiety attached to oxazole or oxadiazole ring are responsible for good antimicrobial activity.

Experimental

Chemistry

Melting points of the synthesized compounds are determined in open-capillaries on a Stuart electric melting point apparatus and are uncorrected. Reactions are monitored by thin-layer chromatography (TLC) on a silica gel coated aluminum sheet (silica gel F254). Elemental analyses were performed by the Microanalysis center, Cairo University. Infrared spectra were recorded on Satellite 2000 spectrometer using KBr discs. Mass spectra were determined on GC-MS (QP/000 EX) Shimadzu spectrometer at an ionizing voltage of 70 eV. ^{1}H NMR and ^{13}C NMR were recorded on Varin Mercury 300 MHz spectrometer (Chemical shift down field from TMS as an internal reference).

Potassium 2-(1,5-diphenyl-1*H*-1,2,4-triazole-3-carbonyl)hydrazinecarbodi-thioate (2)

Carbohydrazide **1** (0.01 mol) was treated with a solution of potassium hydroxide (0.015 mol) dissolved in methanol (30 mL) at 0—5 ℃ under stirring. Then carbon disulfide (0.015 mol) was added slowly and the reaction mixture was stirred overnight at room temperature. The solid product of potassium dithiocarbazinate **2** was filtered, washed with chilled methanol and dried. The resulting solid separated was collected by filtration and recrystallized from water to afford the desired product. Colorless solid (75%): m.p. 165—166 ℃. IR (KBr) *v*: 3296, 3163 (2NH), 1673 (C=O), 1612 (C=N) cm^{-1}.

4-Amino-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (3)

Method 1 0.01 mol of potassium dithiocarbazinate **2** was taken in water (10 mL) and hydrazine hydrate

(0.015 mol) and refluxed for 6 h. During the reaction progress, the reaction mixture turned to greenish with the evolution of H_2S gas and finally it become homogeneous. Then, the reaction mixture was poured onto ice/water mixture and acidified with concentrated hydrochloric acid. The solid was filtered off, washed with cold water and recrystallized from ethanol to give colorless crystals.

Method 2 A solution of **4** (0.01 mol) in ethanol (30 mL) was treated with hydrazine hydrate (0.015 mol) and the reaction mixture was refluxed for 5 h. The solid product obtained after concentration of the solution was collected by filtration. This crude product was recrystallized from ethanol to afford the desired product. Colorless solid (65%), m.p. 180 ℃; ^{1}H NMR (DMSO-d_6) δ: 5.31 (s, 2H, NH_2), 6.82—7.14 (m, 2H, ArH), 7.20—7.42 (m, 4H, ArH), 7.51—7.72 (m, 4H, ArH), 12.43 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: arC: [125.53 (2CH), 127.61 (2CH), 128.01 (2CH), 129.04 (CH), 129.99 (2CH), 131.18 (CH), 131.56 (C), 134.77 (C)], 147.65 (triazole C-5), 153.51 (triazole C-3), 154.88 (triazole C'-3), 181.99 (C=S); IR (KBr) v: 3310, 3320 (NH_2+NH), 1346 (C=S) cm^{-1}; MS *m/z* (%): 335 (M^+, 100), 336 (M^++1, 5.9), 337 (M^++2, 2.3). Anal. calcd for $C_{16}H_{13}N_7S$: C 57.30, H 3.91, N 29.23, S 9.56; found C 57.22, H 4.03, N 29.30, S 9.46.

General method for the synthesis of Schiff bases 5a—5c

To the solution of **3** (0.01 mol) in ethanol (30 mL) containing few drops of conc. H_2SO_4, an equimolar amount of an appropriate aldehyde (0.01 mol) was added. The obtained suspension was heated for 5h. The precipitated solid obtained after concentration of the solution was collected by filtration and recrystallized from dioxane to give yellow crystals.

4-(Benzylideneamino)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (5a) Yellow solid (71%), m.p. 211 ℃; ^{1}H NMR (DMSO-d_6) δ: 6.70—7.05 (m, 3H, ArH), 7.21—7.42 (m, 6H, ArH), 7.51—7.73 (m, 6H, ArH), 8.82 (s, 1H, N=CH), 11.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: arC: [125.22 (2CH), 126.81 (2CH), 128.23 (3CH), 129.12 (3CH), 130.21 (3CH), 131.51 (2CH), 132.19 (C), 135.84 (2C)], 149.01 (triazole C-5), 151.80 (triazole C-3), 153.27 (N=CH), 155 (triazole C'-3), 182.2 (C=S); IR (KBr) v: 3201 (NH), 1327 (C=S) cm^{-1}; MS *m/z* (%): 103 (100), 423 (M^+, 24), 424 (M^++1, 6). Anal. calcd for $C_{23}H_{17}N_7S$: C 65.23, H 4.05, N 23.15, S 7.57; found C 65.12, H 4.03, N 23.20, S 7.62.

4-((4-Methoxybenzylidene)amino)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (5b) Yellow solid (62%), m.p. 200 ℃; ^{1}H NMR (DMSO-d_6) δ: 3.88 (s, 3H, CH_3), 6.91—7.09 (m, 3H, ArH), 7.16—7.40 (m, 5H, ArH), 7.64—7.93 (m, 6H, ArH), 8.52 (s, 1H, N=CH), 12.14 (s, 1H, NH); IR (KBr) v: 3120 (NH), 1317 (C=S) cm^{-1}; MS *m/z* (%): 133 (100), 453 (M^+, 15), 454 (M^++1, 2.2). Anal. calcd for $C_{24}H_{19}N_7OS$: C 63.56, H 4.22, N 21.62, S 7.07; found C 63.42, H 4.15, N 21.54, S 7.11.

4-((4-Nitrobenzylidene)amino)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (5c) Yellow solid (52%), m.p. 232 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.01—7.24 (m, 4H, ArH), 7.32—7.47 (m, 4H, ArH), 7.45—7.55 (m, 2H, ArH) 7.91 (m, 2H, ArH), 8.17 (m, 2H, ArH) 8.68 (s, 1H, N=CH), 12.23 (s, 1H, NH); IR (KBr) v: 3200 (NH), 1322 (C=S) cm^{-1}; MS *m/z* (%): 148 (100), 468 (M^+, 2.7), 469 (M^++1, 1.3). Anal. calcd for $C_{23}H_{16}N_8O_2S$: C 58.97, H 3.44, N 23.92, S 6.84; found C 59.02, H 3.41, N 23.88, S 6.81.

General method for the synthesis of compounds 6a—6f, 7a, 7b, 11a and 12a—12d

To a solution of corresponding compounds **4**, **5a—5c**, **9b**, **9c** and **10** (0.01 mol) in dimethyl formamide (15 mL), formaldehyde (37%, 2 mL) and secondary amines (0.01 mol) were added and the mixture was stirred overnight at room temperature. The resulting solid formed after addition of excess water was filtered, washed with water and recrystallized from dioxane to give yellow crystals.

4-(Benzylideneamino)-1-(morpholinomethyl)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (6a) Yield 52%, m.p. 152 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.81 (t, J=4.7 Hz, 4H, morpholine), 2.34 (t, J=4.7 Hz, 4H, morpholine), 5.11 (s, 2H, NCH_2N), 6.71—7.02 (m, 3H, ArH), 7.13—7.22 (m, 6H, ArH), 7.38—7.51 (m, 6H, ArH), 9.2 (s, 1H, N=CH); ^{13}C NMR (DMSO-d_6) δ: 55.48 ($2CH_2N$), 75.21 ($2CH_2O$), 77.57 (NCH_2N), ArC: [126.30 (2CH), 126.94 (2CH), 128.01 (3CH), 129.42 (3CH), 131.01 (3CH), 132.33 (2CH), 132.14 (C), 134.71 (2C)], 148.57 (triazole C-5), 151.52 (triazole C-3), 154.17 (N=CH), 156.01 (triazole C'-3), 178.16 (C=S); IR (KBr) v: 1605 (CH=N), 1250 (C=S), 1200 (N—CH_2—N), 1090 (CH_2—O—CH_2) cm^{-1}; MS *m/z* (%): 522 (M^+, 100), 523 (M^++1, 16), 524 (M^++2, 2.7). Anal. calcd for $C_{28}H_{26}N_8OS$: C 64.35, H 5.01, N 21.44, S 6.14; found C 64.30, H 5.02, N 21.33, S 6.22;

4-(Benzylideneamino)-1-((4-methylpiperazin-1-yl)methyl)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (6b) Yield 46%, m.p. 182 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.01 (s, 3H, CH_3), 2.31 (s, 8H, piperazine), 5.23 (s, 2H, NCH_2N), 6.88—7.06 (m, 3H, ArH), 7.15—7.25 (m, 6H, ArH), 7.31—7.47 (m, 6H, ArH), 8.72 (s, 1H, N=CH); IR (KBr) v: 1611 (CH=N), 1315 (C=S), 1184 (N—CH_2—N) cm^{-1}; MS *m/z* (%): 535 (M^+, 100), 537 (M^++2, 7). Anal. calcd for $C_{29}H_{29}N_9S$: C 65.02, H 5.46, N 23.53, S 5.99; found C 64.97, H 5.55, N 23.41, S 6.02.

4-((4-Methoxybenzylidene)amino)-1-(morpholinomethyl)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (6c) Yield 62%, m.p. 224 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.34 (t, J=4.5 Hz, 4H, morpholine), 2.73 (t, J=4.5 Hz, 4H, morpholine), 3.27 (s, 3H, OCH_3), 5.20 (s, 2H, NCH_2N), 7.02—7.21 (m, 3H, ArH), 7.25—7.41 (m, 6H, ArH), 7.52—7.69 (m, 5H, ArH), 8.17 (s, 1H, N=CH); IR (KBr) v: 1594 (CH=N),

1327 (C=S), 1201 (N—CH_2—N), 1128 (CH_2—O—CH_2) cm^{-1}; MS *m/z* (%): 552 (M^+, 100), 553 (M^++1, 53), 554 (M^++2, 14). Anal. calcd for $C_{29}H_{28}N_8O_2S$: C 63.03, H 5.11, N 20.28, S 5.80; found C 62.99, H 5.10, N 20.41, S 6.01.

4-((4-Methoxybenzylidene)amino)-1-((4-methylpiperazin-1-yl)-methyl)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (6d) Yield 72%, m.p. 193 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.13 (s, 3H, CH_3), 2.42 (s, 8H, piperazine), 3.41 (s, 3H, OCH_3), 5.36 (s, 2H, NCH_2N), 6.84—6.92 (3H, m, ArH), 7.06—7.21 (m, 6H, ArH), 7.31—7.48 (m, 5H, ArH), 8.31 (s, 1H, N=CH); IR (KBr) *v*: 1607 (CH=N), 1315 (C=S), 1224 (N—CH_2—N) cm^{-1}; MS *m/z* (%): 565 (M^+, 100). Anal. calcd for $C_{30}H_{31}N_9OS$: C 63.70, H 5.52, N 22.28, S 5.67; found C 63.74, H 5.43, N 22.33, S 5.57.

1-(Morpholinomethyl)-4-((4-nitrobenzylidene)-amino)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (6e) Yield 55%, m.p. 236 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.32 (t, *J*=4.5 Hz, 4H, morpholine), 2.80 (t, *J*=4.5 Hz, 4H, morpholine), 5.33 (s, 2H, NCH_2N), 7.05—7.14 (m, 3H, ArH), 7.24—7.38 (m, 6H, ArH), 7.43—7.51 (m, 3H, ArH), 8.04—8.11 (m, 2H, ArH), 8.31 (s, 1H, N=CH); IR (KBr) *v*: 1620 (CH=N), 1343 (C=S), 1188 (N—CH_2—N), 1154 (CH_2—O—CH_2) cm^{-1}; MS *m/z* (%): 148 (100), 567 (M^+, 59), 569 (M^++2, 21). Anal. calcd for $C_{28}H_{25}N_9O_3S$: C 59.25, H 4.44, N 22.21, S 5.65; found C 59.31, H 4.42, N 22.30, S 5.51.

1-((4-Methylpiperazin-1-yl)methyl)-4-((4-nitrobenzylidene)-amino)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (6f) Yield 46%, m.p. 227 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.04 (s, 3H, CH_3), 2.33 (s, 8H, piperazine), 5.47 (s, 2H, NCH_2N), 7.11—7.19 (m, 3H, ArH), 7.27—7.41 (m, 6H, ArH), 7.47—7.54 (m, 3H, ArH), 7.71—7.73 (m, 2H, ArH), 8.22 (s, 1H, N=CH); IR (KBr) *v*: 1614 (CH=N), 1323 (C=S), 1209 (N—CH_2—N) cm^{-1}; MS *m/z* (%): 148 (100), 580 (M^+, 22). Anal. calcd for $C_{29}H_{28}N_{10}O_2S$: C 59.98, H 4.86, N 24.12, S 5.52; found C 60.11, H 4.77, N 24.24, S 5.44.

4.1.4.7.5-(1,5-Diphenyl-1*H*-1,2,4-triazol-3-yl)-3-(morpholinomethyl)-1,3,4-oxadiazole-2(3*H*)-thione (7a) Yield 50%, m.p. 198 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.20 (t, *J*=4.5 Hz, 4H, morpholine), 2.74 (t, *J*=4.5 Hz, 4H, morpholine), 5.21 (s, 2H, NCH_2N), 6.97—7.21 (m, 4H, ArH), 7.34—7.66 (m, 6H, ArH); IR (KBr) *v*: 1601 (C=N), 1333 (C=S), 1133 (N—CH_2—N), 1105 (CH_2—O—CH_2) cm^{-1}; MS *m/z* (%): 220 (100), 420 (M^+, 24), 421 (M^++1, 8). Anal. calcd for $C_{21}H_{20}N_6O_2S$: C 59.98, H 4.79, N 19.99, S 7.63; found C 60.11, H 4.87, N 20.13, S 7.55.

5-(1,5-Diphenyl-1*H*-1,2,4-triazol-3-yl)-3-((4-methylpiperazin-1-yl)methyl)-1,3,4-oxadiazole-2(3*H*)-thione (7b) Yield 54%, m.p. 185 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.22 (s, 3H, CH_3), 2.24 (s, 8H, piperazine), 4.75 (s, 2H, NCH_2N), 6.85—7.10 (m, 4H, ArH), 7.28—7.51 (m, 6H, ArH); IR (KBr) *v*: 1600 (CH=N), 1325 (C=S), 1211 (N—CH_2—N) cm^{-1}; MS *m/z* (%): 220 (100), 433 (M^+, 31), 434 (M^++1, 22), 435 (M^++2, 7). Anal. calcd for $C_{22}H_{23}N_7OS$: C 60.95, H 5.35, N 22.62, S 7.40; found C 60.88, H 5.41, N 22.44, S 7.43.

4-((5-(Methylthio)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazol)]-1-yl)methyl)morpholine (11a) Yield 73%, m.p. 237 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.44 (m, 7H, morpholine+SCH_3), 2.68 (t, *J*=4.7 Hz, 4H, morpholine), 6.13 (s, 2H, NCH_2N), 7.11—7.20 (m, 2H, ArH), 7.34—7.48 (m, 4H, ArH), 7.50—7.64 (m, 4H, ArH); IR (KBr) *v*: 2972 (CH aliphatic), 1587 (C=N), 1127 (N—CH_2—N), 1100 (CH_2—O—CH_2) cm^{-1}; MS *m/z* (%): 103 (100), 433 (M^+, 59), 434 (M^++1, 21). Anal. calcd for $C_{22}H_{23}N_7OS$: C 60.95, H 5.35, N 22.62, S 7.40; found C 60.81, H 5.30, N 22.53, S 7.51.

4-Ethyl-1-(morpholinomethyl)-1',5'-diphenyl-*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (12a) Yield 64%, m.p. 194 ℃; ^{1}H NMR (DMSO-d_6) δ: 1.10 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 2.21 (t, *J*=4.5 Hz, 4H, morpholine), 2.83 (t, *J*=4.5 Hz, 4H, morpholine), 3.55 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 5.21 (s, 2H, NCH_2N), 6.85—7.14 (m, 4H, ArH), 7.27—7.41 (m, 6H, ArH); ^{13}C NMR (DMSO-d_6) δ: 17.22 (CH_2CH_3), 49.51 (CH_2CH_3), 57.28 ($2CH_2N$), 77.28 ($2CH_2O$), 82.67 (NCH_2N), ArC: [127.44 (2CH), 129.37 (2CH), 130.28 (2CH), 131.82 (2CH), 132.22 (2CH), 133.24 (C), 136.22 (C)], 150.23 (triazole C-5), 152.99 (triazole C-3), 156.02, (triazole C'-3), 175.61 (C=S); IR (KBr) *v*: 1284 (C=S), 1215 (N—CH_2—N), 1125 (CH_2—O—CH_2) cm^{-1}; MS *m/z* (%): 220 (100), 447 (M^+, 45), 448 (M^++1, 9), 449 (M^++2, 2.1). Anal. calcd for $C_{23}H_{25}N_7OS$: C 61.72, H 5.63, N 21.91, S 7.16; found C 61.81, H 5.70, N 21.94, S 7.34.

4-Ethyl-1-((4-methylpiperazin-1-yl)methyl)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (12b) Yield 55%, m.p. 186 ℃; ^{1}H NMR (DMSO-d_6) δ: 1.21 (t, *J*=7.2 Hz, 3H, $CH_2C\mathbf{H}_3$), 2.11 (s, 3H, CH_3), 2.30 (s, 8H, piperazine), 3.28 (q, *J*=7.2 Hz, 2H, $C\mathbf{H}_2CH_3$), 5.37 (s, 2H, NCH_2N), 7.22—7.42 (m, 4H, ArH), 7.49—7.61 (m, 6H, ArH); IR (KBr) *v*: 1312 (C=S), 1224 (N—CH_2—N) cm^{-1}; MS *m/z* (%): 460 (M^+, 100), 461 (M^++1, 11), 462 (M^++2, 2). Anal. calcd for $C_{24}H_{28}N_8S$: C 62.58, H 6.13, N 24.33, S 6.96; found C 62.46, H 5.96, N 24.54, S 6.66.

4-Benzyl-1-(morpholinomethyl)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (12c) Yield 71%, m.p. 245 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.15 (t, *J*=5.2 Hz, 4H, morpholine), 2.77 (t, *J*=5.2 Hz, 4H, morpholine), 4.01 (s, 2H, CH_2), 5.57 (s, 2H, NCH_2N), 6.74—6.92 (m, 4H, ArH), 7.07—7.32 (m, 5H, ArH), 7.45—7.66 (m, 6H, ArH); IR (KBr) *v*: 1318 (C=S), 1220 (N—CH_2—N), 1100 (CH_2—O—CH_2) cm^{-1}; MS *m/z* (%): 91 (100), 509 (M^+, 85), 510 (M^++1, 14), 511 (M^++2, 2). Anal. calcd for $C_{28}H_{27}N_7OS$: C 65.99, H 5.34, N 19.24, S 6.29; found C 65.75, H 5.22, N 19.22, S 6.26.

4-Benzyl-1-((4-methylpiperazin-1-yl)methyl)-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-

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thione (12d) Yield 49%, m.p. 244 ℃; ^{1}H NMR (DMSO-d_6) δ: 1.75 (s, 3H, CH_3), 2.12 (s, 8H, piperazine), 4.23 (s, 2H, CH_2), 5.51 (s, 2H, NCH_2N), 7.22—7.42 (m, 3H, ArH), 7.04—7.22 (m, 4H, ArH), 7.29—7.37 (m, 4H, ArH), 7.55—7.63 (m, 4H, ArH); IR (KBr) *v*: 1305 (C=S), 1251 (N—CH_2—N) cm^{-1}; MS *m/z* (%): 91 (100), 522 (M^+, 73), 523 (M^++1, 5.7). Anal. calcd for $C_{29}H_{30}N_8S$ (%): C 66.64, H 5.79, N 21.44, S 6.13; found C 66.56, H 5.67, N 21.29, S 6.24.

2-(1,5-Diphenyl-1*H*-1,2,4-triazole-3-carbonyl)hydrazinecarbo-thioamide (8a)

A mixture of **1** (0.01 mol) and potassium thiocyanate (0.03 mol) in hydrochloric acid (20%, 30 mL) was heated under reflux for 5 h. The reaction mixture was concentrated, cooled and the separated solid was filtered, washed with water, dried and recrystallized from dioxane.

Yellow solid (78%), m.p. 160 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.01—7.27 (m, 4H, ArH+NH_2), 7.30—7.37 (m, 4H, ArH), 7.41—7.56 (m, 4H, ArH), 9.22 (s, 1H, NH), 9.83 (s, 1H, NH); IR (KBr) *v*: 3330—3115 (2NH+NH_2), 1657 (C=O), 1348 (C=S) cm^{-1}; MS *m/z* (%): 220 (100), 338 (M^+, 16), 339 (M^++1, 1.2). Anal. calcd for $C_{16}H_{14}N_6OS$: C 56.79, H 4.17, N 24.84, S 9.48; found C 56.66, H 4.20, N 24.78, S 9.33.

General method for the synthesis of compounds 8b, 8c

A mixture of compound **1** (0.01 mol) and ethyl isothiocyanate (for **8b**) or benzylisothiocyanate (for **8c**) (0.01 mol) was allowed to reflux in ethanol (30 mL) for 4 h. The solution was cooled and a yellow solid appeared. This was filtered and recrystallized from ethanol to give yellow crystals.

2-(1,5-Diphenyl-1*H*-1,2,4-triazole-3-carbonyl)-*N*-ethylhydrazine-carbothioamide (8b) Yield 81%, m.p. 164 ℃; ^{1}H NMR (DMSO-d_6) δ: 1.18 (t, J=7.1 Hz, 3H, CH_3), 3.44 (q, J=7.2 Hz, 2H, CH_2), 6.82—7.02 (m, 4H, ArH), 7.12—7.26 (m, 6H, ArH), 8.43 (s, 1H, NH), 9.10 (s, 1H, NH), 9.67 (s, 1H, NH); IR (KBr) *v*: 3321 and 3217 (3NH), 1662 (C=O), 1327 (C=S) cm^{-1}; MS *m/z* (%): 220 (100), 366 (M^+, 23), 368 (M^++2, 4). Anal. calcd for $C_{18}H_{18}N_6OS$: C 59.00, H 4.95 N 22.93, S 8.75; found C 58.89, H 5.13, N 22.81, S 8.73.

***N*-Benzyl-2-(1,5-diphenyl-1*H*-1,2,4-triazole-3-carbonyl)hydrazine-carbothioamide (8c)** Yield 74%, m.p. 172 ℃; ^{1}H NMR (DMSO-d_6) δ: 4.5 (s, 2H, CH_2), 7.01—7.13 (m, 4H, ArH), 7.21—7.35 (m, 5H, ArH), 7.42—7.56 (m, 3H, ArH), 7.64—7.70 (m, 3H, ArH), 8.22 (s, 1H, NH), 9.51 (s, 1H, NH), 10.12 (s, 1H, NH); IR (KBr) *v*: 3247 and 3158 (3NH), 1669 (C=O), 1315 (C=S) cm^{-1}; MS *m/z* (%): 91 (100), 428 (M^+, 37), 429 (M^++1, 1.9). Anal. calcd for $C_{23}H_{20}N_6OS$: C 64.47, H 4.70, N 19.61, S 7.48; found C 64.41, H 4.65, N 19.51, S 7.50.

General method for the synthesis of compounds 9a—9c

Method 1 A solution of carbothioamides **8a—8c** (0.01 mol) in 2 mol/L NaOH was refluxed for 3 h. The resulting solution was cooled to room temperature and acidified with conc. HCl. The precipitate formed was filtered, washed with water and recrystallized from ethanol to afford the desired compounds.

Method 2 The carbothioamides **8a—8c** (0.01 mol) were heated in an oil path at *ca.* 150 ℃ for 2 h. The formed solid was recrystallized from ethanol to afford the desired compounds. The yields of these two methods are very close to each other.

1',5'-Diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (9a) Yellow solid (71%), m.p. 195 ℃; ^{1}H NMR (DMSO-d_6) δ: 5.02 (s, 1H, NH), 7.05—7.11 (m, 2H, ArH), 7.35—7.44 (m, 4H, ArH), 7.49—7.51 (m, 4H, ArH), 9.72 (s, 1H, NH); IR (KBr) *v*: 3227, 3197 (2NH), 1333 (C=S) cm^{-1}; MS *m/z* (%): 220 (100), 320 (M^+, 11), 321 (M^++1, 1). Anal. calcd for $C_{16}H_{12}N_6S$: C 59.98, H 3.78, N 26.23, S 10.01; found C 60.03, H 3.80, N 26.12, S 9.89.

4-Ethyl-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (9b) Yellow solid (63%), m.p. 179 ℃; ^{1}H NMR (DMSO-d_6) δ: 1.06 (t, J=7.1 Hz, 3H, CH_2CH_3), 3.51 (q, J=7.1 Hz, 2H, CH_2CH_3), 7.03—7.17 (m, 4H, ArH), 7.20—7.27 (m, 6H, ArH), 10.89 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 16.57 (CH_2**C**H_3), 46.49 (**C**H_2CH_3), arC: [126.27 (2CH), 128.05 (2CH), 131.00 (2CH), 131.87 (2CH), 132.31 (2CH), 133.10 (C), 134.47 (C)], 148.20 (triazole C-5), 149.92 (triazole C-3), 157.11(triazole C'-3), 180.22 (C=S); IR (KBr) *v*: 3266 (NH), 1312 (C=S) cm^{-1}; MS *m/z* (%): 348 (M^+, 100), 349 (M^++1, 28), 350 (M^++2, 11). Anal. calcd for $C_{18}H_{16}N_6S$: C 62.05, H 4.63, N 24.12, S 9.20; found C 62.14, H 4.57, N 24.02, S 9.17..

4-Benzyl-1',5'-diphenyl-1*H*,1'*H*-[3,3'-bi(1,2,4-triazole)]-5(4*H*)-thione (9c) Yellow solid (57%), m.p. 221 ℃; ^{1}H NMR (DMSO-d_6) δ: 4.33 (s, 2H, CH_2), 6.67—6.79 (m, 4H, ArH), 6.93—7.25 (m, 5H, ArH), 7.32—7.48 (m, 3H, ArH), 7.57—7.63 (m, 3H, ArH), 10.03 (s, 1H, NH); IR (KBr) *v*: 3249 (NH), 1301 (C=S) cm^{-1}; MS *m/z* (%): 91 (100), 410 (M^+, 45), 411 (M^++1, 15), 412 (M^++2, 3). Anal. calcd for $C_{23}H_{18}N_6S$: C 67.30, H 4.42, N 20.47, S 7.81; found C 67.23, H 4.54, N 20.33, S 7.83.

5'-(Methylthio)-1,5-diphenyl-1*H*,1'*H*-3,3'-bi(1,2,4-triazole) (10)

To a warmed ethanolic potassium hydroxide solution (prepared by dissolving 0.56 g, 0.01 mol of KOH in 50 mL of ethanol) compound **9a** (0.01 mol) was added, and heating was continued for 45 min. The mixture was allowed to cool to room temperature, and methyl iodide (0.015 mol) was added. Then, the mixture was stirred under reflux for 5 h. The reaction mixture was poured into ice water. The precipitate obtained was filtered and washed with water. The compound was purified by crystallization from dioxane. Yellow solid 62%, m.p. 261 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.61 (s, 3H, CH_3), 7.14—7.25 (m, 2H, ArH), 7.51—7.58 (m, 4H, ArH), 8.01—8.26 (m, 4H, ArH), 10.24 (s, 1H, NH); IR (KBr) *v*: 3241 (NH), 2954 (aliph. C—H) cm^{-1}; MS *m/z* (%): 103 (100),

334 (M^+, 27), 335 ($M^+ + 1$, 2.2). Anal. calcd for $C_{17}H_{14}N_6S$: C 61.06, H 4.22, N 25.13, S 9.59; found C 61.11, H 4.26, N 25.00, S 9.63.

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against Gram positive (*Bacillus subtitis* and *Streptococci*) and Gram negative (*Klebsiella pneumoniae* and *Escherichia coli*) stains by serial plate dilution method.[26] Serial dilutions of the drug in Muller Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16—18 h at 37 ℃. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. A number of antibacterial discs were placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. 20 mL of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 ℃ for 1 h. Using a punch, wells were made on these seeds agar plates and minimum inhibitory concentrations of the test compounds in dimethyl sulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using DMSO as a solvent. The Petri dishes were prepared in triplicate and maintained at 37 ℃ for 3—4 d. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with Ciprofloxacin as standard.[27] The results are summarized in Table 1. The MIC values were evaluated at concentration range 1.5—25 μg/mL.

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