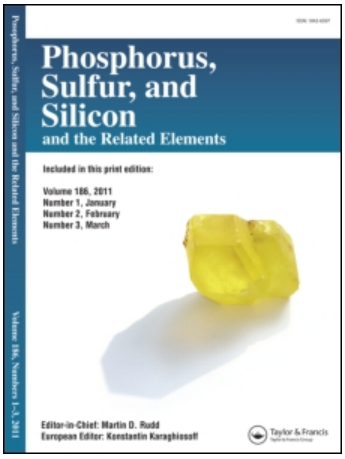

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Structural Study and Biological Evaluation of Some Novel 1,2,4-Triazole, Thiazole, and Bisthiazole Derivatives Bearing a Sulfonamide Moiety

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Structural Study and Biological Evaluation of Some Novel 1,2,4-Triazole, Thiazole, and Bisthiazole Derivatives Bearing a Sulfonamide Moiety

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*The starting material 1,2,4-triazole derivative (**3**) was used to synthesize some novel condensed triazoles. Thus, treatment of compound (**3**) with phenyl isocyanate in refluxing pyridine furnished the novel [1,2,4]triazolo[4,3-b][1,2,4]triazole derivative (**5**). Also, cyclization of compound (**3**) with phenyl isothiocyanate afforded the [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivative (**7**). Hydrazone derivative (**9d**) was allowed to react with some halogenated reagents such as chloroacetone, ethyl chloroacetate, and chloroacetonitrile to furnish thiazole derivatives (**12**), (**13**), and (**15**), respectively. In a similar manner, bishydrazone (**17**) was used to prepare the novel bisthiazoles (**18**) and (**19**). Some of the synthesized compounds were evaluated for their antibacterial activity.*

Keywords Bisthiazole; hydrazone; thiazole; thiocarbohydrazide; 1,2,4-triazole

INTRODUCTION

Recently some new triazoles have been synthesized as possible antibacterial, antimicrobial, antiviral, and antifungal agents.[1–4] Also, a number of thiazoles have been reported to exhibit antitubercular, antimalarial, CNS depressant, and analgesic[5–8] properties and antimicrobial activity against both Gram-positive and Gram-negative bacteria.[9] Furthermore, sulfonamide and azo-sulfonamide derivatives have been found to be biologically versatile anticancer,[10] antimalarial,[11] and antitubercular drugs.[12–14] In continuation of our interest in organic sulfur heterocycles,[15–19] moiety was designed and their biological effects were evaluated in a specific program aimed at the synthesis of some new

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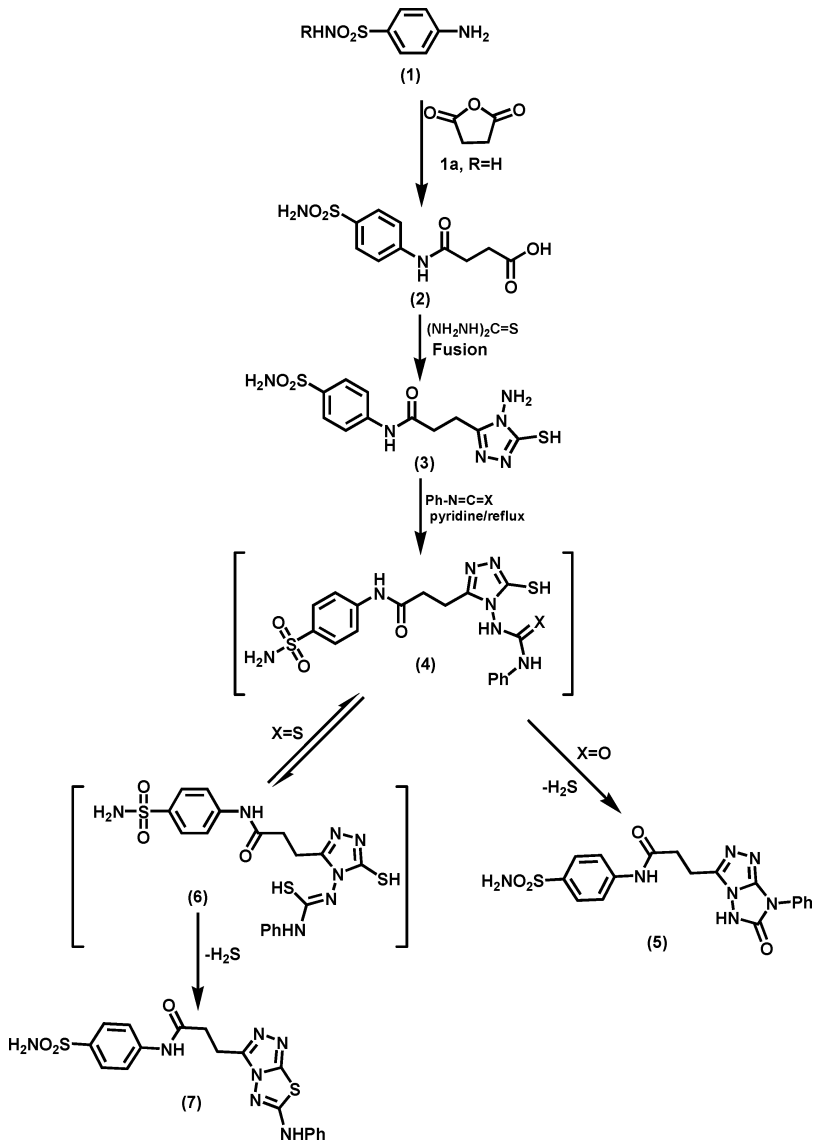
1,2,4-triazole, thiazole, and bisthiazole derivatives containing the sulfonamido moiety for evaluated their biological effects.

RESULTS AND DISCUSSION

When the sulfanilamide (**1a**) was allowed to react with the succinic anhydride under reflux in ethanol in the presence of triethylamine, the corresponding succinamic acid derivative (**2**) was obtained. Its IR spectrum showed bands at 3330–2750 cm^{-1} (broad-COOH), 3320, 3280 cm^{-1} (NH, NH_2), 1750, 1690 cm^{-1} (2 C=O), and its ^1H NMR spectrum revealed signals at 2.4–2.7 (m, 4H, CH_2CH_2), 7.2 (s, 2H, NH_2), 12.1 (br, 1H, OH). 3-(4-Amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl)-*N*-(4-sulfamoyl-phenyl)-propionamide **3** was prepared in a good yield (84%) by fusion of *N*-(4-sulfamoyl-phenyl)-succinamic acid (**2**) with thiocarbohydrazide. The IR spectrum of **3** exhibited the absence of broad band characteristic for the carboxylic group and the presence of 3390, 3260, 3220 cm^{-1} (NH, NH_2). The mass spectrum of **3** showed a molecular ion peak m/z at 342 (M^+; 13.03), 343 (M+1, 33.45%) together with a base peak at 56 (100%), and other significant peaks appeared at 254 (13.03%), 185 (41.55%), 133 (41.20%), 125 (88.87%), 101 (58.15%), 68 (44.01%). The reaction of **3** with phenyl isocyanate in refluxing pyridine gave a product that formulated as the [1,2,4]triazolo[4,3-b][1,2,4]triazole derivative **5**. Its mass spectrum revealed a molecular ion peak m/z 427 (M^+; 7.45%), with a base peak at 158 (100%), and other significant peaks appeared at 408 (10.41%), 373 (0.88%), 329 (12.66%), 254 (80.34%), 217 (18.80%), 108 (34.04%), 92 (88.78%), 76 (4.08%). The formation of the triazolotriazole derivative is assumed to proceed through the urea intermediate **(4)** followed by elimination of hydrogen sulfide,[20] as depicted in Scheme 1.

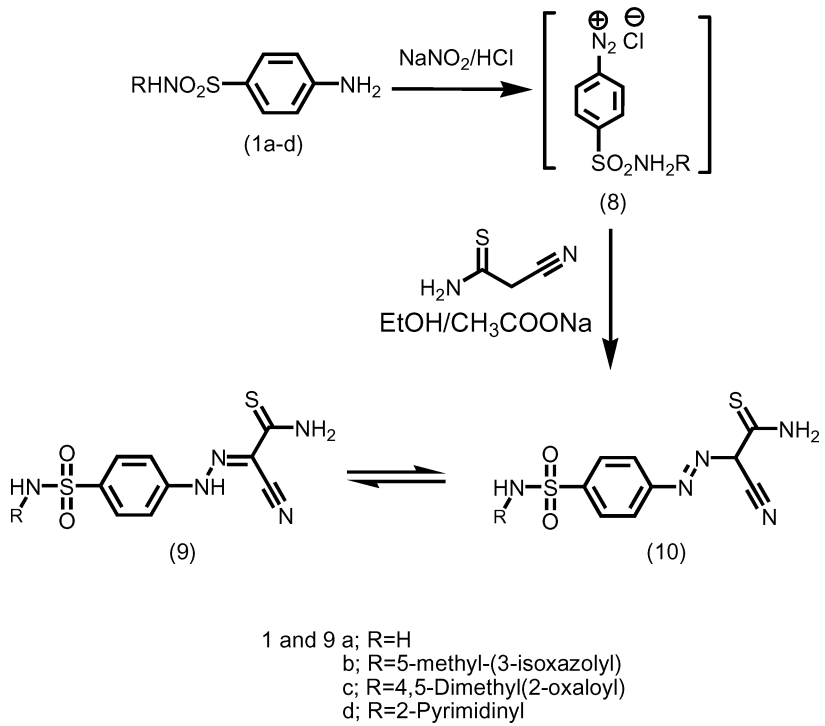
On the other hand, interaction of **3** with phenyl isothiocyanate gave the corresponding 6-anilino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivative **7** via intermediate **6** followed by elimination of hydrogen sulfide. Its IR spectrum showed bands at 3344, 3300, 3280 cm^{-1} (NH, NH_2).

For obtaining the thiazole derivatives, diazotization of sulfanilamide**(1a)** and its derivatives **(1b–c)** followed by coupling with cyanothioacetamide in the presence of sodium acetate in ethanol at 5°C furnished the hydrazone form **(9a–d)** rather than the azo form on the basis of ^{1}HNMR spectra (Scheme 2). The ^1H NMR spectrum of compound **(9a)** recorded in dimethylsulfoxide revealed a signal at $\delta = 11.71$ ppm, which is attributed to hydrazone NH functional group.



SCHEME 1

Due to the possibility of existence in both tautomeric forms, that is, as azo(A)-hydrazo(H) tautomerization, molecular models of possible tautomeric forms were calculated in the gas phase, using semi-empirical AM1, PM3, and MNDO methods using HyperChem 7.5 software. The



SCHEME 2

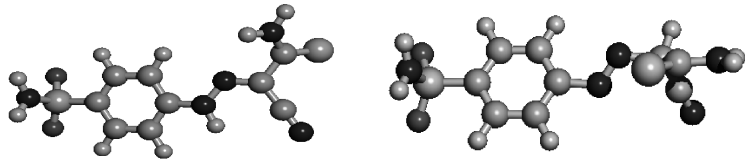
initial geometries of the molecules were built using standard parameters and then optimized using the Polak–Ribiere geometrical optimization. The heat of formation and relative stabilities of the two tautomeric forms **9** and **10** are listed in Table I.

All semi-empirical calculations lead to the same result that the **A**-form has more heat of formation value than the **H**-form. The negative

TABLE I Heat of Formation (ΔH_f°) and Relative Stabilities ($\Delta\Delta H_f^\circ$ kcal.mol^{-1}) of Tautomeric Forms of 9 and 10

Method	ΔH_f°		$\Delta\Delta H_f^\circ$
	10	**9**	
MNDO	222.8	224.5	−1.7
AM1	52.0	59.6	−7.6
PM3	86.5	89.6	−3.1

$\Delta\Delta H_f^\circ = \Delta H_f^\circ(H) - \Delta H_f^\circ(A)$.



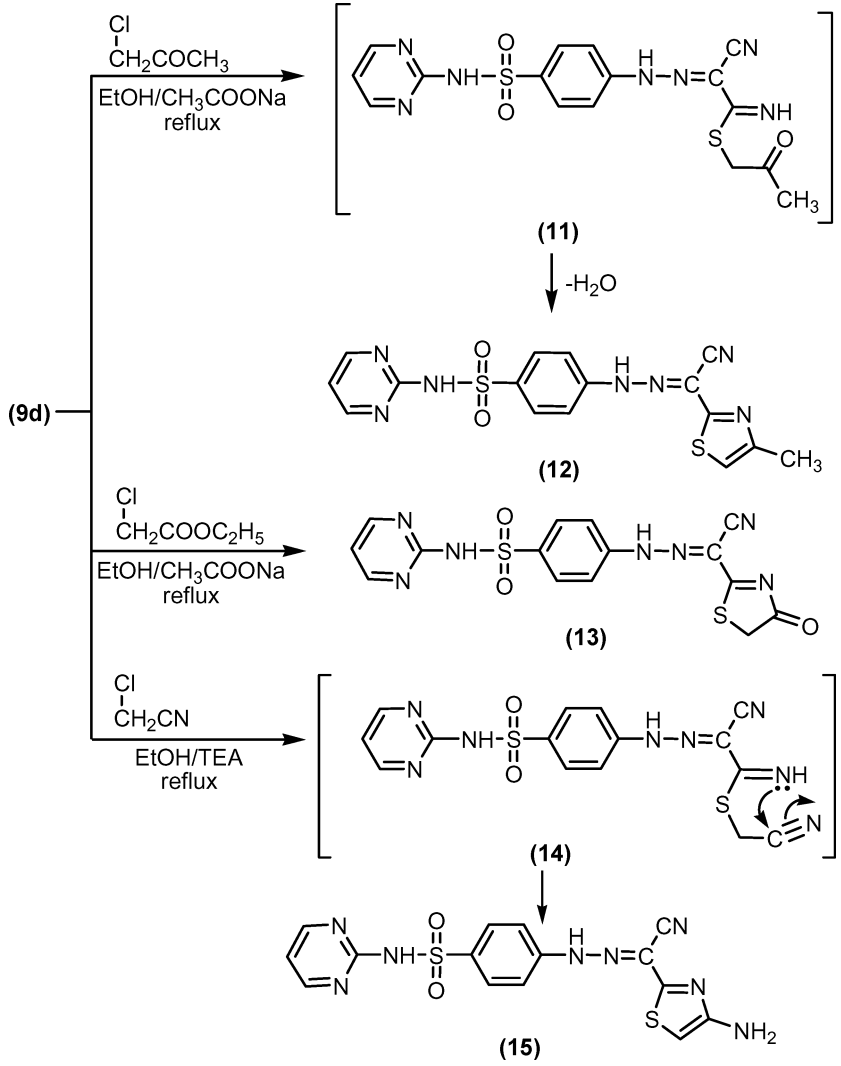
	9 Hydrazo	**10** azo
HF/6-31G*	-1562.876578619	-1562.860886113
ΔE (Kcal/mol)	0	9.8
Dipole	8.1	7.1

FIGURE 1 Optimized geometries of **H**-form (**9**) and **A**-form (**10**).

sign of the $\Delta\Delta\ H_f^\circ$ indicates that the **H**-form is more stable by all computational methods.

The equilibrium geometries have been calculated also by ab initio calculations in the gas phase at 6-31G* basis set level, which were carried out using HyperChem 7.5 software. The optimized structure information is shown in Figure 1 along with the relative energies of **9** and **10**. For all calculations, the most stable tautomer corresponds to the **H**-form structure **9**. This, however, is in agreement with the experiment data.

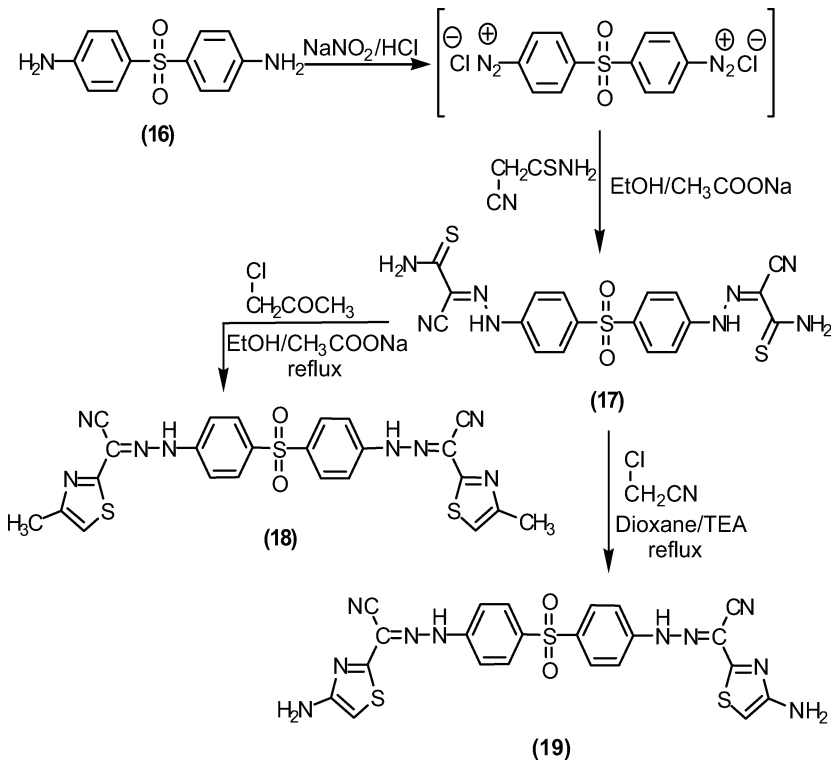
The reactivity of the thiocarbamoyl functional group in compound **(9d)** towards some halogenated reagents was studied. Thus, cycloalkylation of compound **(9d)** with chloroacetone in refluxing ethanol in the presence of fused sodium acetate yielded the corresponding thiazole derivative **(12)**. The structure of the thiazole derivative **(12)** was established by its analytical and spectral data. The infrared spectrum of compound **(12)** exhibited absorption bands characteristic for NH (3326, 3103 cm^{-1}) and C ≡ N (2221 cm^{-1}). Also, the ^1H NMR spectrum of compound **(12)** in DMSO-d_6 showed the presence H-thiazole at $\delta = 5.04$ ppm in addition to NH proton at $\delta = 11.98$ ppm, besides other signals due to methyl and aromatic protons. The formation of compound **(12)** is assumed to proceed via initial alkylation to form intermediate **(11)** followed by intramolecular cyclization[21,22] by elimination of a water molecule. Cyclization of compound **(9d)**, also with ethyl chloroacetate at reflux temperature in ethanol in the presence of fused sodium acetate, afforded thiazole derivative **(13)** via alkylation of thiocarbamoyl functional group and elimination of ethanol molecule. In addition, cyclocondensation of compound **(9d)** with chloroacetonitrile in ethanol in the presence of triethylamine under reflux furnished aminothiazole



SCHEME 3

derivative **(15)**. The formation of thiazole **(15)** is assumed to proceed through initial alkylation to form **(14)** followed by intramolecular nucleophilic cyclization and tautomerization (Scheme 3).

It was of interest to incorporate the moiety of thiazole rings into the well-known antimicrobial diphenyl sulfides.[23,24] We have synthesized some heterocycle compounds containing diphenyl sulfone



SCHEME 4

and thiazole moieties for their useful biological application. 4,4′-Diaminodiphenylsulfone **(16)** was diazotized and coupled with cyanothioacetamide to form bishydrazone derivative **(17)**. Treatment of bishydrazone **(17)** with chloroacetone under reflux in ethanol furnished bisthiazole derivative **(18)**. Finally, condensation of bishydrazone **(17)** with chloroacetonitrile in dioxane in the presence of triethylamine at reflux temperature produced the bisthiazole derivative **(19)** (Scheme 4).

ANTIMICROBIAL SCREENING

The synthesized compounds were evaluated for antibacterial activity using the agar diffusion technique.[25] A 1 mg/mL solution in dimethylformamide was used. All the prepared compounds were tested for antibacterial activity against the following: *Staphylococcus aureus* (NCTC 7447), *Bacillus subtilis* (NCTC 10400), *Sarcina sp.* (NCTC 1117),

TABLE II Antibacterial Property of the Synthesized Compounds

	Gram positive		Gram negative		
Compd. No.	*Staphylococcus aureus* (NCTC 7447)	*Bacillus subtilis* (NCTC 10400)	*Sarcina Sp.* (NCTC 1117)	*Escherichia coli* (NCTC 10416)	*Serratia marcescens* (IMRU 70)
7a	++	++	+	+++	+
7b	+	++	++	+	++
7c	++	+	+	+	++
7d	+	++	++	+	+
9	++	++	+	++	+
11	++	+	+	+	+
13	+++	+	++	++	+
15	++	+++	+	++	+
18	+	+	++	+	+
19	+	++	+	+	+
Standard	++++	++++	++++	++++	++++

+ = Less active (2–5 mm).
++ = Moderately active (6–14 mm).
+++ = Highly activity (15–20 mm).

Escherichia coli (NCTC 10416), and *Serratia marcescens* (IMRU 70). Dimethylformamide showed no inhibition zone. The agar media were incubated with different microorganism cultures; after 24 h of incubation at 30°C for bacteria, the diameter of inhibition zone (mm) was measured. Ampicillin in a concentration 25 μg mL^{-1} was used as reference for antibacterial activity. The minimal inhibitory concentration (MIC) of some of the tested compounds was measured by a twofold serial method.[26] Most of the synthesized compounds exhibited antibacterial activity towards all the microorganisms used (Table II).

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded (KBr) on a Perkin Elmer 1650 spectrophotometer. ^{1}H NMR spectra were recorded on Varian Gemini spectrometer 200 (200 MHz) using DMSO-d_6 as a solvent and TMS as internal standard. Chemical shifts are expressed as δ ppm units. Microanalytical data were obtained from the Microanalytical Data unit at Cairo University. Physical data for the synthesized compounds are given in Table III. The spectral data are collected in Table IV.

TABLE III Physical Data for the Synthesized Compounds

Compd. No.	Mp (°C)	Yield (%) (Color)	Solvent Cryst.	Mol. Formula (M.wt)	Required (found) C	H	N
2	208–210	81 (colorless)	EtOH	$C_{10}H_{12}N_2O_5S$ (272)	44.12 (44.40)	4.41 (4.60)	10.29 (10.40)
3	258–260	84 (colorless)	EtOH	$C_{11}H_{14}N_6O_3S_2$ (342)	38.60 (38.30)	4.09 (4.30)	24.56 (24.80)
5	229–230	73 (colorless)	Dioxane	$C_{18}H_{17}N_7O_4S$ (427)	50.59 (50.80)	3.98 (3.70)	22.95 (23.30)
7	298–300	78 (colorless)	Dioxane	$C_{18}H_{17}N_7O_3S_2$ (443)	48.76 (48.60)	3.84 (3.60)	22.12 (22.40)
9a	157–159	79 (Yellow)	EtOH	$C_9H_9N_5O_2S_2$ (283)	38.16 (38.00)	3.18 (3.10)	24.74 (24.60)
9b	160–162	74 (Yellow)	EtOH	$C_{13}H_{12}N_6O_3S_2$ (364)	42.85 (42.70)	3.30 (3.20)	23.08 (22.90)
9c	180–182	70 (Orange)	EtOH	$C_{14}H_{14}N_6O_3S_2$ (378)	44.44 (44.30)	3.70 (3.75)	22.21 (22.10)
9d	272–274	87 (Yellow)	EtOH	$C_{13}H_{11}N_7O_2S_2$ (361)	43.21 (43.30)	3.07 (2.95)	27.15 (27.00)
12	170–172	68 (Yellow)	Dioxane	$C_{16}H_{13}N_7O_2S_2$ (399)	48.11 (48.00)	3.26 (3.20)	24.55 (24.50)
13	130 dec.	75 (Yellow)	Dioxane	$C_{15}H_{11}N_7O_3S_2$ (401)	44.88 (44.80)	2.74 (2.80)	24.44 (24.30)
15	165–167	77 (Yellow)	Dioxane	$C_{15}H_{12}N_8O_2S_2$ (400)	45.00 (44.90)	3.00 (2.90)	28.00 (28.00)
17	240–242	84 (Orange)	Benzene	$C_{18}H_{14}N_8O_2S_3$ (470)	45.96 (45.80)	2.98 (2.90)	23.83 (23.70)
18	220–222	76 (Orange)	Dioxane	$C_{24}H_{18}N_8O_2S_3$ (546)	52.75 (52.40)	3.30 (3.50)	20.51 (20.30)
19	>300	64 (Orange)	Dioxane	$C_{22}H_{16}N_{10}O_2S_3$ (548)	48.18 (48.10)	2.92 (2.80)	25.55 (25.40)

N-(4-Sulfamoyl-phenyl)-succinamic acid (2)

A mixture of sulfanilamide **1** (0.01 mol; 1.72 g) and succinic anhydride (0.01 mol; 1.00 g) in ethanol (30 mL) containing 3 drops of triethylamine was refluxed for 3 h. The solid obtained was recrystallized from ethanol to give **2**.

3-(4-Amino-5-mercapto-4H-[1,2,4]triazol-3-yl)-N-(4-sulfamoyl-phenyl)-propion-amide (3)

A mixture of **2** (0.01 mol; 2.72 g) and thiocarbohydrazide (0.01 mol; 1.09 g) was fused at 220°C in an oil bath for 15 min. After cooling, the reaction mixture was triturated with ethanol (30 mL) to give **3**.

TABLE IV Spectroscopic Data for the Synthesized Compounds

Compd. No.	IR (KBr, cm^{-1})	^{1}HNMR (ppm, δ) (DMSO-d_6)
2	3330–2750(br-COOH), 3320, 3280 (NH,NH_2), 2940 (CH-aliph), 1750, 1690 (2C=O)	2.7(m, 4H, 2× CH_2), 7.2(s, 2H, NH_2), 7.4–7.9(m, 4H, Ar-H), 10.2(s, 1H, NH), 12.1(br, 1H, COOH)
3	3390, 3260, 3220 (NH, NH_2), 2940 (CH-aliph.), 1700 (C=O), 1620 (C=N)	2.8 (m, 4H, 2 CH_2), 7.3–7.6 (m, 4H, Ar-H), 7.8 (br, 4H, 2 NH_2), 8.3 (s, 2H, 2 NH)
5	3300, 3260 (NH, NH_2), 1708, 1658 (2C=O), 1594 (C=N)	
7	3344, 3300, 3280 (NH, NH_2), 1664 (C=O), 1594 (C=N)	2.7 (m, 4H, 2CH_2), 7.2–7.9 (m, 11H, Ar-H+ NH_2), 10.3 (s, 2H, 2NH)
9a	3362, 3292, 3218 (NH/NH_2), 2220 (C ≡ N), 1598 (N=N), 1330, 1154 (SO_2)	7.31 (s, 2H, SO_2NH_2), 7.81 (m, 4H, Ar-H), 9.43 (s, 1H, NH), 9.85 (s, 1H, SH), 11.7 (s, 1H, hydrazone-H)
9b	3420, 3330, 3160 (NH/NH_2), 2212 (C ≡ N), 1614 (C=N), 1596 (N=N), 1338, 1160 (SO_2)	2.30 (s, 3H, CH_3), 3.90 (br, 2H, NH_2), 6.14 (s, 1H, isooxazole-H), 7.61–7.92 (m, 5H, Ar-H and SO_2NH), 11.46 (s, 1H, hydrazone-H)
9c	3400, 3310, 3200 (NH/NH_2), 2214 (C ≡ N), 1624 (C=N), 1590 (N=N), 1396, 1148 (SO_2)	1.78, 1.95 (2s, 6H, 2CH_3), 7.56–7.87 (m, Ar-H and SO_2NH), 9.5 (s, 1H, NH), 9.80 (s, 1H, SH), 11.80 (s, 1H, hydrazone-H)
9d	3360, 3232, 3190 (NH/NH_2), 2212 (C ≡ N), 1616 (C=N), 1598 (N=N), 1330, 1164 (SO_2)	7.03 (t, 1H, pyrimidine-H), 7.83–7.96 (m, 5H, Ar-H and SO_2NH), 8.50 (d, 2H, pyrimidine-H), 9.48 (s, 1H, NH), 9.86 (s, 1H, SH), 11.80 (s, 1H, hydrazone-H)
12	3326, 3103 (2 NH), 2977 (CH-aliph), 2221 (C ≡ N), 1627 (C=N), 1594 (N=N), 1344, 1140 (SO_2)	2.10 (s, 3H, CH_3), 5.04 (s, 1H, thiazole-H), 7.47–8.04 (m, 8H, Ar-H and SO_2NH), 11.98 (s, 1H, hydrazone-H)
13	3224, 3108 (2 NH), 2224 (C ≡ N), 1737 (C=O), 1580 (N=N), 1339, 1157 (SO_2)	4.80 (s, 2H, CH_2), 7.03 (t, 1H, pyrimidine-H), 7.58–8.03 (m, 5H, Ar-H and SO_2NH), 8.52 (d, 2H, pyrimidine-H), 12.01 (s, 1H, hydrazone-H)
15	3329, 3229, 3111 (NH/NH_2), 2226 (C ≡ N), 1579 (N=N), 1343, 1158 (SO_2)	4.40 (br, 2H, NH_2), 5.21 (s, 1H, thiazole-H), 7.03 (t, 1H, pyrimidine-H), 7.53–8.00 (m, 5H, Ar-H and SO_2NH), 8.50 (d, 2H, pyrimidine-H), 11.80 (s, 1H, hydrazone-H)

(Continued on next page)

TABLE IV Spectroscopic Data for the Synthesized Compounds *(Continued)*

Compd. No.	IR (KBr, cm^{-1})	^{1}HNMR (ppm, δ) (DMSO-d_6)
17	3390, 3300, 3200 (NH/NH_2), 2210 ($C \equiv N$), 1596 (N=N), 1298, 1148 (SO_2)	7.85–7.97 (m, 8H, Ar-H), 9.50, 9.81 (2s, 4H, $2NH_2$), 11.80 (s, 2H, hydrazone-H)
18	3351, 3104 (2 NH), 2219 ($C \equiv N$), 1593 (N=N), 1358, 1148 (SO_2)	2.19, 2.29 (2s, 6H, $2CH_3$), 4.21 (s,2H, thiazole-H), 7.38–8.10 (m, 8H, Ar-H), 12.10 (s, 2H, hydrazone-H)
19	3352, 3223 (2 NH), 2195 ($C \equiv N$), 1593 (N=N), 1348, 1148 (SO_2)	4.20 (s, 2H, thiazole-H), 6.60 (s, 4H, $2NH_2$), 7.67–7.98 (m, 8H, Ar-H), 12.01 (s, 2H,hydrazone-H)

3-(6-Oxo-7-phenyl-6,7-dihydro-5*H*-[1,2,4]triazolo-[4,3-b][1,2,4] triazol-3-yl)-*N*-(4-sulfamoyl-phenyl)-propionamide (5) and 3-(6-Phenylamino-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazol-3-yl)-*N*-(4-sulfamoyl-phenyl)-propionamide (7)

A solution of **3** (0.01 mol) and phenyl isocyanate and/or phenyl isothiocyanate (0.01 mol) in dry pyridine (30 mL) was refluxed until the evolution of H_2S had ceased (12 h). The reaction mixture was poured into ice cold water (100 mL), and the solid product that formed was filtered off and recrystallized from ethanol to give compounds **5** and **7**, respectively.

2-Cyano-2-[(4-sulfamoylphenyl)-hydrazono]thioacetamide (9a–d) and 2-cyano-2 -[(4-{4-[*N*-(cyanothiocarbamoyl-methylene)-hydrazino]-benzenesulfonyl}-phenyl)-hydrazono] thioacetamide (17)

Sulfanilamide **1** or sulfone **16** (0.01 mole) was dissolved in a mixture of concentrated HCl (5 mL) and water (5 mL) and cooled to 0°C in an ice bath. A cold aqueous solution of sodium nitrite (0.01 mole) was then added. The diazonium salt so obtained was filtered into a cooled mixture of sodium acetate (3 g) and cyanothioacetamide (0.01 mole) in ethanol (50 mL). The resulting solid was washed with water and recrystallized from the proper solvent to give **9** and **17**, respectively.

4-{*N*-[Cyano-(4-methylthiazol-2-yl)-methylene]-hydrazino}-*N*-pyrimidin-2-yl-benzenesulfonamide (12) and Bisthiazole Derivatives (18)

A mixture of compound **9d** or **17** (0.01 mole), chloroacetone (0.01 mole), and sodium acetate (2 g) in ethanol (40 mL) was heated under reflux for 2 h, then allowed to cool and poured into water (50 mL). The solid product was collected and recrystallized from the proper solvent to give **12** and **18**, respectively.

4-{*N*-[Cyano-(4-oxo-4,5-dihydrothiazol-2-yl)-methylene] hydrazine}-*N*-pyrimidin- 2-yl-benzenesulfonamide (13)

A mixture of compound **9d** (0.01 mole), ethyl chloroacetate (0.01 mole), and sodium acetate (3 g) in ethanol (30 mL) was heated under reflux for 1 h. The solid product that was produced upon heating was collected and recrystallized to give **13**.

4-{*N*-[4-Aminothiazol-2-yl)-cyano-methylene]hydrazine}-*N*-pyrimidin-2-yl-benz-enesulfonamide (15) and Bisthiazole Derivative (19)

A mixture of compound **9d** or **17** (0.01 mole), chloroacetonitrile (0.01 mole), and triethylamine (0.5 mL) in ethanol (30 mL) was heated under reflux for 24 h, then allowed to cool and poured into cold water (40 mL). The solid product was collected and recrystallized from the proper solvent to give **15** and **19**.

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