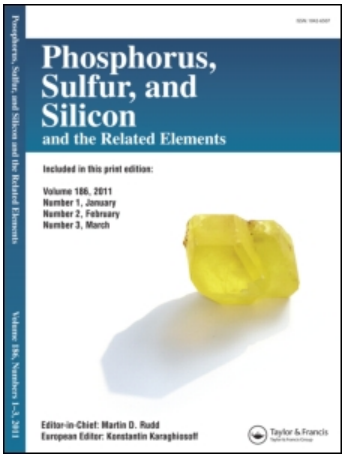

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Dapson in Heterocyclic Chemistry, Part II: Antimicrobial and Antitumor Activities of Some Novel Sulfone Biscompounds Containing Biologically Active Thioureido, Carbamothioate, Quinazoline, Imidazolidine, and Thiazole Moieties

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Dapson in Heterocyclic Chemistry, Part II: Antimicrobial and Antitumor Activities of Some Novel Sulfone Biscompounds Containing Biologically Active Thioureido, Carbamothioate, Quinazoline, Imidazolidine, and Thiazole Moieties

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*The reaction of 4,4′-diisothiocyanato-1,1-diphenylsulfone **2** with aromatic amines and phenol derivatives afforded the corresponding thioureio derivatives **3–9**, respectively. Also, the reaction of **2** with catechol gave the corresponding carbamothioate derivative **11**. Quinazoline derivatives **14** and **15** were obtained in good yield via reaction of **2** with anthranlic acid derivatives. Imidazolidine biscompounds **16** and **17** were readily synthesized from the reaction of **2** with N-(4-substituted-phenyl)cyanothioformanilides. The structure of the products was confirmed from elemental analysis as well as spectral data. Most of the synthesized compounds showed remarkable antimicrobial activity compared with chloramphenicol and Grisofluvine as positive controls. Compound **6** was almost as active an antitumor agent as the reference drug Doxorubicin.*

Keywords Antimicrobial and antitumor agents; biscompounds bearing thioureido, quinazoline, and imidazolidine

INTRODUCTION

A large number of sulfone derivatives have been found to exhibit a wide variety of pharmacological activities.[1–8] In addition the bisheterocyclic compounds quinazoline and imidazolidine derivatives are well known as antifungal[9–11] and antitumor[12–17] agents. In view of these findings,

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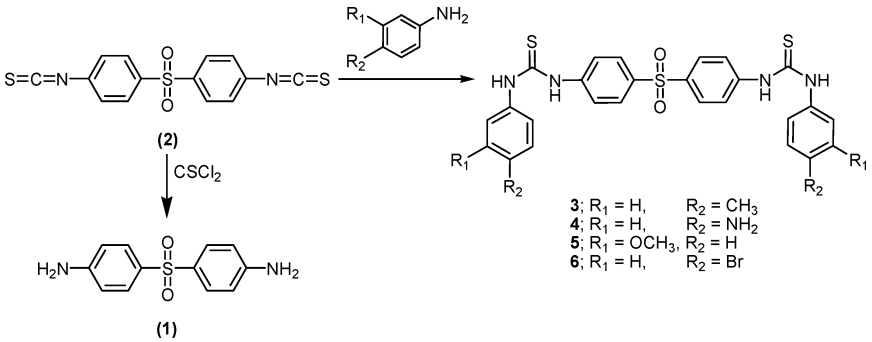
we undertook the synthesis of a new series of bisheterocyclic sulfone compounds incorporating the above-mentioned biologically active moieties in one molecule and evaluated their antimicrobial and antitumor activities.

RESULTS AND DISCUSSION

Several compounds were designed with the aim of exploring their antimicrobial and antitumor properties (Schemes 1–5). Treatment of dapson **1** wtih thiophosgene at room temperature in the presence of dilute HCl furnished the diisothiocyanate **2** in high yield.

Treatment of diisothiocyanate **2** with aromatic amines (1:2 mol) in dioxan afforded the novel thioureido derivatives **3–6**, respectively (Scheme 1).

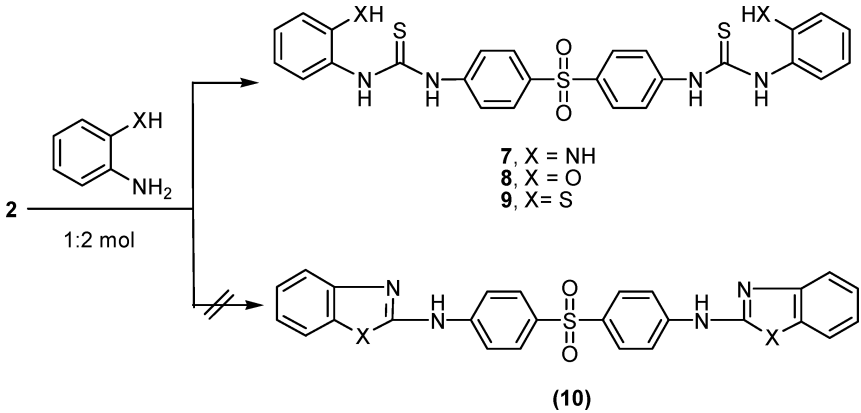


SCHEME 1

The structure of compounds **3–6** was confirmed by analytical and spectral data. IR spectrum of compound **3** revealed bands at 3368 cm^{-1} (NH), 2940 cm^{-1} (CH aliph.), 1314, 1148 cm^{-1} (SO_2), and 1280 cm^{-1} (C=S). ^{1}H-NMR spectrum of (**3** in DMSO-d_6) exhibited signals at 2.23 [s, 6H, $2CH_3$], 7.05–7.5 [m, 16H, Ar-H], 8.4, and 9.2 [2s, 4H, 4NH]. The IR spectrum of compound **4** revealed bands at 3152, 3140 cm^{-1} (NH, NH_2), 1356, 1178 cm^{-1} (SO_2), and 1258 cm^{-1} (C=S). Mass spectrum of compound **4** showed a molecular ion peak m/z at 548 (M^+, 0.84%), with a base peak at 150 (100%), and other significant peaks appeared at 550 (M+2, 0.63%), 551 (M+3, 0.88), 524 (0.8%), 480 (0.2%), 367 (0.10%), 313 (0.14%), 266 (1.05%), 208 (1.13%), 140 (0.48%), 90 (3.78%), and 76 (1.53%). IR spectrum of compound **5** revealed bands at 3460, 3358, 3250 cm^{-1} (NH), 2934 cm^{-1} (CH aliph.), 1314, 1144 cm^{-1} (SO_2), and 1288 cm^{-1} (C=S). ^{1}H-NMR spectrum of (**5** in DMSO-d_6) showed signals at 3.8 [s, 6H, $2OCH_3$], 6.6–8.0 [m, 16H, Ar-H], 8.2, and 8.7 [2s,

4H, 4NH]. Mass spectrum of **5** exhibited a molecular ion peak m/z at 578 (M^+, 29.03%), with a base peak at 52 (100%), and other significant peaks appeared at 562 (41.94%), 506 (32.26%), 438 (29.03%), 375 (29.03%), 269 (61.29%), 199 (41.94%), 134 (61.29%), and 77 (32.26%). The IR spectrum of compound **6** exhibited bands at 3450, 3370 cm^{-1} (NH), 1310, 1146 cm^{-1} (SO_2), and 1290 cm^{-1} (C=S). Mass spectrum of **6** revealed a molecular ion peak m/z at 676 (M^+, 7.05%), with a base peak at 458 (100%), and other significant peaks appeared at 677 (M+1, 20.63%), 678 (M+2, 11.51%), 675 (M-1, 8.17%), 640 (19.12%), 591 (7.96%), 533 (37.98%), 510 (17.71%), 486 (27.03%), 433 (78.39%), 416 (50.69%), 381 (87.72%), 297 (28.20%), 193 (40.17%), 145 (37.66%), and 77 (5.01%).

Our investigation was extended to include the reactivity of di- isothiocyanate **2** toward binucleophiles such as 1,2-phenylenediamine, 2-aminophenol, and/or 2-aminothiophenol. Thus, diisothiocyanate **2** was reacted with 1,2-phenylenediamine or 2-aminophenol and/or 2-aminothiophenol (1:2 mol) in dimethylformamide catalyzed with triethylamine to produce biscompounds **7–9**, respectively (Scheme 2).

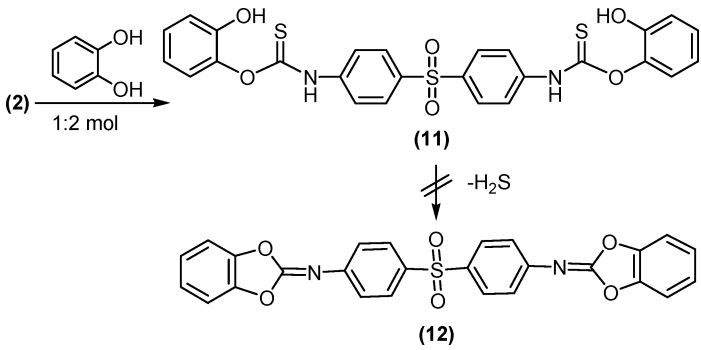


SCHEME 2

Compound **10** was discarded on the basis of analytical and spectral data. The IR spectrum of compound **7** showed bands at 3402 and 3250 cm^{-1} (NH, NH_2). Mass spectrum of compound **7** showed a molecular ion peak m/z at 548 (M^+, 4.70%), with a base peak at 236 (100%), and other significant peaks appeared at 550 (M+2, 17.38%), 552 (M+4, 35.51%), 423 (15.22%), 383 (21.01%), 313 (78.81%), 248 (28.71%), 191 (31.52%), 140 (44.57%), 108 (88.84%), and 78 (48.74%). IR spectrum of **8** revealed bands at 3380 cm^{-1} (OH), 3238, 3200 cm^{-1} (NH), 1340, 1148 cm^{-1} (SO_2), and 1274 cm^{-1} (C=S). Mass spectrum of compound

8 showed a molecular ion peak m/z at 550 (M^+, 1.80%), with a base peak at 147 (100%), and other significant peaks appeared at 552 (M+2, 3.87%), 509 (1.82%), 385 (1.66%), 313 (18.95%), 193 (9.55%), 95 (8.72%), and 72 (7.88%). IR spectrum of compound **9** revealed bands at 3324, 3200 cm^{-1} (NH), 1320, 1144 cm^{-1} (SO_2), and 1288 cm^{-1} (C=S). Mass spectrum of compound **9** showed a molecular ion peak m/z at 582 (M^+, 0.8%), with a base peak at m/z 167 (100%), and other significant peaks appeared at 580 (M-2, 0.20%), 552 (0.31%), 523 (0.93%), 424 (0.35%), 368 (1.45%), 288 (0.72%), 257 (28.98%), 108 (8.57%), and 76 (3.48%).

We also investigated the reactivity of diisothiocyanate **2** toward aromatic hydroxy compounds. Thus, catechol as binucleophile was reacted with diisothiocyanate **2** in dioxan/triethylamine to produce 4,4′-bis(3-(2-hydroxyphenyl)-2-carbamothioate)-1,1-diphenylsulfone **11** (Scheme 3).

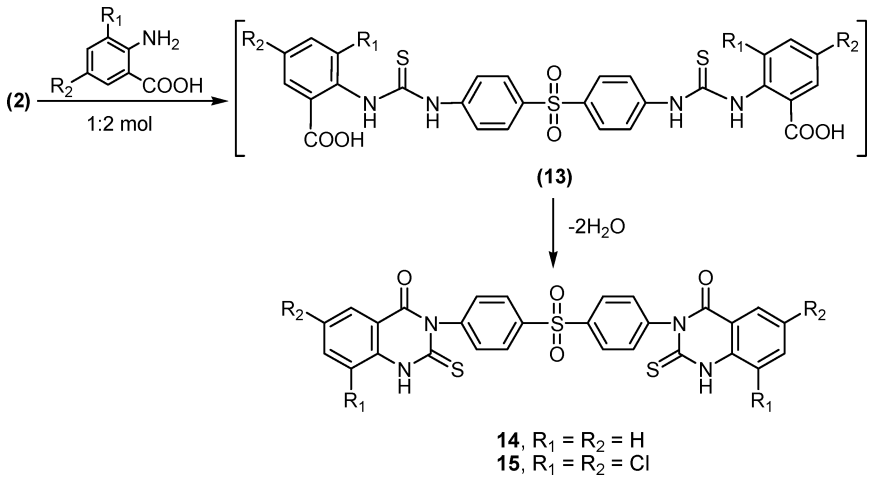


SCHEME 3

Structure **12** was eliminated on the basis of analytical and spectral data. The IR spectrum of compound **11** exhibited bands at 3568 cm^{-1} (OH), 3448 cm^{-1} (NH), 1380, and 1150 cm^{-1} (SO_2). Mass spectrum of compound **11** revealed a molecular ion peak m/z at 551 (M-1, 27.54%), with a base peak at 313 (100%), and other significant peaks appeared at 550 (M-2, 12.00%), 549 (M-3, 18.48%), 548 (M-4, 8.85%), 537 (25.83%), 388 (80.17%), 285 (45.17%), 236 (83.23%), 114 (48.38%), and 55 (42.35%).

Cyclocondensation of 1 mol of diisothiocyanate **2** with 2 mol of anthranilic acid derivatives in dioxane/TEA furnished the novel bisquinazolinone derivatives **14** and **15**, respectively. Analytical and spectral data were compatible with the structure of quinazoline derivatives **14** and **15** (Scheme 4).

The IR spectrum of compound **14** revealed bands at 3372 cm^{-1} (NH), 1676 cm^{-1} (C=O), 1606 cm^{-1} (C=N), 1382, 1124 cm^{-1} (SO_2),

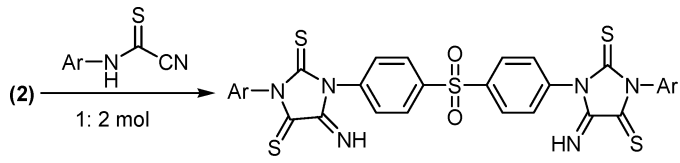


SCHEME 4

and 1262 cm^{-1} (C=S). Mass spectrum of compound **14** showed a molecular ion peak m/z at 570 (M^+, 1.81%), with a base peak at 408 (100%), and other significant peaks appeared at 435 (4.25%), 377 (31.05%), 252 (28.42%), 234 (10.01%), 118 (84.40%), 108 (9.23%), and 78 (8.25%). The IR spectrum of compound **15** revealed bands at 3366 cm^{-1} (NH), 3084 cm^{-1} (CH arom.), 1702 cm^{-1} (C=O), 1610 cm^{-1} (C=N), 1374, 1148 cm^{-1} (SO_2), and 1292 cm^{-1} (C=S). Mass spectrum of compound **15** exhibited a molecular ion peak m/z at 708 (M^+, 0.11%), with a base peak at 88 (100%), and other significant peaks appeared at 710 (M+2, 0.28%), 677 (0.28%), 651 (0.28%), 551 (5.38%), 439 (2.51%), 256 (11.82%), 187 (41.28%), 149 (11.40%), 111 (9.18%), and 73 (17.81).

This investigation was extended to cover the behavior of diisothiocyanate **2** towards cyanothioformanilides. Thus, compound **2** reacted with N-phenylcyanothioformanilides (1:2 mol) where 2 mol were consumed and yielded 4,4′-bis(5-imino-1-(4-tolyl)-2,4-dithioxo-imidazolidine-3-yl)-1,1-diphenyl sulfone **16** and 4,4′-bis(5-imino-1-(4-methoxyphenyl)-2,4-dithioxo-imidazolidine-3-yl)-1,1-diphenylsulfone **17**, respectively (Scheme 5).

The structure of **16** and **17** was confirmed by analytical and spectral data. The IR spectrum of compound **16** showed bands at 3448 cm^{-1} (NH), 2924 cm^{-1} (CH aliph.), 1592 cm^{-1} (C=N), 1384, 1156 cm^{-1} (SO_2), and 1304 cm^{-1} (C=S). ^{1}H-NMR spectrum of compound (**16** in DMSO-d_6) exhibited signals at 2.3 [s, 6H, $2CH_3$], 6.6–8.0 [m, 16H, Ar-H], 8.3, and 8.4 [2s, 4H, 4NH]. Mass spectrum of compound **16** showed a molecular ion peak m/z at 683 (M-1, 0.55%), with a base peak at 91 (100%),

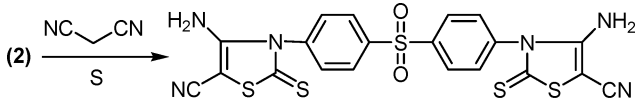


16, Ar = C_6H_4-CH_3-4
17, Ar= C_6H_4-OCH_3-4

SCHEME 5

and other significant peaks appeared at 551 (0.55%), 523 (0.84%), 370 (2.14%), 313 (3.18%), 224 (4.28%), 196 (1.08%), 128 (2.46%), and 76 (54.10%). The IR spectrum of compound **17** revealed bands at 3398 cm^{-1} (NH), 2924 cm^{-1} (CH aliph.), 1386, 1154 cm^{-1} (SO_2), and 1252 cm^{-1} (C=S). ^{1}H-NMR spectrum of (**17** in DMSO-d_6) showed signals at 3.8 [s, 6H, 2OCH_3], 7.1–8.2 [m, 16H, Ar-H], 9.9 [s, 2H, 2NH]. Mass spectrum of compound **17** showed a molecular ion peak m/z at 716 (M^+, 4.00%), with a base peak at 165 (100%), and other significant peaks appeared at 486 (4.27%), 461 (5.87%), 326 (8.80%), 241 (16.80%), 215 (3.47%), 144 (21.80%), 104 (12.27%), and 77 (18.40%).

Finally, the thiazole derivative **18** was prepared by reaction of diisothiocyanate **2** with malononitrile and sulfur in the presence of triethylamine (Scheme 6).



(18)

SCHEME 6

IR spectrum of compound **18** showed bands at 3320, 3200 cm^{-1} (NH_2), 2198 cm^{-1} (C≡N), 1390, 1148 cm^{-1} (SO_2), and 1280 cm^{-1} (C=S). Mass spectrum of compound **18** showed a molecular ion peak m/z at 527 (M-1, 8.35%), with a base peak at 86 (100%), and other significant peaks appeared at 415 (2.73%), 354 (5.49%), 295 (10.35%), 281 (37.31%), 257 (9.07%), 207 (4.75%), 192 (40.82%), 134 (9.0%), 101 (41.97%), and 77 (43.14%).

Antimicrobial Activity

Some of the newly synthesized compounds were screened for their antimicrobial activity using the diffusion agar technique.[18] The tested compounds were dissolved in *N*, *N*-dimethylformamide (DMF), which

TABLE I Antibacterial Activity of Some Synthesized Compounds

	Salmonella			*Staphylococcus*			*Bacillus*					
	E. coli			*typhi*			*aureus*			*subtillus*		
Compound No.	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
2	++	++	++	+	+	+	+	++	++	+	++	++
3	+	++	++	++	++	+	0	0	++	0	+	+
5	+	++	++	0	+	+	+	+	+	++	++	++
6	+	++	++	+	+	++	+	+	++	+	++	++
16	+	+	+	+	++	++	+	+	+	+	+	+
DMF	0	0	0	0	0	0	0	0	0	0	0	0
Chloramphenicol	++	+++	+++	+++	+++	+++	++	++	+++	++	+++	+++

Well diameter 1 cm (100 mL of each conc. was tested.
Inhibition values = 0.1–0.5 cm beyond control = +
Inhibition values = 0.6–0.1 cm beyond control = ++
Inhibition values = 1.1–1.5 cm beyond control = +++
Inhibition values =>1 cm beyond control = ++++, 0 = not detected.

showed no inhibition zones. Tables I and II lists the screening results of the tested compounds against the Gram-negative bacteria *Escherichia coli* and *Salmonella typhi*, Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtillus*, and pathogenic fungi *Aspergillus niger* and *Aspergillus flavus*. The reference antibiotic chloramphenicol and fungicide Grisofluvine were used as positive controls for comparison. The fungi cultures were maintained on Czapek's Dox agar media.

Most of the synthesized compounds showed remarkable activity toward the tested microorganisms but were less active than the standard chloramphenicol and Grisofluvine.

TABLE II Antifungal Activity of Some Synthesized Compounds

	Aspergillus niger			*Aspergillus vlavu*		
Compound No.	1	2.5	5	1	2.5	5
2	+	++	++	+	+	+
3	0	+	++	0	+	+
5	0	+	+	+	+	+
6	+	++	++	0	++	++
16	0	+	++	+	+	++
DMF	0	0	0	0	0	0
Grisofluvine	+++	+++	+++	+++	+++	+++

Well diameter 1 cm (100 mL of each conc. was tested
Inhibition values = 0.1–0.5 cm beyond control = +
Inhibition values = 0.6–0.1 cm beyond control = ++
Inhibition values = 1.1–1.5 cm beyond control = +++
Inhibition values =>1 cm beyond control = ++++, 0 = not detected.

Antitumor Activity

Reagents

1. RPMI 1640 medium (sigma).
2. Ehrlich Ascites Carcinoma cells (EAC) suspension (2.5×10^5 mL).
3. Trypan blue dye: A stock solution was prepared by dissolving 1 g of the dye in distilled water (100 mL). The working solution was then prepared by diluting 1 mL of the stock solution with 9 mL of distilled water. The stain was used then for staining the dead EAC cells.
4. The compounds tested were **(2–15)**.

Procedure

1. EAC cells were obtained by needle aspiration of the ascetic fluid from preinoculated mice under aseptic conditions.[19]
2. The cells were tested for viability and contamination by staining a certain cell volume of this fluid by an equal volume of the working solution of trypan blue dye.[20,21]
3. The ascetic fluid was diluted with saline (1:10) to contain 2.5×10^6 mL cells on a hemocytometer.

In a set of sterile test tubes 0.1 mL of tumor cells suspension, 0.8 mL RPMI 1640 media and 0.1 mL of each tested compound (corresponding to 100, 50 and 25 μg/mL) were mixed. The test tubes were incubated at 37°C for 2 hr. A trypan blue exclusion test[20,21] was carried out to calculate the presence of nonviable cells. Compounds producing more than 70% non viable cells are considered active.[21]

$$\%\,\text{of non-viable cells} = \frac{\text{No. of non viable}}{\text{Total No. of cells}} \times 100$$

The relationship between the surviving fraction and drug concentration was plotted to obtain the survival curve of EAC cell. The response parameter calculated was the IC_{50} value, which corresponds to the compound concentration causing 50% mortality in net cells (Table III).

From these results, it was found that the biscompound bearing bromophenylthioureido diphenylsulfone **6** exhibited higher activity than the positive control Doxorubicin against EAC cell; the nonviable cell about 100%, 95%, 85% at a concentration (100, 50, and 25 μg /mL); and IC_{50} of 0.5 μg/mL.

TABLE III In Vitro Antitumor Activity of Some Newly Synthesized Compounds

	Non-viable cells (%)			
	Concentration (μg/mL)			
Compound No.	100	50	25	IC_{50}
2	0	0	0	>100[a]
3	0	0	0	<100[a]
4	10	0	0	<100[a]
5	20	10	0	<100[a]
6	100	95	85	0.5
8	0	0	0	>100
15	100	0	0	>100
Doxorubicin	100	55	20	52

[a]IC_{50} >100 μg/mL is considered to be inactive.

EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded (KBr) on a Perkin Elmer 1650 spectrophotometer. ^{1}H-NMR spectra were recorded on a varian Gemini spectrometer 300 (300 MHz) using DMSO-d_6 as a solvent, and TMS as internal standard chemical shifts were expressed as δ ppm units. Mass spectra were recorded on a gas chromatography GC-MS qp 100 Ex (schimadzu instrument) at 70 ev. Microanalytical data were obtained from the Microanalytical Data Unit at the Cairo University.

4,4′-Bis(3-(4-tolyl)-2-thioureido)-1,1′-diphenylsulfone (3), 4,4′-Bis(3-(4-aminophenyl)-2-thioureido)-1,1′-diphenylsulfone (4), 4,4′-Bis(3-(3-anisyl)-2-thioureido)-1,1′-diphenylsulfone (5), and 4,4′-Bis(3-(4-bromo-phenyl)-2-thioureido)-1,1′-diphenylsulfone (6)

A mixture of **2** (0.01 mol) and aromatic amines (0.02 mol) in dioxan (30 mL) containing triethylamine (0.5 mL) was refluxed until the clear solution was obtained (6 hr). The solid residue was collected by filtration, washed with cold water, and recrystallized from ethanol to give (**3–6**), (Table 4).

TABLE IV Physical and Analytical Data of the Synthesized Compounds

Compound No.	m.p (°C)	Yield %	Mol. Formula (Mol. Wt)	Analyses % Required/Found			
				C	H	N	S
2	145	88	$C_{14}H_8N_2O_2S_3$ (332)	50.60	2.40	8.43	28.91
				50.40	2.60	8.60	29.20
3	170–172	79	$C_{28}H_{26}N_4O_2S_3$ (546)	61.53	4.76	10.25	17.58
				61.70	4.90	10.50	17.90
4	>300	81	$C_{26}H_{24}N_6O_2S_3$ (548)	56.93	4.37	15.32	17.51
				57.20	4.20	15.60	17.20
5	60–62	77	$C_{28}H_{26}N_4O_4S_3$ (578)	58.13	4.49	9.68	16.60
				58.40	4.20	9.50	16.90
6	158–159	69	$C_{26}H_{20}Br_2N_4O_2S_3$ (676)	46.15	2.95	8.28	14.20
				46.50	3.30	8.60	14.50
7	>300	72	$C_{26}H_{24}N_6O_2S_3$ (548)	56.93	4.37	15.32	17.51
				57.20	4.60	15.20	17.80
8	135–137	80	$C_{26}H_{22}N_4O_4S_3$ (550)	56.73	4.00	10.18	17.45
				56.50	4.30	10.10	17.30
9	93–95	82	$C_{26}H_{22}N_4O_2S_5$ (582)	60.70	3.50	10.90	18.68
				60.90	3.20	11.20	18.50
11	260–262	85	$C_{26}H_{20}N_2O_6S_3$ (552)	56.52	3.62	5.07	17.39
				56.20	3.90	5.30	17.70
14	>300	75	$C_{28}H_{18}N_4O_4S_3$ (570)	58.94	3.15	9.82	16.84
				59.30	3.40	9.70	16.50
15	>300	78	$C_{28}H_{14}Cl_4N_4O_4S_3$ (708)	47.46	1.98	7.91	13.56
				47.30	1.80	8.20	13.70
16	105–107	84	$C_{32}H_{24}N_6O_2S_5$ (684)	56.14	3.50	12.28	23.39
				56.40	3.40	12.50	23.60
17	125–127	82	$C_{32}H_{24}N_6O_4S_5$ (716)	53.63	3.35	11.73	22.34
				53.30	3.20	11.40	22.60
18	>300	78	$C_{20}H_{12}N_6O_2S_5$ (528)	45.45	2.27	15.90	30.30
				45.10	2.10	16.20	30.50

4,4′-Bis(3-(2-aminophenyl)-2-thioureido)-1,1′-diphenylsulfone (7), 4,4′-Bis(3-(2-hydroxyphenyl)-2-thioureido)-1,1′-diphenylsulfone (8), and 4,4′-Bis(3-(2-mercaptophenyl)-2-thioureido)-1,1′-diphenylsulfone (9)

A mixture of **2** (0.01 mol) and 1,2-phenylenediamine, 2-amino-phenol, and/or 2-aminothiophenol (0.02 mol) in dimethylformamide (10 mL) containing, triethylamine (0.5 mL) was refluxed for 8 hr. The reaction mixture was poured into cold water, and the solid product was collected by filtration and recrystallized from dioxan to give (**7**–**9**) (Table IV).

4,4′-Bis(3-(2-hydroxyphenyl)-2-carbamothioate)-1,1′-diphenylsulfone (11)

To a mixture of **2** (0.01 mol), catechol (0.02 mol) in dioxan (30 mL) containing a few drops of triethylamine. The reaction mixture was refluxed for 24 h. After cooling the obtained solid was recrystallized from ethanol, to give (**11**) (Table IV).

4,4′-Bis(2,3-dihydro-2-thioxo-4-oxo-1H-quinazolin-3-yl)-1,1′-diphe-nylsulfone (14) and 4,4′-Bis(6,8-dichloro-2,3-dihydro-2-thioxo-4-oxo-1H-quinazolin-3-yl)-1,1′-diphenylsulfone (15)

To a stirred suspension of **2** (0.01 mol), anthranilic acid derivatives (0.02 mol) in dioxan (20 mL) containing triethylamine (0.5 mL) was added. The reaction mixture was heated under reflux for 30 min, filtered while hot, and then cooled. The solid obtained was collected by filtration and recrystallized from dioxan to give (**14**) and (**15**) (Table IV).

4,4′-Bis(5-imino-1-(4-tolyl)-2,4-dithioxo-imidazolidine-3-yl)-1,1′-diphenylsulfone (16) and 4,4′-Bis(5-imino-1-(4-methoxyphenyl)-2,4-dithioxo-imidazolidine-3-yl)-1,1′-diphenylsulfone (17)

A solution of **2** (0.01 mol) and N-(4-substituted phenyl) cyanothioformanilide (0.02 mol) in tetrahydrofuram (20 mL) containing (0.5 mL) triethylamine was refluxed for 3 hr. The solid that formed when heated was collected and washed with dioxan to give **16**, **17** (Table IV).

4,4′-Bis(4-amino-5-cyano-2-thioxo-3H-thiazol-3-yl)-1,1′-diphenyl-sulfone (18)

To a stirred solution of malononitrile (0.01 mole), finely divided sulfur (0.01 mol), and triethylamine (0.5 mL) in absolute ethanol (30 mL), the diisothiocyanate **2** (0.01 mole) was added. The reaction mixture was heated under reflux for 1 hr. The obtained product was filtered, washed with ethanol, dried, and recrystallized from dioxan to give (**18**) (Table IV).

REFERENCES

[1] P. Lluis, H. C. Carlos, G. David, M. B. Lisa, L. S. Joseph, and P. Z. Juan, *American J. Enolog. Viticulture*, **53**(2), 110–115 (2002).

[2] M. Ziqiang, G. Hong, B. Juli, and Y. Guanghai, *Inhalation Toxicology*, **15**(9), 951–959 (2003).
[3] K. Grela and M. Bieniek, *Tetrahedron Lett.*, **42**(36), 6425–6428 (2001).
[4] X. Huang and De. H. Duan, *Chem. Commun.*, **17,** 1741–1742 (1999).
[5] A. Nangia, G. R. Desiraju, *Journal of Molecular Structure*, **474**(1–3), 65–79 (1999).
[6] N. S. Simpkins, *Tetrahedron*, **47**(2), 323–332 (1991).
[7] T. E. Gund, L. Tamas, and S. Salyi, *Tetrahedron Lett.*, **39**(19), 3061–3064 (1998).
[8] G. C. Batzias, E. Theodosiadou, and G. A. Delis, *Journal of Pharmaceutical and Biomedical Analysis*, **35**(5), 1191–1202 (2004).
[9] M. M. Ghorab, A. M. Sh. El-Sharief, Y. A. Ammar, and Sh. I. Mohamed, *Il Farmaco*, **55,** 354–361 (2000).
[10] M. M. Ghorab, H. I. Heiba, and N. E. Amin, *Pharmazie*, **54,** 226–227 (1999).
[11] M. M. Ghorab and A. I. El-Batal, *Boll. Chim. Farmac.*, **141,** 110–117 (2002).
[12] M. M. Ghorab, *Egypt. J. Rad. Sci. Applic.*, **8**(2), 179–190 (1995).
[13] M. M. Ghorab, S. G. Abdel-Hamide, and A. E. El-Hakim, *Indian J. Heterocyclic Chem.*, **5,** 115–120 (1995).
[14] M. M. Ghorab and S. G. Abdel-Hamide, *Phosphorus, Sulfur, and Silicon*, **106,** 9–20 (1995).
[15] H. I. Heiba, M. M. Ghorab, and M. A. El-Gawish, *Phosphorus, Sulfur, and Silicon*, **131,** 197–205 (1997).
[16] M. M. Ghorab, O. M. Nassar, H. I. Heiba, and N. E. Amin, *Acta Pharm.*, **48**, 101–110 (1998).
[17] A. M. Sh. El-Sharief, M. M. Ghorab, M. S. A. El-Gaby, Sh. I. Mohamed, and Y. A. Ammar, *Heteroatom. Chem.*, **13,** 316–323 (2002).
[18] L. P. Carrod and F. D. Grady, *Antibiotic and Chemotherapy*, 3rd Ed., Churchill Livingestone, Edinburgh, UK, p. 477 (1972).
[19] M. M. El-Merzabani, A. A. ElAaser, and M. A. Attia, *J. Planta Medica*, **36,** 150 (1972).
[20] H. Lazarus, M. Targela, H. Mazzone, J. Lepoy, B. Boone, and G. Foley, *Cancer Chemotherapy*, **50,** 543 (1966).
[21] D. J. Takamoto, C. Dunfoed, and M. M. McMuiray, *Toxicon.*, **20,** 293 (1982).