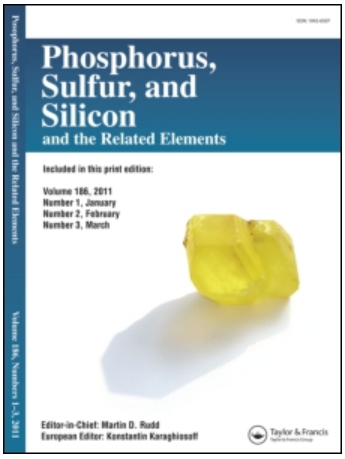

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Dapson in Heterocyclic Chemistry, Part I: Novel Synthesis of Sulfone Biscompounds for Antimicrobial and Antitumor Activities

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Dapson in Heterocyclic Chemistry, Part I: Novel Synthesis of Sulfone Biscompounds for Antimicrobial and Antitumor Activities

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*This article describes the synthesis of some novel sulfone bis- compounds bearing the biologically active thioether **3–6**; thioureido **7**, **8**, **15**, **16**; triazole **10**, **11**; thiosemicarbazido **9**, **12**, **13**; and 1,3,4-thiadiazole **14**, 17 moieties starting with 4,4′-diisothiocyanato-1,1-diphenylsulfone **2**. The structures of newly synthesized compounds were confirmed by elemental analysis, IR, ^{1}H-NMR and mass spectral data. Compound **3** was found to be the most active compound against* Escherichia coli. *Also, compound **15** acted as potent cytotoxic agent.*

Keywords Antimicrobial and antitumor agents; sulfone derivatives

INTRODUCTION

Bisheterocyclic compounds are currently an important group of organic compounds that are used as bactericides,[1] fungicides,[2,3] antitumor agents,[4] and for their radioprotective effects.[5] In addition, sulfone derivatives are known to possess interesting biological properties that show antitumor[6] and antimicrobial[7] activities. In addition, several types of compounds containing thioether, thioreado, triazole, thiosemicarbazido, and 1,3,4-thiadiazole have been shown to possess antitumor and antimicrobial[8–10] properties. The interesting antitumor and antimicrobial properties of sulfone derivatives prompted us to

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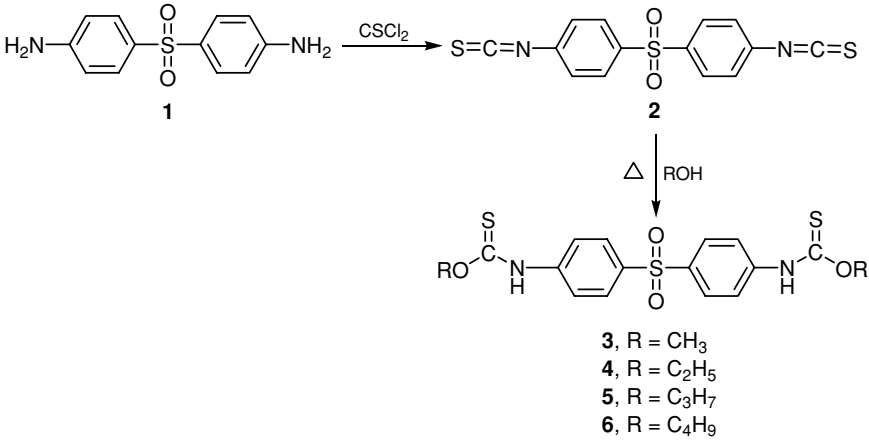
investigate in some detail this relatively unexplored class of potential antitumor and antimicrobial agents. Here we report the synthesis of some biscompounds bearing sulfone groups with the above-mentioned biologically active moieties to evaluate their antitumor and antimicrobial activities.

RESULTS AND DISCUSSION

Treatment of dapson **1** with thiophosgene at room temperature in the presence of dilute hydrochloric acid[9] furnished the corresponding 4,4′-diisothiocyanato-1,1-diphenylsulfone **2**. The IR spectrum of compound **2** showed the absence of (NH_2) bands and presence of bands at 3090 cm^{-1} (CH arom.), 2102 cm^{-1} (NCS), 1318, and 1146 cm^{-1} (SO_2).

The reactivity of diisothiocyanate **2** toward some oxygen and nitrogen nucleophiles was investigated. The reaction of diisothiocyanate **2** with methanol, ethanol, propanol, and/or butanol yielded the corresponding thiocarbamate derivatives (**3–6**) (Scheme 1). The structure of compounds **3–6** was proved by analytical and spectral data.

The IR spectrum of compound **3** showed the absence of a N=C=S band and showed the presence of bands at 3278 cm^{-1} (NH), 2944 cm^{-1} (CH aliph.), 1360, 1146 cm^{-1} (SO_2), and 1288 cm^{-1} (C=S). ^{1}H-NMR spectrum of (**3** in DMSO-d_6) revealed signals at 3.9 [s, 3H, $2OCH_3$], 7.4–8.0 [m, 8H, Ar—H], and 11.4 [s, 2H, 2NH]. Mass spectrum of compound **3** showed a molecular ion peak m/z 396 (M^+, 27.03%) with a base peak at 57 (100%), and other significant peaks appeared at 378 (40.54%), 243

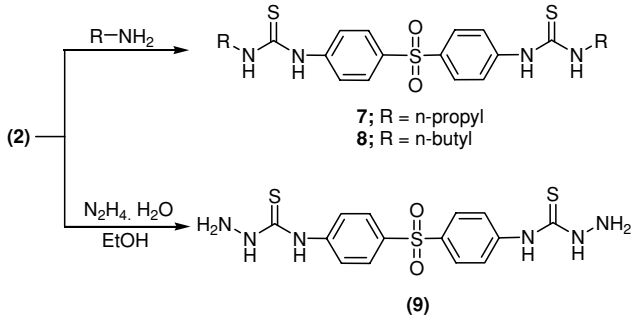


SCHEME 1

(43.24%), 153 (35.14%), 94 (45.95%), and 78 (37.84%). The IR spectrum of compound **4** revealed bands at 3252 cm^{-1} (NH), 3040 cm^{-1} (CH arom.), 2946, 2850 cm^{-1} (CH aliph.), 1320, 1156 cm^{-1} (SO_2), and 1200 cm^{-1} (C=S). ^{1}H-NMR spectrum of (**4** in DMSO-d_6) showed signals at 1.39 [t, 6H, $2CH_3$], 4.6 [q, 4H, $2CH_2$], 7.6–8.0 [m, 8H, Ar-H], and 11.4 [s, 2H, 2NH]. Mass spectrum of compound **4** exhibited a molecular ion peak m/z at 424 (M-CH_3, 9.7%) with a base peak at 57 (100%), and other significant peaks appeared at 350 (92.9%), 317 (66.1%), 290 (60.7%), 182 (74.9%), 150 (59.5%), 108 (73.7%), 90 (46.9%), and 76 (26.1%). IR spectrum of **5** showed bands at 3240 cm^{-1} (NH), 3276 cm^{-1} (CH arom.), 2970, 2840 cm^{-1} (CH aliph.), 1337, 1186 cm^{-1} (SO_2), and 1289 cm^{-1} (C=S). ^{1}H–NMR spectrum of (**5** in DMSO-d_6) revealed signals at 0.9 [t, 6H, $2CH_3$], 1.7 [m, 4H, $2CH_2$], 4.4 [t, 4H, $2CH_2O$], 7.5–8.0 [m, 8H, Ar-H], and 11.5 [s, 2H, 2NH]. IR spectrum of compound **6** exhibited bands at 3278 cm^{-1} (NH), 3100 cm^{-1} (CH arom.), 2958, 2870 cm^{-1} (CH aliph.), 1330, 1146 cm^{-1} (SO_2), and 1288 cm^{-1} (C=S). ^{1}H-NMR spectrum of (**6** in DMSO-d_6) exhibited signals at 0.9 [t, 6H, $2CH_3$], 1.3, 1.7 [m, 8H, $4CH_2$], 4.4 [t, 4H, $2OCH_2$], 7.4–8.0 [m, 8H, Ar-H], and 11.4 [s, 2H, 2NH].

The novel thioureido derivatives **7** and **8** were synthesized when diisothiocyanate **2** was allowed to react with propylamine and/or butylamine as nitrogen nucleophile (Scheme 2).

The IR spectrum of compound **7** revealed bands at 3240 cm^{-1} (NH), 3064 cm^{-1} (CH arom.), 2960, 2930, 2874 cm^{-1} (CH aliph.), 1318, 1154 cm^{-1} (SO_2), and 1220 cm^{-1} (C=S). ^{1}H-NMR spectrum of (**7** in DMSO-d_6) showed signals at 0.9 [t, 10H, $2CH_3$+ $2CH_2N$], 1.5 [m, 4H, $2CH_2$], 7.7, 7.9 [2d, 8H, Ar-H], and 9.9 [s, 2H, 2NH]. Mass spectrum of compound **7** revealed a molecular ion peak m/z at 450 (M^+, 75%), with a base peak at 291 (100%), and other significant peaks appeared at 324 (75%), 268 (68.75%), and 77 (75%). The IR spectrum of compound **8** revealed bands



SCHEME 2

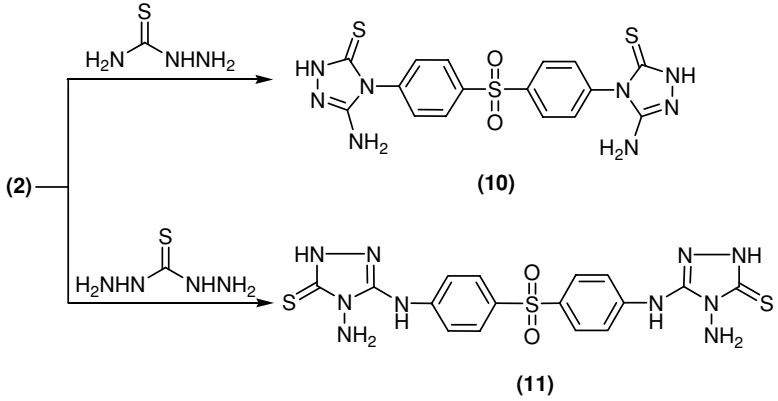
at 3246 cm^{-1} (NH), 3062 cm^{-1} (CH arom.), 2958, 2930, 2872 cm^{-1} (CH aliph.), 1320, 1152 cm^{-1} (SO_2), and 1250 cm^{-1} (C=S). ^{1}H-NMR spectrum of (**8** in DMSO-d_6) exhibited signals at 0.8 [t, 6H, $2CH_3$], 1.3 [q, 4H, $2CH_2NH$, 1.4–1.5 [m, 8H, $4CH_2$], 7.5–7.9 [2d, 8H, AB system], and 9.9 [s, 2H, 2NH]. Mass spectrum of compound **8** showed a molecular ion peak m/z at 478 (M^+, 0.2%), with a base peak at 332 (100%), and other significant peaks appeared at 477 (M-1, 0.5%), 446 (0.86%), 371 (4.19%), 290 (19.16%), 268 (3.24%), 182 (36.48%), 150 (15.64%), 134 (26.27%), 90 (3.67%), and 76 (0.19%).

It is observed from the literature that the thiosemicarbazide moiety plays a vital role in many biological activities, such as antibacterial[11] antitumor[12] activities. Thus treatment of diisothiocyanate **2** with hydrazine hydrate in ethanol at room temperature afforded the corresponding thiosemicarbazide derivative **9** (Scheme 2).

The IR spectrum of **9** revealed bands at 3372, 3278 cm^{-1} (NH, NH_2), 2926 cm^{-1} (CH aliph.), 1382, 1174 cm^{-1} (SO_2), and 1224 cm^{-1} (C=S). Mass spectrum of compound **9** exhibited a molecular ion peak m/z at 396 (M^+, 0.50%), 395 (M−1, 0.84%) with a base peak at 108 (100%), and other significant peaks appeared at 368 (8.76%), 313 (8.88%), 285 (5.51%), 248 (80.24%), 184 (10.33%), 140 (62.55%), 118 (8.18%), and 55 (71.08%).

1,2,4-triazole derivatives **10**, **11** were obtained via a reaction of compound **2** with thiosemicarbazide and/or thiocarbohydrazide. The reaction progress was followed easily by testing for the evolution of hydrogen sulfide (lead acetate paper) (Scheme 3).

The IR spectrum of compound **10** revealed bands at 3436, 3352, 3225 cm^{-1} (NH, NH_2), 1630 cm^{-1} (C=N), 1328, and 1142 cm^{-1} (SO_2).



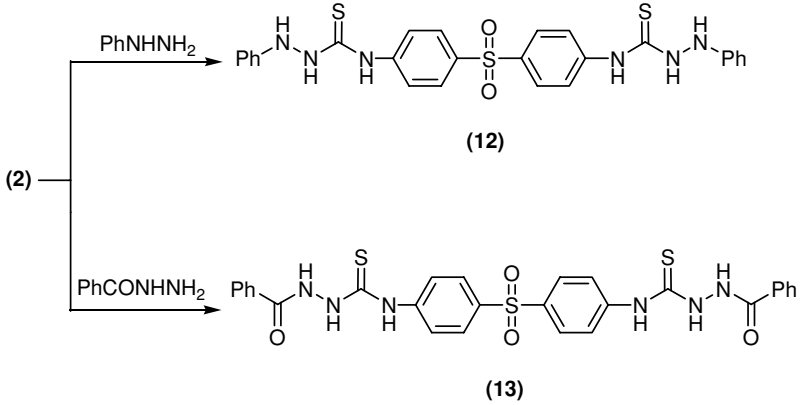
SCHEME 3

Mass spectrum of compound **10** revealed a molecular ion peak m/z at 446 (M^+, 0.46%), with a base peak at 78 (100%), and other significant peaks appeared at 381 (7.30%), 347 (8.11%), 290 (0.66%), 248 (48.82%), 192 (15.05%), 188 (0.88%), 140 (24.82%), 108 (34.84%), 92 (18.88%), and 77 (5.20%). The IR spectrum of compound **11** showed bands at 3450, 3368, 3200 cm^{-1} (NH, NH_2), 1630, cm^{-1} (C=N), 1408, 1146 cm^{-1} (SO_2), and 1290 cm^{-1} (C=S). Mass spectrum of compound **11** revealed a molecular ion peak m/z at 476 (M^+, 0.87%), with a base peak at 78 (100%), and other significant peaks appeared at 382 (0.78%), 332 (4.63%), 276 (8.38%), 248 (8.55%), 160 (20.11%), 108 (35.06%), and 77 (9.85%).

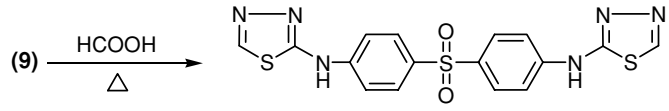
When compound **2** was allowed to react with phenyl hydrazine and/or benzoyl hydrazine, the thiosemicarbazide derivatives **12** and **13** were obtained (Scheme 4).

The IR spectrum of compound **12** revealed bands 3234, 3200 cm^{-1} (NH), 2924 cm^{-1} (CH aliph.), 1300, 1148 cm^{-1} (SO_2), and 1274 cm^{-1} (C=S). ^{1}H-NMR spectrum of compound (**12** in DMSO-d_6) showed signals at 6.8–7.9 [m, 18H, Ar-H], 8.3, 10.1, and 10.3 [3s, 6H, 6NH). Mass spectrum of compound **12** revealed a molecular ion peak m/z at 548 (M^+, 5.58%), with a base peak at 66 (100%), and other significant peaks appeared at 549 (M+1, 1.72%), 496 (5.04%), 438 (6.31%), 342 (10.04%), 250 (32.94%), 218 (38.13%), 156 (10.74%), and 78 (67.78%).

The IR spectrum of **13** showed bands at 3348, 3250 cm^{-1} (NH), 3100 cm^{-1} (CH arom.), 2926 cm^{-1} (CH aliph.), 1726 cm^{-1} (C=O), 1390, 1146 cm^{-1} (SO_2), and 1290 cm^{-1} (C=S). Mass spectrum of compound **13** revealed a molecular ion peak m/z at 604 (M^+, 1.87%), with a base



SCHEME 4



(14)

SCHEME 5

peak at 248 (100%), and other significant peaks appeared at 605 (M+1, 1.71%), 603 (M−1, 4.10%), 578 (12.10%), 552 (8.22%), 368 (38.10%), 313 (1.25%), 178 (22.38%), 108 (83.81%), and 78 (3.20%).

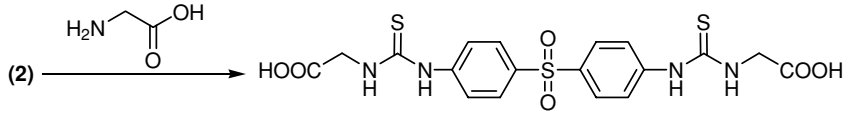
We also investigated the reactivity of compound **9** toward acid. Thus, compound **9** was reacted with formic acid to produce the corresponding the 1,3,4-thiadiazole derivative **14** (Scheme 5).

The IR spectrum of compound **14** exhibited absorption bands at 3370 cm^{-1} (NH), 1592 cm^{-1} (C=N), 1310, and 1146 cm^{-1} (SO_2). ^{1}H-NMR spectrum of compound (**14** in DMSO-d_6) revealed signals at 7.7–8.0 [m, 8H, Ar-H], 9.0 [s, 2H, 2NH], and 11.0 [s, 2H, 2N=CH]. Mass spectrum of compound **14** exhibited a molecular ion peak m/z at 416 (M^+, 1.15%), with a base peak at 108 (100%), and other significant peaks appeared at 417 (M+1, 0.38%), 418 (M+2, 0.23%), 374 (5.73%), 332 (47.78%), 290 (13.07%), 276 (31.18%), 192 (10.08%), 141 (12.08%), 90 (12.88%), and 59 (81.88%).

Also, when diisothiocyanate derivative **2** was treated with glycine as another nucleophile, the corresponding 4,4′-bis(3-carboxymethy-thioureido)-1,1′-diphenylsulfone was obtained. The structure of **15** was proved on the basis of elemental analyses as well as spectroscopic data (Scheme 6).

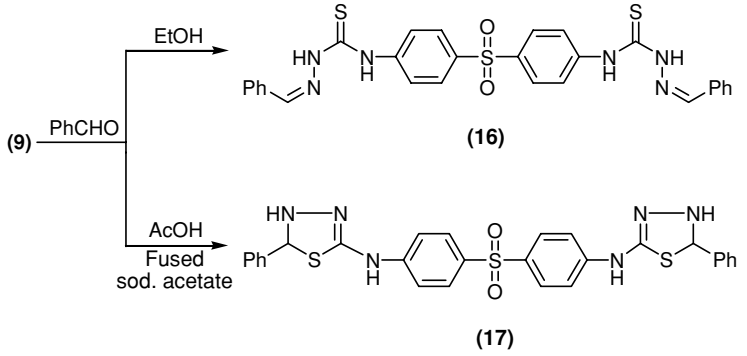
The IR spectrum of **15** revealed bands at 3422 cm^{-1} (br, NH, OH), 1720 cm^{-1} (C=O), 1314, 1150 cm^{-1} (SO_2), and 1250 cm^{-1} (C=S). ^{1}H-NMR spectrum of (**15** in DMSO-d_6) exhibited signals at 6.7 [d, 4H, 2CH_2], 7.4–8.0 [m, 8H, Ar-H], 10.0 [s, 2H, 2NH], 10.9 [s, 2H, 2OH].

Finally, the Schiff's base **16** was achieved by condensing compound **9** with benzaldehyde in ethanol under reflux, while the cyclic compound



(15)

SCHEME 6



SCHEME 7

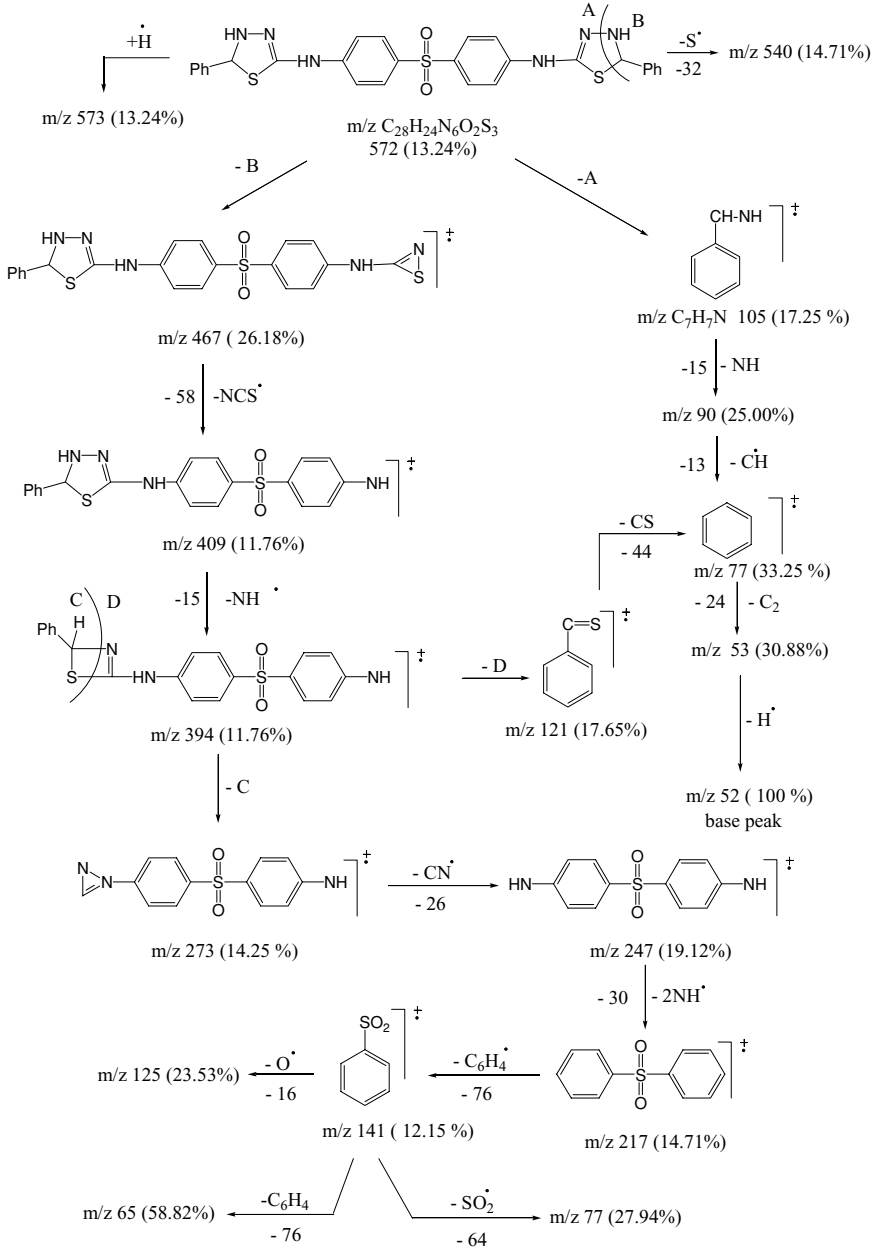
17 was obtained via reaction of **9** with benzaldehyde in acetic acid in presence of fused sodium acetate (Scheme 7).

The IR spectrum of **16** showed bands at 3306 cm^{-1} (NH), 1592 cm^{-1} (C=N), 1320, 1148 cm^{-1} (SO_2), and 1280 cm^{-1} (C=S). Mass spectrum of **16** revealed a molecular ion peak m/z 573 (M+1, 6.04%) with a base peak at 77 (100%). IR spectrum of compound **17** exhibited bands at 3234 cm^{-1} (NH), 1594 cm^{-1} (C=N), 1326, and 1144 cm^{-1} (SO_2). Mass spectrum of compound **17** showed a molecular ion peak m/z 572 (M^+, 13.24%) with a base peak at 52 (100%) (Chart 1).

Antimicrobial Activity

Some of the newly synthesized compounds were screened for their antimicrobial activity using the diffusion agar technique.[13] The tested compounds were dissolved in *N*, *N*-dimethylformamide (DMF), which showed no inhibition zones. Tables 1 and 2 list 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.

Diphenylsulfone bearing thiocarbamic acid o-methyl ester **3** was found to be the most active compound against Gram-negative bacteria *Es-cherichia coli*. The results indicated that the biologically active compound **3** was almost as potent as the standard antibiotic chloramphenicol as positive control.



SCHEME Mass fragmentation pattern of compound **17**.

TABLE I Antibacterial Activity of Some Synthesized Compounds

	E. coli			*Salmonella typhi*			*Staphylococcus aureus*			*Bacillus subtillus*		
Compd No.	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
2	++	++	++	+	+	+	+	++	++	+	++	++
3	++	+++	+++	+	+	++	+	+	+	++	++	+++
7	0	+	+	0	0	+	0	0	0	+	+	+
10	++	++	++	+	+	++	+	+	+	0	+	+
12	+	++	++	++	++	++	++	++	++	+	+	++
16	++	++	++	0	0	+	0	0	0	+	++	++
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.

Antitumor Activity (In Vitro Study)

Reagents

1) RPMI 1640 medium (sigma).
2) Ehrlich Ascites Carcinoma cells (EAC) suspension (2.5×10^5 mL).

TABLE II Antifungal Activity of Some Synthesized Compounds

	Aspergillusniger			*Aspergillus vlavus*		
Compd. No.	1	2.5	5	1	2.5	5
2	+	+	++	+	+	+
3	+	++	++	+	+	++
7	0	0	+	0	0	+
10	+	+	++	+	++	++
12	+	++	++	++	++	++
16	+	+	+	+	+	++
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.

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.[14]
2) The cells were tested for viability and contamination by staining a certain cell volume of this fluid with an equal volume of the working solution of trypan blue dye.[15,16]
3) The ascetic fluid was diluted with saline (1:10) to contain 2.5×10^6 mL cells on a hemocytometer.
4) 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[15,16] was carried out to calculate the presence of nonviable cells. Compounds producing more than 70% nonviable cells are considered active.[16]

$$\% \text{ of non-viable cells } = \frac{\text{No. of non viable}}{\text{Total No. of cells}} \times 100 \qquad (1)$$

The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of EAC cells. The response parameter calculated was the IC_{50} value, which corresponds to the compound concentration causing 50% mortality in net cells (Table 3).

The results indicated that biologically active compound **15** was almost more active than the reference drug (Doxorubicin). From these results it was found that diphenylsulfone having carboxymethylthioureido moiety **15** exhibited nonviable cells of about 90% at a concentration of 50 μg/mL.

EXPERIMENTAL

Melting points were 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 were expressed as δ ppm units. Mass spectra were recorded on a gas chromatography

TABLE III In Vitro Antitumor Activity of Some Newly Synthesized Compounds

	Non-viable cells (%) Concentration (μg/mL)			
Compound No.	100	50	25	IC_{50}^{a}
2	0	0	0	>100
4	20	10	0	>100
7	10	0	0	>100
8	20	0	0	>100
9	0	0	0	>100
11	0	0	0	>100
14	20	10	0	>100
15	100	90	85	0.5
Doxorubicin	100	55	20	52

$^{a}IC_{50}$ >100 Mg/mL is considered to be inactive.

GC-MS 9p 100 Ex (schiumadzu instrument) at 70 ev. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University.

4,4′-Diisothiocyanato-1,1′-diphenylsulfone (2)

Dapson **1** (0.01 mol) was dissolved in 200 mL of H_2O containing 50 mL concentrated HCl. To this 0.02 mol of $CSCl_2$ was added in one portion. Stirring began immediately and continued until all of the red color of $CSCl_2$ had disappeared (1 hr) and the product was precipitate as white crystals. The resulting precipitate was filtered off, dried, and recrystallized from acetone to give (**2**, Table 4).

4,4′-Bis[thiocarbamic acid-O-methyl ester]-1,1′-diphenylsulfone (3), 4,4′-Bis[thiocarbamic acid-O-ethyl ester]-1,1′-diphenylsulfone (4), 4,4′-bis[thiocarbamic acid-O-propylester]-1,1′-diphenylsulfone (5), and 4,4′-Bis[thiocarbamic acid-O-butyl ester]-1,1′-diphenylsulfone (6)

A solution of **2** (0.01 mol) in alcohol (methyl, ethyl, propyl, butyl) (20 mL) was refluxed for 8 hr. The solid obtained was recrystallized from dioxane to give (**3–6**), respectively (Table 4).

TABLE IV Physical and Analytical Data of the Newly Synthesized Compounds

Compound	m.p [°C]	Yield [%]	Mol. Formula (Mol. Wt)	Analyses % Required/Found			
				C	H	N	S
2	145–47	88	$C_{14}H_8N_2O_2S_3$ (332)	50.60 50.40	2.40 2.70	8.43 8.70	28.91 29.20
3	150–152	75	$C_{16}H_{16}N_2O_4S_3$ (396)	48.48 48.60	4.04 4.30	7.07 7.20	24.24 24.50
4	214–215	78	$C_{18}H_{20}N_2O_4S_3$ (424)	50.94 51.20	4.71 4.40	6.60 6.80	22.64 22.90
5	198–200	76	$C_{20}H_{24}N_2O_4S_3$ (452)	53.09 53.00	5.31 5.40	6.19 6.10	21.24 21.50
6	169–170	74	$C_{22}H_{28}N_2O_4S_3$ (480)	55.00 54.80	5.83 5.50	5.83 5.60	20.00 19.70
7	175–177	81	$C_{20}H_{26}N_4O_2S_3$ (450)	53.33 53.20	5.78 5.50	12.44 12.10	21.33 21.60
8	185–187	74	$C_{22}H_{30}N_4O_2S_3$ (478)	55.23 55.50	6.28 6.50	11.71 11.40	20.08 20.30
9	161–163	86	$C_{14}H_{16}N_6O_2S_3$ (396)	42.42 42.10	4.04 4.30	21.21 21.50	24.24 24.50
10	260–262	82	$C_{16}H_{14}N_8O_2S_3$ (446)	43.05 43.30	3.14 3.40	25.11 25.40	21.52 21.80
11	208–210	79	$C_{16}H_{16}N_{10}O_2S_3$ (476)	40.33 40.70	3.36 3.10	29.41 29.70	20.17 20.40
12	165–167	71	$C_{26}H_{24}N_6O_2S_3$ (548)	56.93 56.70	4.38 4.10	15.32 15.60	17.51 17.80
13	240–242	69	$C_{28}H_{24}N_6O_4S_3$ (604)	55.63 55.80	3.97 3.70	13.91 14.20	15.89 15.50
14	268–270	72	$C_{16}H_{12}N_6O_2S_3$ (416)	46.15 46.50	2.88 3.20	20.19 20.40	23.08 23.40
15	195–197	81	$C_{18}H_{18}N_4O_6S_3$ (482)	44.81 44.50	3.73 3.40	11.62 11.40	19.92 19.60
16	83–85	80	$C_{28}H_{24}N_6O_2S_3$ (572)	58.74 58.90	4.20 4.50	14.68 14.50	16.78 16.90
17	260–262	78	$C_{28}H_{24}N_6O_2S_3$ (572)	58.74 58.90	4.20 4.50	14.68 14.40	16.78 16.30

4,4′-Bis(3-propyl-2-thioxo)-1,1′-diphenylsulfone (7) and 4,4′-bis(3-butyl-2-thioxo)-1,1′-diphenylsulfone(8)

A mixture of **2** (0.01 mol) and propylamine and/or butyl amine (0.02 mol) in dioxane (30 mL) containing few drops of triethylamine was refluxed for 6 hr. The solid that formed upon heating was recrystallized from dioxane to give (**7, 8**), respectively (Table 4).

4,4′-Bis(thiosemicarbazid-4-yl)-1,1′-diphenylsulfone(9)

A solution of **2** (0.01 mol) and hydrazine hydrate (0.02 mol) in ethanol (30 mL) was stirred for 3 hr. The solid that formed was collected and recrystallized from ethanol to give (**9**), (Table 4).

4,4′-Bis(5-amino-3-thioxo-2,4-dihydro,1,2,4-triazol-4-yl)-1,1′-diphe-nylsulfone 10 and 4,4′-Bis[1-(5-mercapto-4-amino)-4H-1,2,4-triazolo-3-yl)thiosemicarbazid-4-yl)-1,1′-diphenylsulfone(11)

A mixture of **2** (0.01 mol) and thiosemicarbazide and/or thiocarbohydrazide (0.02 mol) in ethanol (30 mL) containing a few drops of triethylamine was refluxed until evolution of hydrogen sulfide had stopped (8 hr). The solid product was collected and recrystallized from ethanol to give (**10**, **11**), respectively (Table 4).

4,4′-Bis(phenylthiosemicarbazide-4-yl)-1,1′-diphenylsulfone (12) and 4,4′-Bis(benzoylthiosemicarbazide-4-yl)-1,1′-diphenylsulfone(13)

A solution of **2** (0.01 mol) and phenyl hydrazine and/or benzoyl hydrazine (0.02 mol) in dioxane (30 mL) was refluxed for 3 hr. The solid obtained was recrystallized from acetic acid to give (**12)** and **(13)**, respectively (Table 4).

4,4′-Bis(1,3,4-thiadiazolylamino)-1,1′-diphenylsulfone (14)

A solution of compound **9** (0.01 mol) in formic acid (20 mL) was heated under reflux for 4 hr. After cooling, the precipitate was filtered off and recrystallized from dioxane to give (**14)** (Table 4).

4,4′-Bis(3-carboxymethyl-thioureido)-1,1′-diphenylsulfone (15)

A mixture of **2** (0.01 mol) and glycine (0.02 mol) in dioxane (30 mL) containing 3 drops of triethylamine was refluxed for 6 hr. The obtained solid was recrystallized from dioxane to give **(15)** (Table 4).

4,4′-Bis(1-benzylidene-thiosemicarbazide-4-yl)-1,1′-diphenylsulfone (16)

A mixture of **9** (0.01 mol) and benzaldehyde (0.02 mol) in ethanol (50 mL) was refluxed for 5 hr. The obtained solid was recrystallized from ethanol to give **(16)** (Table 4).

4,4′-Bis[(5-phenyl-4,5-dihydro[1,3,4]thiadiazol-2-yl)amino]-1,1′-diphenylsulfone (17)

A mixture of **9** (0.01 mol) and benzaldehyde (0.02 mol) in acetic acid (30 mL) containing 1 g fused sodium acetate was refluxed for 10 hr. The reaction mixture was poured into ice water. The obtained solid was recrystallized from dimethylformamide/ethanol to give **(17**) (Table 4).

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