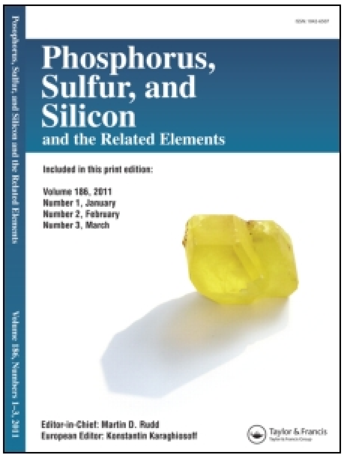

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Dapson in Heterocyclic Chemistry, Part III: Synthesis, Antimicrobial, and Antitumor Activities of Some New Bisheterocyclic Compounds Containing Biologically Active Diphenylsulfone Moiety

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Dapson in Heterocyclic Chemistry, Part III: Synthesis, Antimicrobial, and Antitumor Activities of Some New Bisheterocyclic Compounds Containing Biologically Active Diphenylsulfone Moiety

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The key intermediate diisothiocyanate ***2*** *was allowed to react with 5-amino-3-methyl-pyrazole-4-carbonitrile* ***3,*** *ethyl 5-amino-1-phenyl-pyrazole-4-carboxylate* ***6****, 2-amino-tetrahydrobenzo[b]thiophene-3-car-bonitrile* ***9****, ethyl-2-amino-tetra-hydrobenzo[b]thiophene-3-carboxylate* ***12****, and / or 1,2,4-triazole* ***15*** *to give the corresponding biscompounds* ***4****,* ***5****,* ***7****,* ***8****,* **10***,* **11***,* **13***,* **14***, and* ***16****, respectively. The structure of the synthesized compounds was elucidated by elemental analyses and spectral data. Some of the prepared compounds were tested for their antimicrobial and antitumor activities.*

Keywords Antimicrobial and antitumor activities; biscompounds having diphenylsulfone moiety

INTRODUCTION

Diphenylsulfone and bisheterocyclic compounds are reported to have a broad spectrum of biological activities. Some are endowed with antifungal,[1] antitumor,[2] or radioprotective[3] properties. Some pyrazolopyrimidine, benzothienopyrimidine, and 1,2,4-triazole derivatives

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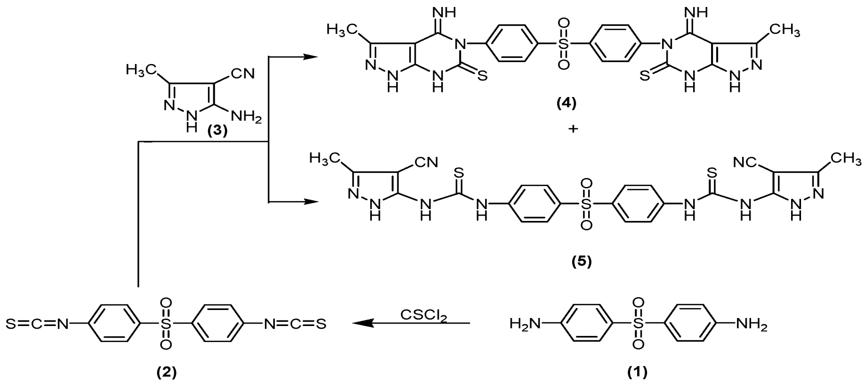
also have various biological properties such as antimicrobial,[4–7] anticancer,[8,10] antifungal,[11–14] and insecticidal.[15]

In addition many investigators have reported that sulfur-containing compounds have a radioprotective capacity, since a free SH group that acts as –OH scavenger or H-donating agent reacts with primary lesions, thus leading to a chemical restitution of the damaged site.[16] Based on the preceding, a symbiotic approach was utilized via a combination of the sulfone, bisheterocyclic compounds in one structural formula aiming to produce new compounds with possible antimicrobial and antitumor activities.

RESULTS AND DISCUSSION

Treatment of dapson**1** with thiophosgene at room temperature in the presence ofdilute hydrochloric acid furnished the corresponding diisothiocyanate deriviative **2**.

The reactivity of diisothiocyanate **2** toward heterocyclic orthoaminocarbonitrile and ortho-aminoester was discussed. Thus, when diisothiocyanate **2** (1 mol) was reacted with 5-amino-3-methyl-pyrazole-4-carbo-nitrile **3** (2 mol) in ethanol containing triethylamine, the cyclic compound **4** was isolated while hot. The pyrazole derivative **5** was obtained from the mother liquor of the reaction mixture. The proposed structures were based on correct elemental analyses and spectral data (Scheme 1).



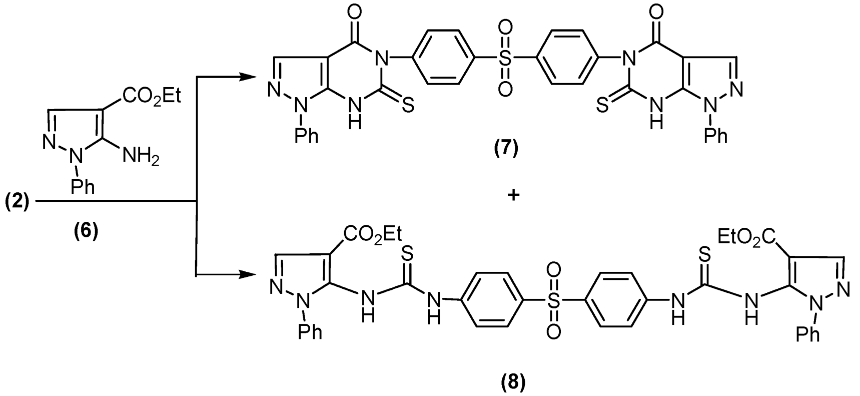
SCHEME 1

The IR spectrum of **4** showed bands at 3470, 3374, 3270 cm^{-1} (NH), 3076 cm^{-1} (CH arom.), 1374, 1150 cm^{-1} (SO_2), and 1290 cm^{-1} (C=S). Mass spectrum of compound **4** revealed a molecular ion peak m/z at

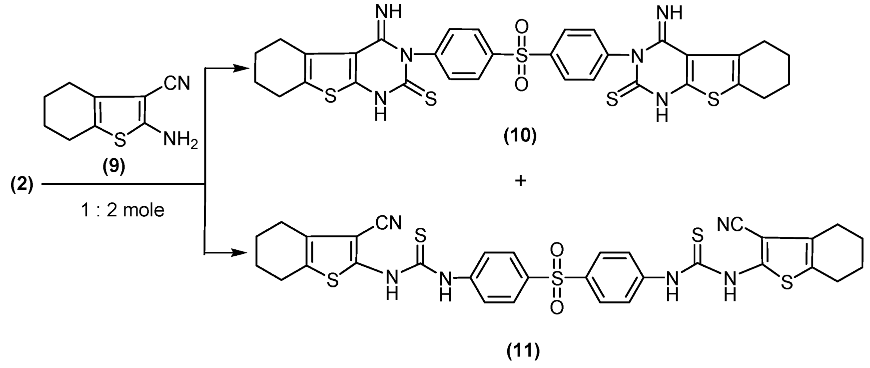
576 (M^+, 2.83%), with a base peak at 108 (100%), and other significant peaks appeared at 577 (M+1, 4.72%), 578 (M+2, 1.83%), 552 (8.52%), 393 (2.30%), 332 (25.35%), 290 (87.37%), 248 (31.35%), 140 (60.24%), 92 (28.29%), and 76 (6.47%). The IR spectrum of compound **5** revealed bands at 3296 cm^{-1} (NH), 2216 cm^{-1} (C≡N), 1590 cm^{-1} (C=N), 1312, 1148 cm^{-1} (SO_2), and 1250 cm^{-1} (C=S). ^{1}H-NMR spectrum of compound (**5** in DMSO-d_6) showed signals at 2.4 [s, 6H, $2CH_3$], 6.2, 6.6, 7.5 [3s, 6H, 6NH], 7.6, and 7.8 [2d, 8H, Ar-H, AB system]. Mass spectrum of compound **5** exhibited a molecular ion peak m/z at 576 (M^+, 36%), with a base peak at 65 (100%), and other significant peaks appeared at 575 (M-1, 40%), 490 (72%), 399 (32%), 354 (48%), 263 (48%), 218 (56%), 131 (48%), and 90 (92%).

Also, interaction of isothiocyanate **2** (1 mol), with ethyl-5-amino-1-phenylpyrazol-4-carboxylate **6** (2 mol) in dimethylformamide containing triethylamine gave the corresponding the pyrazolopyrimidine derivative **7** while hot, while pyrazole derivative **8** was isolated from the cooled filtered product of the reaction mixture (Scheme 2).

The IR spectrum of compound **7** exhibited bands at 3464 cm^{-1} (NH), 1640 cm^{-1} (C=O), 1588 cm^{-1} (C=N), 1310, 1150 (SO_2), and 1224 cm^{-1} (C=S). Mass spectrum of **7** showed a molecular ion peak m/z at 702 (M^+, 0.78%), with a base peak at 73 (100%), and other significant peaks appeared at 635 (1.14%), 579 (2.65%), 537 (4.68%), 383 (8.40%), 331 (5.14%), 256 (23.64%), 149 (37.88%), 128 (33.71%), and 97 (37.18%). The IR spectrum of compound **8** exhibited bands at 3396, 3268, 3198 cm^{-1} (NH), 2990, 2946 cm^{-1} (CH aliph.), 1750, 1684 cm^{-1} (C=O), 1624, 1600 cm^{-1} (C=N), 1382, 1148 cm^{-1} (SO_2), and 1260 cm^{-1} (C=S). ^{1}H–NMR spectrum of compound (**8** in DMSO-d_6) showed signals at 1.3 [t, 6H, $2CH_3$], 4.2 [q, 4H, $2CH_2$], 6.4 [s, 2H, 2CH pyrazole], 7.3–7.7



SCHEME 2



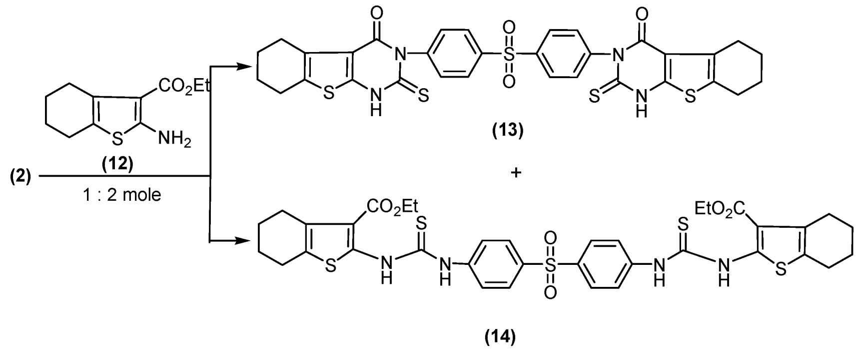
SCHEME 3

[m, 18H, Ar-H], and 7.8 [s, 4H, 4NH]. Mass spectrum of compound **8** revealed a molecular ion peak m/z at 794 (M^+, 0.7%), with a base peak at 184 (100%), and other significant peaks appeared at 615 (0.7%), 528 (0.14%), 439 (0.9%), 396 (0.17%), 307 (0.36%), 231 (90.59%), and 77 (52.94%).

In a similar manner, 1 mol of diisothiocyanate **2** was reacted with 2 mol of 2-amino-tetrahydrobenzo[b]thiophene-3-carbonitrile **9** to give the corresponding bisthienopyrimidine derivative **10** while hot, while the benzothiophene **11** was obtained from the filtered product of the reaction mixture (Scheme 3).

The IR spectrum of compound **10** revealed bands at 3430, 3352 cm^{-1} (NH), 2932 cm^{-1} (CH aliph.), 1626, 1592 cm^{-1} (C=N), 1374, 1148 cm^{-1} (SO_2), and 1250 cm^{-1} (C=S). Mass spectrum of compound **10** showed a molecular ion peak m/z at 688 (M^+, 1.48%), with a base peak at 232 (100%), and other significant peaks appeared at 691 (M+3, 1.2%), 618 (1.41%), 575 (2.88%), 533 (8.80%), 445 (4.50%), 396 (5.24%), 265 (20.44%), 204 (95.83%), and 118 (17.00%). The IR spectrum of compound **11** revealed bands at 3434, 3334, 3222 cm^{-1} (NH), 2938, 2838 cm^{-1} (CH aliph.), 2196 cm^{-1} (C≡N), 1376, 1148 cm^{-1} (SO_2), and 1284 cm^{-1} (C=S). ^1H-NMR spectrum of (**11** in DMSO-d_6) exhibited signals at 1.6 [m, 8H, $4CH_2$], 2.3, 2.4 [m, 8H, $4CH_2$], 6.6–8.0 [m, 8H, Ar-H], 11.4, and 11.6 [2s, 4H, 4NH]. Mass spectrum of compound **11** revealed a molecular ion peak m/z at 688 (M^+, 36.36%), with a base peak at 239 (100%), and other significant peaks appeared at 658 (50.00%), 550 (54.53%), 480 (68.18%), 444 (45.45%), 347 (59.09%), 194 (63.64%), 122 (68.18%), and 77 (68.18%).

In addition, the corresponding benzothienopyrimidine **13** was obtained while hot via the reaction of **2** with ethyl-2-amino-tetrahydrobenzo[b]-thiophene-3-carboxylate **12** (1:2 mol), while the

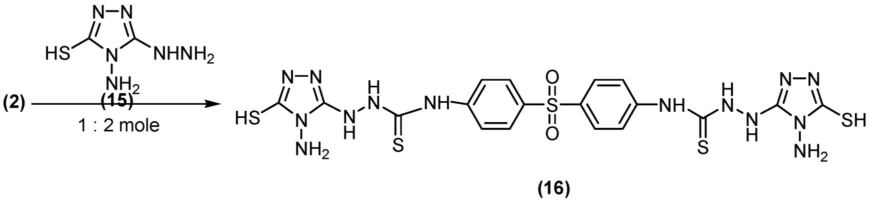


SCHEME 4

benzothiophene derivative **14** was isolated from the filtered product of the reaction mixture (Scheme 4).

The IR spectrum of **13** revealed bands at 3450 cm^{-1} (NH), 3094 cm^{-1} (CH arom.), 2980 cm^{-1} (CH aliph.), 1636 cm^{-1} (C=O), 1314, 1146 cm^{-1} (SO_2), and 1248 cm^{-1} (C=S). Mass spectrum of compound **13** exhibited a molecular ion peak m/z at 690 (M^+, 0.3%), with a base peak at 66 (100%), and other significant peaks appeared at 689 (M-1, 0.83%), 552 (0.38%), 524 (0.70%), 423 (0.32%), 290 (8.15%), 225 (8.18%), 179 (24.82%), 101 (18.88%), and 75 (44.57%). The IR spectrum of **14** exhibited bands at 3404, 3300 cm^{-1} (NH), 2986, 2938 cm^{-1} (CH aliph.), 1648 cm^{-1} (C=O), 1384, 1152 cm^{-1} (SO_2), 1294 cm^{-1} (C=S). ^{1}H-NMR spectrum of (**14** in DMSO-d_6) revealed signals at 1.3 [t, 6H, 2CH_3 ester], 1.7 [m, 8H, 4CH_2 cyclo], 2.4, 2.6 [m, 8H, 4CH_2 cyclo], 4.2 [q, 4H, 2CH_2 ester], and 6.6–8.0 [m, 12H, Ar-H + 4NH]. Mass spectrum of compound **14** exhibited a molecular ion peak m/z at 782 (M^+, 1.56%), with a base peak at 55 (100%), and other significant peaks appeared at 738 (2.54%), 684 (2.54%), 599 (2.73%), 480 (2.73%), 366 (3.52%), 271 (4.30%), 233 (2.15%), 179 (38.48%), 151 (3.32%), and 78 (2.34%).

Finally, interaction of compound **2** with 1,2,4-triazole derivative **15** yielded the novel condensed bisheterocyclic compound **16** (Scheme 5).



SCHEME 5

The IR spectrum of compound **16** revealed bands at 3450, 3354, 3210 cm^{-1} (NH, NH_2), 1626, 1594 cm^{-1} (C=N), 1364, 1146 cm^{-1} (SO_2), and 1292 cm^{-1} (C=S). Mass spectrum of compound **16** showed a molecular ion peak m/z at 608 (M-NH_2, 0.38%), with a base peak at 341 (100%), and other significant peaks appeared at 578 (3.27%), 552 (5.33%), 538 (2.12%), 423 (1.57%), 324 (47.10%), 248 (44.10%), 140 (22.22%), 108 (27.40%), and 90 (2.75%).

Antimicrobial Activity

Some of the newly synthesized compounds were screened for their antimicrobial activity using the diffusion agar technique.[17] The tested compounds were dissolved in *N*,*N*-dimethylformamide (DMF), which showed no inhibition zones. Tables I and II 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 the 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 tested compounds showed a remarkable activity toward the tested microorganisms and were less active than the standard chloramphenicol and Grisofluvine.

TABLE I Antibacterial Activity of Some Synthesized Compounds

Compound No.	*E. coli*			*Salmonella typhi*			*Staphylococcus aureus*			*Bacillus subtillus*		
	1	2.5	5	1	2.5	5	1	2.5	5	1	2.5	5
2	++	++	++	+	+	+	+	++	++	+	++	++
4	0	0	0	0	0	+	0	0	0	+	+	+
8	+	+	+	+	+	++	0	0	+	0	+	+
11	++	++	++	+	++	++	++	++	++	++	++	++
14	++	++	++	0	+	+	+	+	+	+	++	++
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.

TABLE II Antifungal Activity of Some Synthesized Compounds

	Aspergillus niger			*Aspergillus vlavus*		
Compound No.	1	2.5	5	1	2.5	5
2	+	+	++	+	+	+
4	+	++	++	+	++	++
8	+	+	+	+	+	+
11	+	+	+	0	+	+
14	+	+	+	+	++	++
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.

In-Vitro 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 (**2–16**).

Procedure

1. EAC cells were obtained by needle aspiration of the ascetic fluid from preinoculated mice under aseptic conditions.[18]
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.[19,20]
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. Trypan blue exclusion test[19,20] was carried out

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	$>100^a$
4	20	10	0	$>100^a$
7	0	0	0	$>100^a$
10	10	0	0	$>100^a$
13	30	10	0	$>100^a$
16	0	0	0	$>100^a$
Doxorubicin	100	55	20	52

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

to calculate the presence of nonviable cells. Compounds producing more than 70% non viable cells are considered active.[20]

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

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 all tested compounds showed no activity against EAC cells.

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

TABLE IV Physicochemical Data of the Synthesized Compounds

Comound No.	m.p. (°C)	Yield [%]	Mol. Formula (Mol. Wt)	Elemental analyses% Required/Found C	H	N	S
2	145–147	88	$C_{14}H_{8}N_{2}O_{2}S_{3}$ (332)	50.60 50.40	2.40 2.10	8.43 8.10	28.91 29.20
4	238–240	52	$C_{24}H_{20}N_{10}O_{2}S_{3}$ (576)	50.00 50.30	3.47 3.10	24.30 24.60	16.66 16.40
5	>300	39	$C_{24}H_{20}N_{10}O_{2}S_{3}$ (576)	50.00 50.30	3.47 3.70	24.30 24.10	16.66 16.30
7	270–272	61	$C_{34}H_{22}N_{8}O_{4}S_{3}$ (702)	58.12 58.40	3.13 3.50	15.96 16.20	13.68 13.40
8	88–90	34	$C_{38}H_{34}N_{8}O_{6}S_{3}$ (794)	57.43 57.10	4.28 4.50	14.11 14.30	12.09 12.30
10	253–255	46	$C_{32}H_{28}N_{6}O_{2}S_{5}$ (688)	55.81 55.50	4.06 4.30	12.20 12.40	23.25 23.50
11	126–128	41	$C_{32}H_{28}N_{6}O_{2}S_{5}$ (688)	55.81 55.50	4.06 4.30	12.20 12.50	23.25 23.60
13	173–175	35	$C_{32}H_{26}N_{4}O_{4}S_{5}$ (690)	55.65 55.40	3.77 3.40	8.12 8.40	23.19 23.15
14	98–100	48	$C_{36}H_{38}N_{4}O_{6}S_{5}$ (782)	55.24 55.50	4.86 4.50	7.16 7.50	20.46 20.10
16	165–167	81	$C_{18}H_{20}N_{14}O_{2}S_{5}$ (624)	34.61 34.80	3.20 2.90	31.41 31.60	25.64 25.40

4,4′-Bis(6,7-dihydro-3-methyl-4-oxo-6-thioxo-1H,5H-pyrazolo [3,4-pyrimidin-5-yl]-1,1′-diphenylsulfone (4) and 4,4′-bis (3-(4-cyano- 3-methyl-1H-pyrazol-5-yl)thioureido)-1,1′-diphenylsulfone (5)

A mixture of **2** (0.01 mole) and 5-amino-3-methyl-pyrazole-4-carbonitrile **3** (0.02 mole) in ethanol (20 mL) containing 3 drops of triethylamine was refluxed for 30 minutes. The reaction mixture was filtered while hote to give compound **4**, while, the pyrazole derivative **5** was isolated from the mother liquer of the reaction mixture (Table IV).

4,4′-Bis(6,7-dihydro-1-phenyl-4-oxo-6-thioxo-1H,5H-pyrazolo[3,4-d]-pyrimidin-5-yl)-1,1′-diphenylsulfone (7) and 4,4′-bis(3-(4-ethyloxy-1-phenyl-1H-pyrazol-5-yl)thioureido)-1,1′-diphenylsulfone (8)

A mixture of **2** (0.01 mole) and ethyl-5-amino-1-phenylpyrazole-4-carboxylate **6** (0.02 mole) in dioxane (20 mL) containing triethylamine (0.5 mL) was refluxed for 1 hr. The reaction mixture was filtered while hot to give **7**, while pyrazole derivative **8** was isolated from the filtered of the reaction mixture and recrystallized from ethanol (Table IV).

4,4′-Bis(4-imino-2-thioxo-3,4,5,6,7,8-hexahydro-1H-benzo[4,5]thieno-[2,3-d]pyrimidin-3-yl]-1,1′diphenylsulfone (10) and 4,4′-bis(3-(3-cyano-4,5,6,7-tetrahydrobenzo[b] thiophen-2-yl)-2-thioureido)-1,1′-diphenylsulfone (11)

A mixture of **2** (0.01 mole) and 2-amino-tetrahydrobenzo[b]-thiophene-3-carbonitrile **9** (0.02 mole) in ethanol (30 mL) containing triet-hylamine (0.5 mL) was refluxed for 1 hr. The cyclic compound **10** was obtained on hot and recrystallized from dioxane, while the benzothio-phene **11** was isolated from the filtered of the reaction mixture and recry-stallized from ethanol (Table IV).

4,4′-Bis(4-oxo-2-thioxo-3,4,5,6,7,8-hexahydro-1H-benzo[4,5]thieno-[2,3-d]pyrimidin-3-yl]-1,1′diphenylsulfone (13) and 4,4′-bis(3-(3-ethyloxy-4,5,6,7-tetrahydrobenzo[b] thiophen-2-yl)-2-thioureido)-1,1′-diphenylsulfone (14)

A mixture of **2** (0.01 mole) and ethyl 2-amino-tetrahydrobenzo[b]-thiophene-3-carboxylate **12** (0.02 mole) in dioxan (20 mL) containing triethylamine (0.5 mL) was refluxed for 1 hr. The cyclic compound **13** was obtained on hot and recrystallized from dimethylformamide, while the benzothiophene derivative **14** was isolated from the filtered of the reaction mixture and recrystallized from ethanol (Table IV).

4,4′-Bis(1-(5-mercapto-4-amino-4H-1,2,4-triazolo-3-yl) thiosemicarbazid-4-yl)-1,1′-diphenylsulfone (16)

A mixture of **2** (0.01 mol) and 1,2,4-triazole **15** (0.02 mol) in dimethylformamide (20 mL) containing triethylamine (0.5 mL) was refluxed for 2 hr. The solid product was collected and recrystallized from dioxan to give (**16**) (Table IV).

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