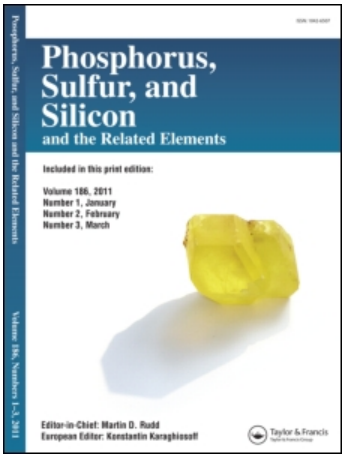

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Dapson in Heterocyclic Chemistry, Part IV: Synthesis of Some Novel Diphenylsulfones Containing Acetamide, Pyrrolidine, Piperazine, and Thiomorpholine Moieties as Antimicrobial and Antitumor Agents

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Dapson in Heterocyclic Chemistry, Part IV: Synthesis of Some Novel Diphenylsulfones Containing Acetamide, Pyrrolidine, Piperazine, and Thiomorpholine Moieties as Antimicrobial and Antitumor Agents

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Interaction of dapson [bis(4-aminophenyl)sulfone] ***1*** *with [bis-(methylsulfonyl) methylidine]malononitrile* ***2*** *yielded the corresponding dicyano derivative* ***3****, which was reacted with acetic anhydride, succinic anhydride, 4-chlorobenzaldehyde, phenyl isothiocyanate to give the corresponding acetamide* ***4****, succinamic acid* ***5****, pyrrolidine* ***6****, Shiff base* ***7*** *and thiourea* ***8****, respectively. Treatment of* ***3*** *with chloroacetyl chloride afforded the aminoacetyl chloride derivative* ***9****. Further, the interaction of compound* ***9*** *with thioglycolic acid, malononitrile, ethyl glycinate hydrochloride, and/or potassium thiocyanate furnished compounds* ***10–15****, respectively. The structural characterization of the prepared compounds was based on microanalytical and spectroscopic analyses. Some of the prepared compounds were tested for their antimicrobial and antitumor activities. Compounds* ***9*** *and* ***12*** *showed promising antitumor activity compared with Doxorubicin as positive control.*

Keywords Diphenylsulfone having acetamide; pyrrolidine; piperazine; thiomorpholine as antitumor and antimicrobial activities

INTRODUCTION

The fusion of diphenylsulfone with other biologically active nuclei arouses considerable interest for synthetic organic chemists due to an

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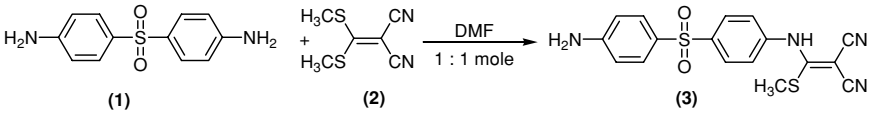
important biological activity, property that many members of this family exhibit.[1–5] Some pyrrolidine, thiomorpholine and piperazine derivatives are well known as cytotoxic[6-9] with radioprotective activity.[10–12] As a part of our studies on new heterocyclic compounds as new potential antitumor and radioprotective agents, we synthesized and tested some new diphenylsulfone derivatives.

RESULTS AND DISCUSSION

The sequence of reactions that followed from the synthesis of the designed compounds is summarized in Scheme 1.

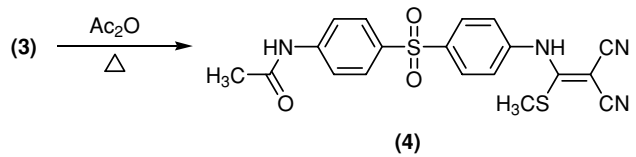


SCHEME 1

The reactivity of dapson **1** towards some electrophilic reagents was studied. Thus, dapson **1** was reacted with [bis(methylsulfanyl)-methylidene]malononitrile **2** in dimethylformamide under reflux. That reaction furnished the corresponding 2-{[4-(4-amino-benzensulfonyl)-phenyl-amino]-methylsu-lfanyl-methylene}-malononitrile **3**. The structure of compound **3** was pro-ved by analytical and spectral data.

The IR spectrum of **3** revealed bands at 3457, 3372, 3338, 3256 cm^{-1} (NH, NH_2), 3039 cm^{-1} (CH arom.), 2984, 2932 cm^{-1} (CH aliph.), 2218 cm^{-1} (C≡N), 1332, and 1144 cm^{-1} (SO_2). ^{1}H–NMR spectrum of (**3** in DMSO-d_6) showed signals at 2.8 [s, 3H, SCH_3], 3.6 [hump, 3H, NH + NH_2], 6.5, and 7.5 [2d, 8H, Ar-H, AB system]. Mass spectrum of **3** exhibited a molecular ion peak m/z at 369 (M-1, 2.23%) with a base peak at 248 (100%), and other significant peaks appeared at 368 (M-2, 0.43%), 313 (1.53%), 261 (2.44%), 184 (7.88%), 140 (56.12%), 108 (78.37%), and 65 (37.61%).

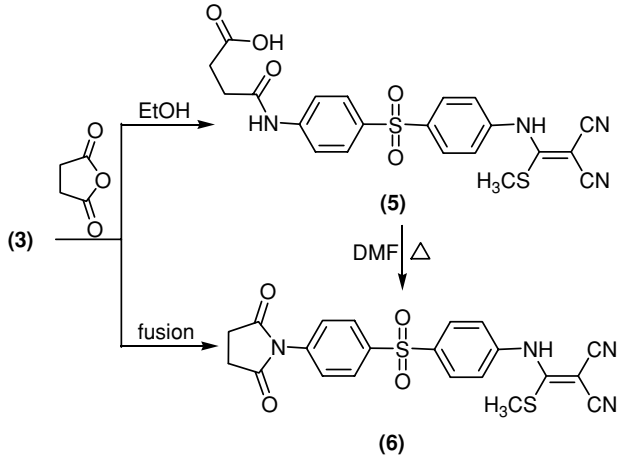
The acetamide derivative **4** was obtained via reaction of **3** with acetic anhydride (Scheme 2).



SCHEME 2

The IR spectrum of **4** showed bands at 3334, 3256 cm^{-1} (NH), 3100 cm^{-1} (CH arom.), 2940 cm^{-1} (CH aliph.), 1684 cm^{-1} (C=O), 1368, and 1150 cm^{-1} (SO_2). ^{1}H-NMR spectrum of (**5** in DMSO-d_6) revealed signals at 2.2 [s, 3H, SCH_3], 2.6 [s, 3H, $COCH_3$], 7.7, 7.9 [2d, 8H, Ar-H AB system], and 10.3 [s, 2H, 2NH].

In addition, the behaviour of **3** towards succinic anhydride under different conditions was also studied. Thus, refluxing of compound **3** with succinic anhydride in boiling ethanol afforded a product ($C_{21}H_{18}N_4O_5S_2$) for which two structure, **5** and, **6** seemed possible. Structure **5** was established for the reaction product on the basis of its IR spectrum, while under condition of fusion the corresponding pyrrolidine **6** was obtained. Compound **6** was also obtained via heating of compound **5** in dimethylformamide (Scheme 3).

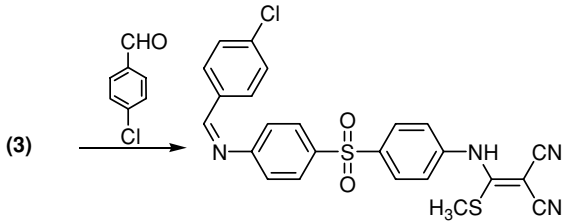


SCHEME 3

The IR spectrum of compound **5** revealed bands at 3450 cm^{-1} (OH), 3374 cm^{-1} (NH), 2926 cm^{-1} (CH aliph.), 2210, 2200 cm^{-1} (2C≡N), 1660, 1650 cm^{-1} (2C=O), 1316, and 1148 cm^{-1} (SO_2). Mass spectrum of compound **5** showed a molecular ion peak m/z at 471 (M+1, 3.04%), with a base peak at 82 (100%), and other significant peaks appeared at 452 (4.11%), 395 (5.38%), 338 (7.32%), 271 (20.88%), 234 (11.07%), 170 (3.75%), 110 (65.22%), and 75 (28.08%). The IR spectrum of **6** revealed bands at 3416 cm^{-1} (NH), 3100 cm^{-1} (CH arom.), 2950 cm^{-1} (CH aliph.), 2198, 2190 cm^{-1} (2C≡N), 1705, 1696 cm^{-1} (2C=O), 1334, and 1158 cm^{-1} (SO_2). ^{1}H-NMR spectrum of (**6** in DMSO-d_6) exhibited signals at 1.2 [t, 4H, $2CH_2$], 2.9 [s, 3H, SCH_3], 7.0, 7.5 [2d, 8H, Ar-H, AB system], and 8.4 [s, 1H, NH]. Mass spectrum of **6** revealed

a molecular ion peak m/z at 450 (M^+, 2.02%), with a base peak at 65 (100%), and other significant peaks appeared at 358 (3.04%), 338 (2.04%), 261 (0.78%), 248 (43.83%), 184 (8.83%), 108 (10.53%), and 75 (1.20%).

The schiff's base **7** was achieved by condensing compound **3** with 4-chlorobenzaldehyde (Scheme 4).

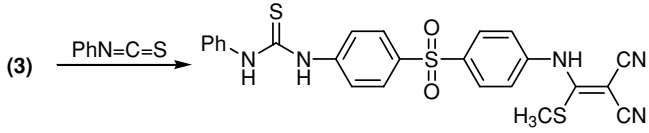


(7)

SCHEME 4

The IR spectrum of **7** showed bands at 3366 cm^{-1} (NH), 3060 cm^{-1} (CH arom.), 2212, 2198 cm^{-1} (2C≡N),1350, and 1144 cm^{-1} (SO_2). ^{1}H-NMR spectrum of (**7** in DMSO-d_6) revealed signals at 2.8 [s, 3H, SCH_3], 6.5, 7.5 [2d, 8H, Ar-H, AB system], 7.7, 7.9 [2d, 4H, benzilidin Ar-H, AB system], and 10.0 [s, 2H, NH, N = CH].

When compound **3** was allowed to react with phenyl isothiocyanate in absolute ethanol containing triethylamine under refux the thiosemicarbazide derivative **8** was obtained (Scheme 5).

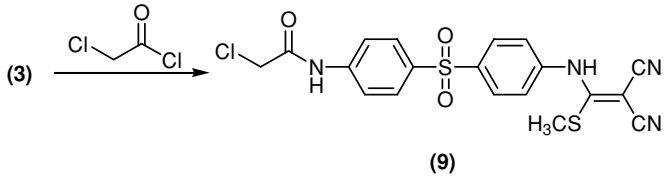


(8)

SCHEME 5

The IR spectrum of **8** showed bands at 3390, 3282 cm^{-1} (NH), 2200, 2192 cm^{-1} (2C ≡ N), 1314, and 1146 cm^{-1} (SO_2). ^{1}H-NMR spectrum of (**8** in DMSO-d_6) reveled signals at 2.4 [s, 3H, SCH_3], 6.6–7.9 [m, 13H, Ar-H], 11.2, 11.4, and 11.6 [3s, 3H, 3NH].

Treatment of compound **3** with chloroacetyl chloride in dimethylformamide at room temperature afforded the corresponding N-[4-(4-(2,2-dicyano-1-(methylthio)vinylamino)phenyl-sulfonyl)phenyl)-2-chloroethanethioamide **9** in high yield (Scheme 6).

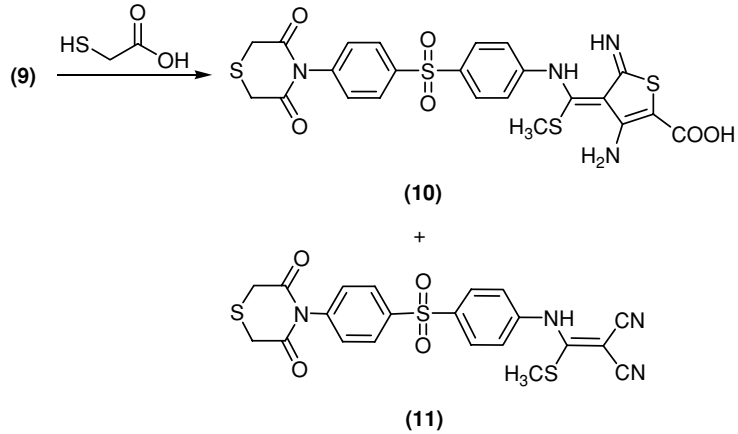


(9)

SCHEME 6

The IR spectrum of **9** exhibited bands at 3270, 3198 cm^{-1} (NH), 3100 cm^{-1} (CH arom.), 2940 cm^{-1} (CH aliph.), 2212, 2205 cm^{-1} (2 C≡N), 1686 cm^{-1} (C=O), 1340, and 1152 cm^{-1} (SO_2). Mass spectrum of compound **9** revealed a molecular ion peaks at m/z 402 (M-SCH_3, 66.4%), with a base peak at 77 (100%), and other significant peaks appeared at 351 (37.2%), 324 (61.1%), 216, (36.3%), 184 (32.7%), 156 (18.6%), 140 (85.8%), 108 (97.3%), and 78 (38.1%).

The synthesis of thiomorpholine derivative **10** was isolated on hot via reaction of compound **9** with thioglycolic acid in pyridine, while thiomorpholine derivative **11** was obtained from the filtered of the reaction mixture (Scheme 7).

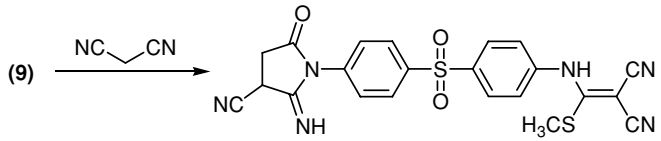


SCHEME 7

IR spectrum compound **10** revealed bands at 3394 cm^{-1} (br, NH, NH_2, OH), 2926 cm^{-1} (CH aliph.), 1702, 1680, 1654 cm^{-1} (3C=O), 1356, and 1150 cm^{-1} (SO_2). ^{1}H-NMR spectrum of (**10** in DMSO-d_6) exhibited signal, at 2.4 [s, 3H, SCH_3], 5.8 [s, 4H, $2CH_2$], 7.6–8.6 [m, 10H, Ar-H + NH_2], 9.0, 9.1 [2s, 2H, 2NH], and 11.8 [s, 1H, OH]. Mass spectrum of compound **10** showed a molecular ion peak m/z at 576 (M^+, 1.19%),

with a base peak at 51 (100%) and other significant peaks appeared at 577 (M+1, 1.27%), 480 (1.52%), 398 (1.78%), 362 (1.44%), 314 (1.69%), 202 (2.12%), 152 (3.98%), 79 (20.24). The IR spectrum of compound **11** revealed bands at 3250 cm^{-1} (NH), 2218 cm^{-1} (C≡N), 1706, 1670 cm^{-1} (2C=O), 1366, and 1150 cm^{-1} (SO_2). ^{1}H-NMR spectrum of (**11** in DMSO-d_6) exhibited signals at 2.4 [s, 3H, SCH_3], 5.8 [s, 4H, $2CH_2$], 7.4–8.4 [m, 8H, Ar-H], and 11.1 [s, 1H, NH]. Mass spectrum of compound **11** revealed a molecular ion peak m/z at 484 (M^+, 16.90%), with a base peak at 51 (100%) and other significant peaks appeared at 312 (19.72%), 260 (21.13%), 115 (26.76%), and 78 (32.39%).

The reaction of malononitrile with compound **9** was conducted through normal addition reaction to yield the pyrrolidine derivative **12** (Scheme 8).

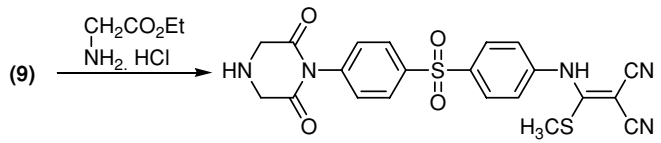


(12)

SCHEME 8

The IR spectrum of compound **12** showed bands at 3322 cm^{-1} (NH), 2938, 2856 cm^{-1} (CH aliph.), 2188 cm^{-1} (C≡N), 1694 cm^{-1} (C=O), 1356, and 1150 cm^{-1} (SO_2). ^{1}H-NMR spectrum of compound (**12** in DMSO-d_6) revealed signals at 2.1 [s, 3H, SCH_3], 4.1 [s, 2H, CH_2], 7.5–8.0 [m, 8H, Ar-H], 10.4, and 10.9 [2s, 2H, 2NH]. Mass spectrum of compound **12** exhibited a molecular ion peak m/z at 474 (M^+, 14.71%), with a base peak at 57 (100%), and other significant peaks appeared at 213 (17.65%), 143 (27.94%), 113 (26.47%), 83 (29.41%), 72 (25.00%), and 53 (32.35%).

The piperazine derivative **13** was obtained also via reaction of compound **9** with ethylglycinate hydrochloride (Scheme 9).

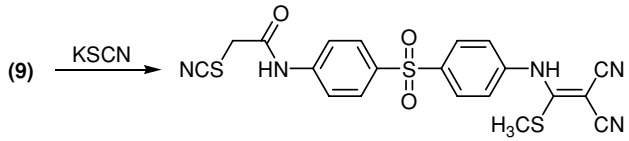


(13)

SCHEME 9

The IR spectrum of compound **13** exhibited bands at 3370 cm^{-1} (NH), 2924, 2854 cm^{-1} (CH aliph.), 2206 cm^{-1} (C≡N), 1700, 1650 cm^{-1} (2C=O), 1300, and 1148 cm^{-1} (SO_2). Mass spectrum of compound **13** showed a molecular ion peak m/z at 467 (M^+, 12.79%), with a base peak at 65 (100%), and other significant peaks appeared at 328 (12.79%), 300 (15.12%), 212 (20.93%), 167 (22.79%), 108 (37.21%), and 75 (17.44%).

Treatment of compound **9** with potassium thiocyanate in dimethy-lformamide afforded isothiocyanatoacetamide derivative **14** (Scheme 10).



(14)

SCHEME 10

The IR spectrum of compound **14** revealed bands at 3370 cm^{-1} (NH), 2208 cm^{-1} (C≡N), 1654 cm^{-1} (C=O), 1390, and 1150 cm^{-1} (SO_2). ^{1}H-NMR spectrum of compound (**14** in DMSO-d_6) showed signals at 2.8 (s, 3H, SCH_3), 4.0 [s, 2H, CH_2], and 6.6–8.0 [m, 10H, Ar-H + 2NH]. Mass spectrum of compound **14** exhibited a molecular ion peak m/z at 469 (M^+, 4.71%), with a base peak at 69 (100%), and other significant peaks appeared at 399 (5.49%), 365 (5.10%), 279 (7.06%), 217 (7.84%), 161 (8.63%), 149 (40.78%), 132 (16.08%), 97 (22.35%), and 76 (12.55%).

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. Table (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 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.

Diphenylsulfone having free amino group and aminomethylsulf-anyl methylenemalononiitrile moiety **3** and diphenyl containing 4-chlorobenzylidene and aminomethylsulfanylmethylenemalononitrile **4** were found to be the most active compounds against Gram-negative bac-

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
3	+++	+++	+++	+++	+++	+++	+++	+++	++++	++	+++	+++
4	++	++	++	++	++	++	0	0	+	+	++	++
7	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
11	0	0	+	0	+	+	0	+	+	+	+	+
12	+	+	++	+	+	+	+	+	+	+	+	+
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

teria *Escherichia coli* and *salmonella typhi*. Also, compound **3** and **7** showed high activity against Gram-positive bacteria *staphylococcus aureus* and *bacillus subtillus*, while compound **7** revealed remarkable activity against *Aspergillus niger* and *Aspergillus flavus*. These results indicated that the biologically active compounds **3** and **7** were almost as potent as the standard antibiotic chloramphenicol as positive control. In addition, compound **7** was nearly as active as Grisofluvine as positive control.

Antitumor Activity (in-vitro study)

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 **(3–14)**.

Procedure

1. EAC cells were obtained by needle aspiration of the ascetic fluid from preinoculated mice under aseptic conditions.[14]

TABLE II Antifungal Activity of Some Synthesized Compounds

	Aspergillus niger			*Aspergillus vlavus*		
Compound. No.	1	2.5	5	1	2.5	5
3	++	++	++	+	++	++
4	+	+	++	+	+	+
7	++	++	+++	++	++	+++
11	+	+	+	+	+	+
12	+	+	+	+	++	++
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

TABLE III In-vitro Antitumor Activity of Some Newly Synthesized Compounds

	Non-viable cells (%)			
	Concentration (μg/ml)			
Compound. No.	100	50	25	IC_{50}
3	10	0	0	>100
9	100	90	85	0.5
10	40	20	0	>100
11	10	0	0	>100
12	100	90	80	0.5
14	20	10	0	>100
Doxorubicin	100	55	20	52

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

2. The cells were tested for viability and contamination by staining certain cell volume of this fluid by 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 $\times$ 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[15–16] was carried out to calculate the presence of nonviable cells. Compounds producing more than 70% nonviable cells are considered active.[16]

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

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

The results obtained from the study exhibited that the diphenylsulfone having dicyano- and 2-chloroethane-thioamide moieties **9** and diphenylsulphone bearing pyrrolidinone and malononitrile moieties **12** were almost active than the reference drug Doxorubicin as positive control. These compounds exhibited non-viable cells about 85% and 80% at a concentration of 25 μg/ml with IC_{50} of 0.5 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 GC-MS 9p 100 Ex (schiumadzu instrument) at 70 ev. Microanalytical data were obtained from the Microanalytical Data Unit at the Cairo University.

2−{4-(4-Amino-benzenesulfonyl)-phenylamino]-methylsulfanylmethylene}-malononitrile (3)

Dapson **1** (0.01 mol) was mixed with [bis(methylsulfanyl)-methylidene] malononitrile **2** (0.01 mol) in dimethylformamide (15 ml). The reaction mixture was refluxed for 3 hr and then allowed to cool. The solid precipitate was collected by filtration and recrystallized from dioxan to give **(3)** (Table IV).

N-{4-[4-(2,2-Dicyano-1-methylsulfanyl-vinylamino)-benzenesulfonyl]-phenyl}-acetamide (4)

A solution of **3** (0.01 mol) and acetic anhydride (10 mL) was heated under refluxed for 5 hr. then allowed to cool. The solid product was collected and recrystallized from ethanol to give **(4)** (Table IV).

N-{4-[4-(2,2-Dicyano-1-methylsulfanyl-vinylamino)-benzenesulfonyl]-phenyl}-succinamic acid (5)

A mixture of **3** (0.01 mol) and suiccinic anhydride (0.01 mol) in ethanol (50 mL) was refluxed for 8 hr. The solid obtained was recr-ystallized from dioxan to give **(5)** (Table IV).

2-({4-[4-(2,5-Dioxo-pyrrolidin-1-yl)benzenesulfonyl]-phenylamino}-methylsulfanyl-methylene)-malononitrile (6)

Method (A)

A mixture of **3** (0.01 mol) and succinic anhydride (0.01 mol) was fused in an oil bath at 220°C for 15 min. The obtained solid was recrystallized from dioxan to give **(6)** (Table IV).

TABLE IV Physical and Analytical Data of the Synthesized Compounds

Compound No.	m.p (°C)	yield	Mol. Formul (Mol. Wt)	Elemental analyses % Required/Found			
				C	H	N	S
3	115–117	89	$C_{17}H_{14}N_4O_2S_2$	55.13	3.78	15.13	17.29
			(370)	55.50	3.50	15.40	17.50
4	270–272	86	$C_{19}H_{16}N_4O_3S_2$	55.33	3.88	13.59	15.53
			(412)	55.10	3.50	13.30	15.20
5	65–67	91	$C_{21}H_{18}N_4O_5S_2$	53.62	3.83	11.92	13.62
			(470)	53.90	3.50	12.20	13.40
6	182–184	79	$C_{21}H_{16}N_4O_4S_2$	55.75	3.54	12.39	14.16
			(452)	55.50	3.20	12.70	14.40
7	62–64	64	$C_{24}H_{17}N_4O_2S_2Cl$	58.48	3.45	11.37	12.99
			(492.5)	58.20	3.30	11.50	12.70
8	167–169	75	$C_{24}H_{19}N_5O_2S_3$	57.03	3.76	13.86	19.00
			(505)	57.30	3.50	13.60	19.30
9	145–147	71	$C_{19}H_{15}N_4O_3S_2Cl$	51.06	3.35	12.54	14.33
			(446.5)	51.30	3.60	12.80	14.60
10	>300	48	$C_{23}H_{20}N_4O_6S_4$	47.91	3.47	9.72	22.22
			(576)	48.20	3.20	9.40	22.40
11	260–262	42	$C_{21}H_{16}N_4O_4S_3$	52.06	3.30	11.57	19.83
			(484)	52.20	3.10	11.30	19.50
12	84–86	66	$C_{22}H_{14}N_6O_3S_2$	55.69	2.95	17.72	13.50
			(474)	55.40	2.70	17.50	13.30
13	>300	68	$C_{21}H_{17}N_5O_4S_2$	53.96	3.64	14.98	13.70
			(467)	53.70	3.40	14.70	13.50
14	>300	74	$C_{20}H_{15}N_5O_3S_3$	51.17	3.19	14.92	20.46
			(469)	51.30	3.40	15.20	20.20

Method (B)

A solution of **5** (0.01 mol) in dimethylformamide (20 mL) was refluxed for 14 hr. The reaction mixture was cooled and the obtained solid was recrystallized from dioxan to give **(6)** (Table IV).

2-[(4-{4-(4-chloro-benzylidene)-amino]-benzenesulfonyl}-phenyl-amino)-methylsulfanyl-methylene]-malononitrile (7)

A mixture of **3** (0.01 mol) and p-chlorobenzaldehyde (0.012 mol) in ethanol (30 ml) containing triethylamine (0.5 ml) was refluxed for 5 hr. The solid obtained was recrystallized from ethanol, to give **(7)** (Table IV).

1-{4-[4-(2,2-Dicyano-1-methylsulfanyl-vinylamino)-benzenesulfonyl]-phenyl}-3-phenyl-thiourea (8)

A solution of **3** (0.01 mol) and phenyl isothiocyanate (0.01 mol) in ethanol (30 mL) containing triethylamine (0.5 mL) was refluxed for 5 hr. The solid product was recrystallized from ethanol to give **(8)** (Table IV).

N-(4-(4-(2,2-dicyano-1-(methylthio)vinylamino) phenylsulfonyl)-phe-nyl)-2-chloroethane thioamide (9)

A solution of **3** (0.01 mol) in dimethylformamide (20 mL), chloroacetyl chloride (0.01 mol) was added dropwise, then stirred for 1 hr at room temperature and poured into ice water. The solid thus obtained was recrystallized from acetic acid to give **(9)** (Table IV).

3-Amino-4-({4-[4-(3,5-dioxo-thiomorpholin-4-yl)-benzenesulfonyl]-phenylamino}-methylsulfanyl-methylene)-5-imino- 4,5-dihydro-thio-phene-2-carboxylic acid (10)

A mixture of compound **9** (0.01 mol) and thioglycolic acid (0.01 mol) in pyridine (20 mL) was refluxed for 8 hr. The reaction mixture was filtered while hot to give **10**, while compound **11** was isolated from the filtered of the reaction mixture and recrystallized from ethanol to give **(10)** (Table IV).

2-({4-[4-(3-Cyano-2-imino-5-oxo-pyrrolidin-1-yl)-benzenesulfonyl]-phenylamino}-methylsulfanyl-methylene)-malononitrile (12)

A mixture of compound **9** (0.01 mol) and malononitrile (0.01 mol) in pipredine (10 mL) was refluxed for 24 hr. Coold and diluted with dil HCl. The precipitated solid was filtered and recrystallized from ethanol to give **(12)** (Table IV).

2-({4-[4-(2,6-Dioxo-piperazin-1-yl)-benzenesulfonyl]-phenylamino}-methylsulfanyl-methylene)-malononitrile (13)

A mixture of compound **9** (0.01 mol) and ethylglycinate hydrochloride (0.01 mol) in piperidine (10 ml) was refluxed for 8 hr, cooled, poured

into ice-HCl and filtered. The solid obtained was recrystallized from ethanol to give **(13)** (Table IV).

N-{4-[4-(2,2-Dicyano-1-methylsulfanyl-vinylamino-benzene-sulfonyl]-pheny}-2-isothiocyanatoacetamide (14)

A mixture of compound **9** (0.01 mol) and potassium thiocyanate (0.02 mol) in dimethylformamide (15 mL) was refluxed for 5 hr, cooled, and poured in to ice water. The solid obtained was recrystallized from dioxan to give **(14)** (Table IV).

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