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DRUG SYNTHESIS

SEMISYNTHSIS OF NOVEL SULFONAMIDES, THIOUREAS AND BIPHENYLSULFONES AS A NEW CLASS OF ANTICANCER AGENTS BY USING L-NOREPHEDRINE AS STRATEGIC STARTING MATERIAL

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Abstract: In continuation of our work on synthesis of novel anticancer agents, a new series of sulfonamides carrying a biologically active thiourea **3**, **4,** biphenylsulfones bearing thiourea **8**-**10** and oxazole thione **11** were designed and synthesized using L-norephedrine [phenylpropanolamine (PPA)] as strategic starting material. The synthesized compounds were evaluated *in vitro* for their anticancer activity against the human breast (MCF-7), human liver (HEPG2) and human colon (HCT116) cancer cell lines. Bisthiourea compound **8** is nearly as active as doxorubicin against (MCF-7 and HEPG2) cell lines with value (IC_{50} = 6.93 and 4.0 µg/mL). Compounds **3**, **4**, **9**-**11** exhibited a moderate activity compared with doxorubicin as reference drug.

Keywords: l-norephedrine, sulfonamides, thiourea, biphenylsulfones, anticancer activity

Cancer is continuing to be a major health problem in developing as well as undeveloped countries (1-5). The great cancer incidence worldwide increases the search for new, safer and efficient anticancer agents, aiming the prevention or the cure of this illness. In spite of all the efforts to combat cancer, the success of the treatment of certain types of tumors has shown little progress due to their aggressiveness and the mechanisms of malignant cell metastasis. Although many classes of drugs are being used for the treatment of cancer, the need for more potent selective antitumor agents is still not precluded. From literature survey it has been reported that sulfonamides possess manifold biological activities. Representatives of this class of pharmacological agents are widely used clinically for their antibacterial (6), hypoglycemic (7), diuretic (8), antimicrobial (9), anti-carbonic anhydrase (10) and anti-thyroid activities (11). Recently, sulfonamides have been reported to show substantial anticancer activity *in vitro* and *in vivo* (12-16). E7070 (**I**) and E7010 (**II**), are examples for anticancer sulfonamides in advanced clinical trials (17) (Fig. 1). Sulfone derivatives have been found to exhibit a wide variety of pharmacological activities (18-25). Also, diphenylsulfones and bisheterocyclic compounds are reported to have a broad spectrum of biological activities. Some are endowed with antitumor (26), or antifungal properties (27). On the other hand, some pyridine and isoquinoline derivatives have various biological properties such as antimicrobial (28) and anticancer (29-32) activities. Recent studies have proved the remarkable effect of dapsone on inhibiting cell growth in glioblastoma by acting as anti-VEGF and anti-angiogenic agent *via* depriving glioblastoma of neutrophil-mediated growth promoting effects (33). Allantadapsone **III** (Fig. 1), a dapsone derivative showed high anticancer activity through inhibition of arginine methyltranseferase (PRMT1), an enzyme which plays an important role in hormone dependant cancers. A series of acylated diarylsulfone derivatives were evaluated for the same activity and compound **IV** exihibited good activity as PRMT1 inhibitor (34).

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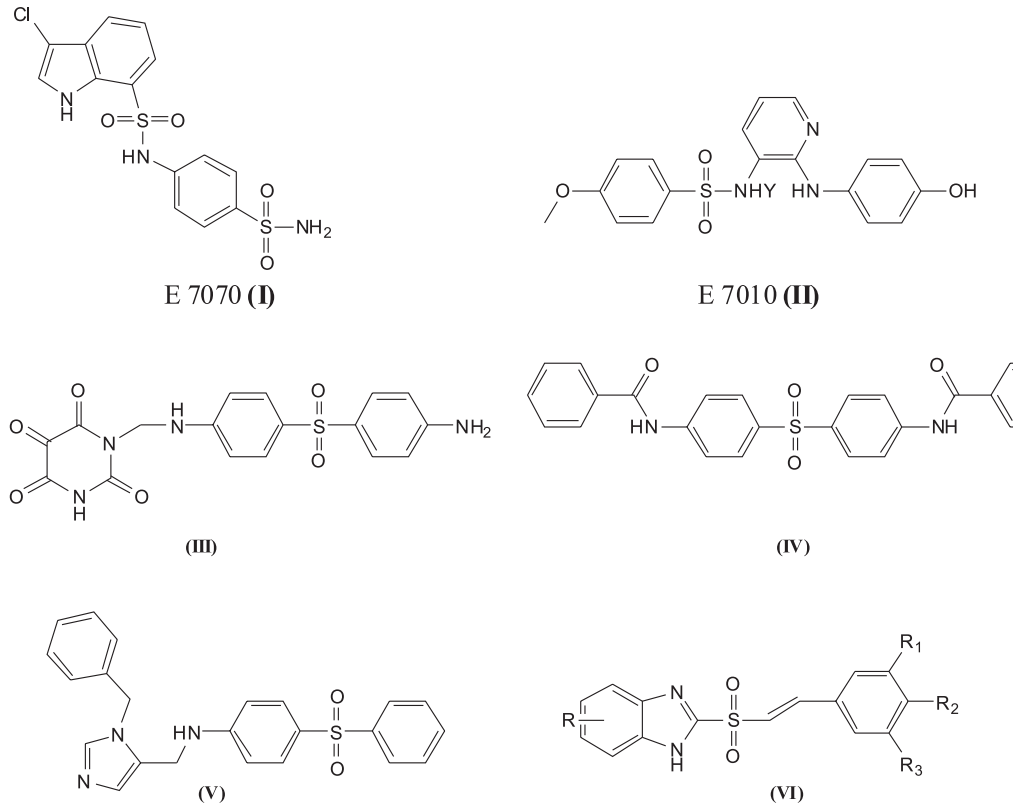


Figure 1. Sulfonamide and sulfone containing compounds in advanced clinical trials as anticancer agents

Some diarylsulfone derivatives bearing imidazole ring were evaluated for their anticancer activity through their action on inhibition of farnesyl-protein transferase (FTase), a zinc metalloenzyme which catalyzes the lipidation of 3,4-cysteine in the C-terminal tetrapeptide sequence. Compound **V** showed the lowest IC_{50} as FTase inhibitor (35). Some other styryl heterocyclic sulfone derivative **VI** (Fig. 1) was interesting as anticancer agent as they block the mitogen activated protein kinase (MAPK) cascade which phosphorylates a variety of proteins including several transcription factors, which translocate into the nucleus and activate gene transcription. Negative regulation of this pathway could arrest the cascade of these events and will inhibit the proliferation of cancer cells (36, 37). Based on all these findings and as a continuation of our search in the synthesis of some novel anticancer heterocyclic compounds (38-41), the aim of this investigation was to semisynthesize some novel analogues of sulfonamide, thiourea and biphenylsulfone derivatives hoping to obtain novel compounds with significant cytotoxic activity.

EXPERIMENTAL

Chemistry

Reagents were obtained from commercial suppliers and were used without purification. Melting points were determined in open capillary tubes using Thermosystem FP800 Mettler FP80 central processor supplied with FP81 MBC cell apparatus, and were uncorrected. Specific rotations were measured on a Jasco P-2000 polarimeter, using a one-decimeter tube. Elemental analyses (C, H, N) were performed on a Perkin Elmer 2400 Instrument (USA). All values were within ±0.4% of the theoretical values. Infrared (IR) spectra (KBr discs) were recorded on FT-IR spectrophotometer (Perkin Elmer) at the Research Center, College of Pharmacy, King Saud University, Saudi Arabia.^{1}H and ^{13}C NMR spectra were recorded on a UltraShield Plus 500MHz (Bruker) (NMR Unite, College of Pharmacy, Salman Bin Abdulaziz University) spectrometer operating at 500 MHz for proton and 125 MHz for carbon, respectively. The chemical shift values are reported in δ (ppm) rela-

tive to the residual solvent peak, the coupling constants (*J*) are reported in Hertz (Hz). 2D-NMR experiments (COSY, NOESY, HSQC and HMBC) were obtained using standard Bruker programs. Mass spectra were run using a HP Model MS-5988 (Hewlett Packard).

4-[3-(1-Hydroxy-1-phenylpropan-2-yl)thioureido] benzenesulfonamide (3)

A mixture of PPA (1.51 g, 0.0l mol) and **2** (2.14 g, .0.01 mol) in chloroform (20 mL) containing a catalytic amount of triethylamine was stirred at room temperature for 5 min. The reaction mixture gave **3**; yield 98%, m.p. 188.5°C, IR (KBr, cm^{-1}): OH (3460), NH_2 and NH (3380, 3291, 3180), SO_2 (1381, 1156) and C=S (1271). ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm): 0.94 (d, *J* = 5.5 Hz, 3H), 4.58 (bs, 1H, C<u>H</u>-NH), 4.94 (bs, 1H, C<u>H</u>-OH), 5.63 (bs, 1H, CH-O<u>H</u>). 7.27-7.74 (m, 11H, 9 arom., SO_2NH_2), 8.05 (d, *J* = 7.5 Hz, 1H, CH-N<u>H</u> l-norephedrine), 9.92 (s, 1H, N<u>H</u> of sufonamide); ^{13}C-NMR (125 MHz, DMSO-d_6, δ, ppm): 12.40, 54.57, 72.96, 121.26- 127.97 (9), 138.36, 142.68, 143.16, 179.18. EIMS m/z (%): 366 (11.2, M^+ + 1), 365 (9.5, M^+), 63 (100). Analysis: calcd. for $C_{16}H_{19}N_3O_3S_2$ (365): C, 52.58; H, 5.24; N, 11.50; S, 17.55%; found: C, 52.31; H, 5.49; N, 11.29; S, 17.77%.

1-Phenyl-2-[3-(4-sulfamoylphenyl)thioureido] propyl-2-chloroacetate (4)

A mixture of **3** (0.365 g, 0.00l mol) and chloroacetyl chloride (0.0112 g, 0.00l mol) in chloroform (10 mL) containing 3 drops of triethylamine was stirred at room temperature for 1 h. The obtained products was purified by column chromatography (2 mm i.d., 30 g) eluted with chloroform and polarity was increased with methanol in a gradient system. Fractions of 50 mL were collected, screened by TLC and similar fractions were pooled. Fractions 9-16 afforded compound **4**. Yield: 88%, m.p. 223.8°C, IR (KBr, cm^{-1}): NH_2, NH (3405, 3330, 3205), C=O (1694), SO_2 (1374, 1161) and C-Cl (753). ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm): 0.98 (bs, 3H), 3.80 (s, 2H), 4.32 (d, *J* = 6 Hz, 1H, C<u>H</u>-NH), 5.04 (d, *J* = 6.8 Hz, 1H, C<u>H</u>-OH), 7.25-7.77 (m, 11H, 9 arom., SO_2NH_2), 8.05 (d, *J* = 7 Hz, 1H, CH-N<u>H</u> l-norephedrine), 10.49 (s, 1H, N<u>H</u> of sufonamide); ^{13}C-NMR (125 MHz, DMSO-d_6, δ, ppm): 17.55, 34.04, 54.98, 65.87, 118.63-128.50 (9), 138.36, 138.49, 141.85, 164.79, 167.38. EIMS m/z (%): 442 (29.4, M^+), 81 (100). Analysis: calcd. for $C_{18}H_{20}ClN_3O_4S_2$ (442): C, 48.92; H, 4.56; N, 9.51; S, 14.51%; found: C, 48.68; H, 4.29; N, 9.87; S, 14.31%.

1,1'-(4,4'-Sulfonylbis(4,1-phenylene)-bis(3-(1-hydroxy-1-phenylpropan-2-yl)thiourea) (8)

A mixture of biphenylsulfone isothiocyanate **7** (0.332 g, 0.001 mol) and PPA (0.302 g, 0.002 mol) in 10 mL of chloroform containing 3 drops of triethylamine was stirred at room temperature for 2 h. The reaction mixture was crystallized from MeOH to afford compound **8**. Yield: 93%, m.p. 202.3°C, IR (KBr, cm^{-1}): OH (3417), NH (3336, 3291), CH aromatic (3097), CH aliphatic (2954, 2863), SO_2 (1383, 1161), C=S (1272). ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm): 0.94 (d, *J* = 6 Hz, 3H), 4.56 (bs, 1H, C<u>H</u>-NH), 4.93 (bs, 1H, C<u>H</u>-OH), 5.62 (s, 1H, CH-O<u>H</u>), 7.26-8.11 (m, 9H, arom.), 8.12 (d, *J* = 7.5 Hz, 1H, CH-N<u>H</u> l-norephedrine), 10.02 (s, 1H, N<u>H</u> of dapsone); ^{13}C-NMR (125 MHz, DMSO-d_6, δ, ppm): 12.31, 55.03, 72.86, 121.15-127.97 (9), 135.05, 143.09, 144.34, 178.99. EIMS m/z (%): 635 (17.9, M^+), 182 (100). Analysis: calcd. for $C_{32}H_{34}N_4O_4S_3$ (635): C, 60.54; H, 5.40; N, 8.83; S, 15.15%; found: C, 60.18; H, 5.64; N, 8.58; S, 15.36%.

Synthesis of compounds (8-11)

A mixture of biphenylsulfone isothiocyanate **7** (0.332 g, 0.001 mol) and PPA (0.302 g, 0.002 mol) in 10 mL of dioxane containing 3 drops of triethylamine was heated under reflux for 2 h. The reaction mixture was cooled and purified by column chromatography (3 mm i.d., 60 g) using 10% acetone in $CHCl_3$ with few drops of acetic acid as mobile phase. The polarity was increased by increasing the proportion of acetone in a gradient system. Fractions 50 mL each were collected, screened by TLC and similar fractions were pooled. Fractions 2-6 afforded 22 mg of **11** after crystallization from MeOH, 5.73% yield. Fractions 9-11 were repurified on RP 18 column (1 mm i.d., 30 g) eluted with 25% H_2O in MeOH to afford 51 mg of **10**, 12.36% yield. Fractions 13-22 (450 mg) eluted with 20% acetone in $CHCl_3$ were subjected to CPTLC (4 mm silica gel GF_{254} disk, solvent: $CHCl_3$-acetone-HOAc; 85 : 15 : 0.1, v/v/v) to afford 366 mg of **8**, 67.78% yield and 63 mg of **9**, 13.59% yield.

The oxazolidine-2-thione derivative **11** was also obtained *via* reaction of PPA (0.151 g, 0.001 mol) and CS_2 (0.158 g, 0.002 mol) in dry pyridine (10 mL) under reflux for 30 min. The reaction mixture was dried under vacuum to give **11**.

O-1-amino-1-phenylpropan-2-yl-4-(4-(3-(1-hydroxy-1-phenylpropan-2-yl)-thioureido)phenylsulfonyl) phenylcarbamothioate (9)

M.p. 138.1°C, IR (KBr, cm^{-1}): OH (3407), NH (3386, 3310), CH aromatic (3100), CH aliphatic

(2922, 2836), SO_2 (1376, 1154), C=S (1238). ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm): 0.68 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6 Hz, 3H), 4.41 (bs, 1H, CH-NH), 4.55 (bs, 1H, CH-NH), 4.92 (bs, 1H, CH-OH), 5.63 (bs, 1H, CH-OH), 5.73 (d, *J* = 8.5 Hz, 1H, CH-O-), 7.26-8.11 (m, 18H, arom.), 7.92 (d, *J* = 7.5 Hz, 2H, CH-NH_2 l-norephedrine), 8.12 (d, *J* = 7.5 Hz, 1H, CH-NH l-norephedrine), 9.96 (s, 1H, NH of dapsone), 10.04 (s, 1H, NH of dapsone); ^{13}C-NMR (125 MHz, DMSO-d_6, δ, ppm): 12.29, 17.86, 55.02, 59.72, 72.86, 81.82, 121.14-128.40 (22), 135.05, 143.09, 144.34, 178.99. EIMS m/z (%): 635 (11.74, M^+), 194 (100). Analysis: calcd. for $C_{32}H_{34}N_4O_4S_3$ (635): C, 60.54; H, 5.40; N, 8.83; S, 15.15%; found: C, 60.79; H, 5.19; N, 9.12; S, 14.86%.

1-[4-(4-Aminophenylsulfonyl)phenyl]-3-(1-hydroxy-1-phenylpropan-2-yl) thiourea (10)

M.p. 217.7°C, IR (KBr, cm^{-1}): OH (3398), NH_2, NH (3369, 3312, 3262), CH aromatic (3055), CH aliphatic (2972, 2844), SO_2 (1368, 1165), C=S (1212). ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm): 0.93 (d, *J* = 6 Hz, 3H), 4.54 (bs, 1H, CH-NH), 4.93 (bs, 1H, CH-OH), 5.62 (bs, 1H, CH-OH), 6.14 (s, 2H, NH_2), 6.62 (d, *J* = 7 Hz, 2H), 7.26-7.42 (m, 5H, arom.), 7.54 (d, *J* = 7 Hz, 2H,), 7.71-7.75 (m, 4H, arom.), 8.12 (d, *J* = 7.5 Hz, 1H, CH-NH l-norephedrine), 9.97 (s,1H, NH of dapsone); ^{13}C-NMR (125 MHz, DMSO-d_6, δ, ppm): 12.32, 55.01, 73.83, 112.95-129.21 (14), 136.21, 136.95, 143.09, 143.54, 178.98. EIMS m/z (%): 442 (13.63, M^+), 149 (100). Analysis: calcd. for $C_{22}H_{23}N_3O_3S_2$ (442): C, 59.84; H, 5.25; N, 9.52; S, 14.52%; found: C, 59.54; H, 5.51; N, 9.24; S, 14.19%.

4-Methyl-5-phenyloxazolidine-2-thione (11)

M.p. as reported (42), ^{1}H-NMR (500 MHz, DMSO-d_6, δ, ppm): 0.66 (d, *J* = 6.5 Hz, 3H), 4.42 (m, 1H, CH-NH), 6.00 (d, *J* = 9 Hz, 1H, CH-O), 7.26-7.46 (m, 5H, arom.), 10.19 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6, δ, ppm): 16.05, 54.87, 84.85, 126.12-128.41 (5), 134.86, 187.46.

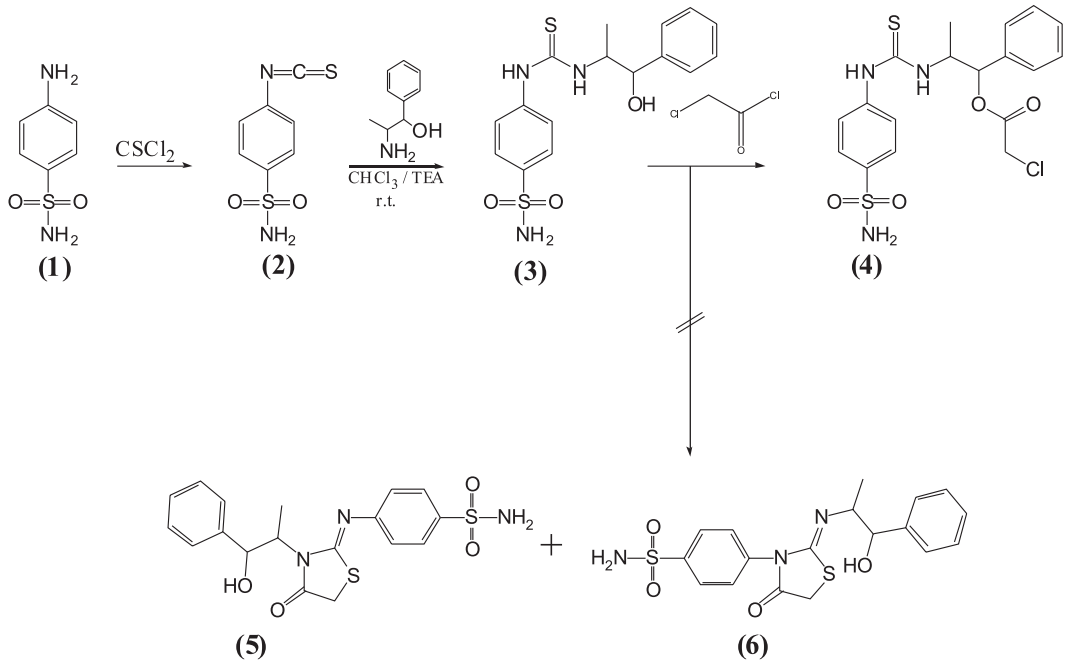
***In vitro* antitumor activity**

The cytotoxic activity was measured *in vitro* for the newly synthesized compounds using the Sulforhodamine-B stain (SRB) assay using the method of Skehan et al. (43). The *in vitro* anticancer screening was done at the Pharmacology Unit, the National Cancer Institute, Cairo University. Cells were plated in 96-multiwall microtiter plate (104 cells/well) for 24 h before treatment with the compound(s) to allow the attachment of cells to the wall of the plate. Test compounds were dissolved in DMSO and diluted with saline to the appropriate volume. Different concentrations of the compound under test (5, 12.5, 25 and 50 µg/mL) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37°C and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed, and stained for 30 min with 0.4% (w/v) SRB dissolved in 1% acetic acid. The excess of unbound dye was removed by four washes with 1% acetic acid and attached stain was recovered with Tris-EDTA buffer. Color intensity was measured in an enzyme-linked immunosorbent assay ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve for breast tumor cell line after the specified time (43). The molar concentration required for 50% inhibition of cell viability (IC_{50}) was calculated and the results are given in Table 1. The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of breast cancer cell line (MCF-7), (HepG2) and (HCT 116).

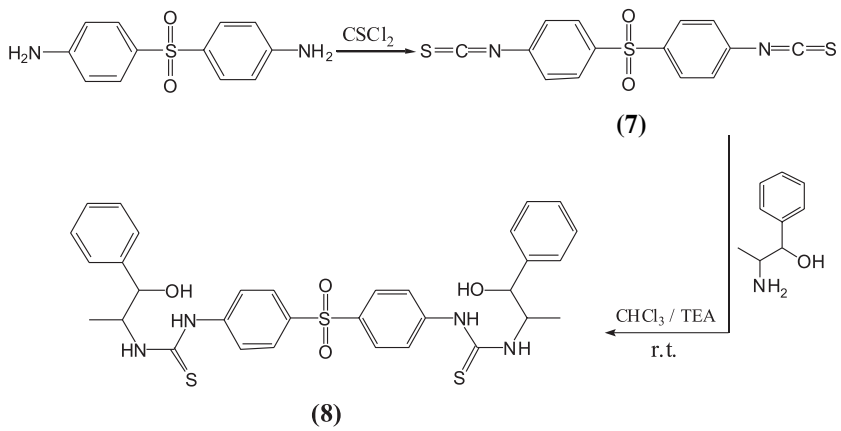
Table 1. *In vitro* anticancer screening of the newly synthesized compounds against human breast (MCF-7), liver (HEPG2), and colon (HCT 116) cancer cell lines.

Comp. No.	IC_{50} (µg/mL)[a]		
	MCF-7	HEPG2	HCT116
Doxorubicin	5.40	2.97	5.26
3	15.2	22.0	19.9
4	17.1	15.2	16.7
8	6.93	4.0	11.5
9	11.2	14.3	14.4
10	17.0	14.3	14.4
11	18.7	11.3	17.8

[a] IC_{50} value: Concentration causing 50% inhibition of cell viability



Scheme 1. Formation of compound **4**



Scheme 2. Formation of compound **8**

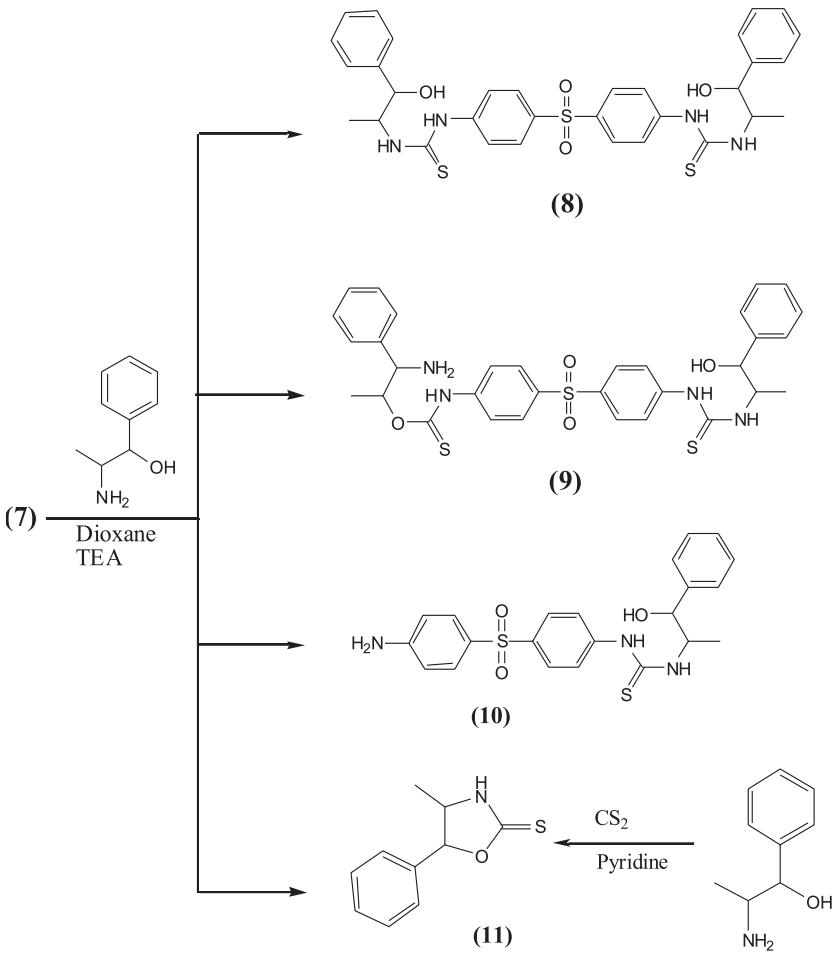
The response parameter calculated was IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability.

RESULTS AND DISCUSSION

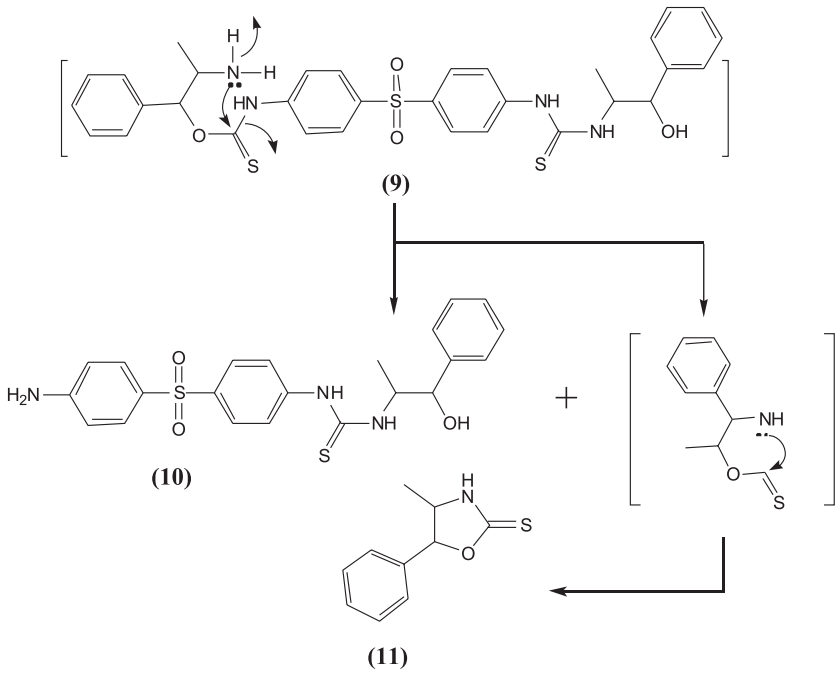
Chemistry

This study was carried out, hoping that a group of a newly semisynthesized compounds might exhibit significant cytotoxic activity; l-norephedrine (PPA) could be a strategic intermediate for the semisynthesis of various heterocyclic systems. The number of publications on the semisynthesis and reactivity of PPA is very limited (24). This prompted the authors to undertake the semisynthesis of the corresponding thiourea **3** from the reaction of sulfonamide isothiocyanate **2** with PPA. Since PPA contains two nucleophiles: nitrogen and oxygen, it was expected to react with isothiocyanate derivatives to furnish a series of heterocyclic systems containing a

biologically active sulfonamide or biphenylsulfone moieties, which are known for their potential cytotoxic activity. The sequence of reactions leading to the formation of the target compounds is depicted in Schemes 1-4. Optical rotation of the products indicated that they retain the orientation of PPA. The behavior of PPA towards isothiocyanate was investigated .Thus, interaction of sulfanilamide isothiocyanate **2** with PPA furnish the corresponding thiourea derivative **3**, which upon reaction with chloroacetyl chloride in chloroform containing a catalytic amount of triethylamine at room temperature yielded the unexpected thioureido-propyl 2-chloroacetate derivative **4** (Scheme 1). The expected thiazolidinones **5** and **6** were eliminated from consideration on the basis of elemental analysis ^{1}H-, ^{13}C-NMR and mass spectral data. The IR spectrum of **3** revealed the absence of NCS band and the presence of characteristic bands for NH_2, NH, OH, SO_2 and C=S. ^{1}H-NMR of **3** showed NH signal at δ_H 9.92 ppm assigned for S=C-NH. On the other hand, the NH_2 of PPA was replaced by NH at δ_H 8.54 ppm (bd, J = 7 Hz) as proved by COSY and HSQC experiments. The remaining aliphatic signals were assigned to PPA moiety based on DEPT, COSY, HSQC and HMBC experiments. The region between δ_H 7.27-7.74 ppm showed signal integrated for 11 protons including 9 aromatic protons in addition to PPA protons of SO_2NH_2. Comparing the ^{13}C-NMR of **3** with PPA, additional 6 aromatic resonances were observed as well as a signal at δ_C 179.18 ppm diagnostic for C=S group. The structure of **4** was confirmed on the basis of elemental analysis, IR, ^{1}H-, ^{13}C-NMR and mass spectral data. IR spectrum of **4** showed the presence of characteristic bands for NH_2, NH, C=O, SO_2 and C-Cl. The main difference in the NMR data of **4** compared with that of **3** is the new signals for chloroacetyl moiety at δ_H



Scheme 3. Formation of compounds **9-11**



Scheme 4. Postulated formation of compounds **10** and **11**

3.80 ppm (2H) correlated with δ_C 34.04 ppm (CH_2Cl) in an HSQC experiment and the δ_C 167.38 ppm (C=O). The disappearance of the OH proton, the shift of the CH-O- group signal to δ_H 5.04 ppm (d, J = 6.8 Hz), δ_C 65.87 ppm clearly indicated the acylation of the OH group. When biphenylsulfone isothiocyanate **7** was allowed to react with PPA in chloroform in the presence of triethylamine as catalyst at room temperature, the corresponding 1,1'-(4,4'-sulfonylbis(4,1-phenylene)-bis(3-(1-hydroxy-1-phenylpropan-2-yl)thiourea) **8** was obtained in good yield.

However, when the reaction was performed under reflux in dioxane containing triethylamine, a mixture of compounds **8**-**11** were obtained and isolated by column chromatography. The structure of compounds **8**-**11** was established on the basis of microanalytical and spectral data. IR spectrum of **8** exhibited the presence of bands for OH, NH, CH aromatic, CH aliphatic, SO_2 and C=S groups. ^{13}C-NMR spectrum of **8** showed in addition to the overlapped aromatic carbons four signals at δ_C 12.31, 55.03, 72.86 and 178.99 ppm assigned for the PPA moiety and C=S group as indicated from DEPT, COSY, HSQC and HMBC experiments. The integration of the amine proton of this moiety indicated one proton because of the consumption of the second proton in the reaction with isothiocyanate group of compound **7**. Mass spectrum of compound **8** revealed a molecular ion peak m/z 635 (M^+, 17.9%), with a base peak at 182 (100%) consistent with the molecular formula $C_{32}H_{34}N_4O_4S_3$ indicating the dimeric nature of compound **8** where a molecule of PPA coupled to each isothiocyanate group. The ^{1}H-, ^{13}C-NMR and DEPT 1-D spectra and COSY, HSQC and HMBC 2-D spectra of **9** showed two sets of signals for PPA moieties. One set is closely related to that of **8**. However, in the other set, a clear shift in the CH-O- signals was observed (δ_H 5.73 ppm, d, J = 8.5 Hz, δ_C 81.82 ppm) indicating that the reaction involved the OH group rather than NH_2. Mass spectrum of **9** exhibited a molecular ion peak m/z at 635 [M^+], (11.74%), with a base peak at 194 (100%) fully supporting the above structure. The yield of compound **9** was much less than that of the major reaction product **8**. This can be explained by the relative instability of the carbamothioate moiety in comparison with the thioureido group. Consequently, dissociation of **9** takes place leading to the formation of **10** and **11**. The mechanism of this dissociation involved the attack of the lone pair of electron of the PPA nitrogen atom on the highly positive carbon atom of the thione moiety leading to the cleavage of the thioamide bond and formation of compounds **10**. The released PPA thioate intermediate undergoes cyclization to form the oxazolidine-2-

thione derivative **11** (42) (Scheme 4). IR spectrum of **10** showed characteristic bands for OH, NH, NH_2, CH aromatic, CH aliphatic, SO_2 and C=S groups. In both ^{1}H-, ^{13}C-NMR DEPT, COSY and HSQC spectra of **10**, the signals of the PPA moiety are closely related to that of **8**. A key signal of an NH_2 group at δ_H 6.14 ppm indicated that one side of biphenylsulfone is bearing a primary amine after the release of the PPA moiety. The chemical shift of signals of the oxazolidine-2-thione ring of **11** were: δ_H 4.42 ppm (m), δ_C 54.87 ppm (CH-N), δ_H 6.00 ppm (d, J = 9 Hz), δ_C 84.85 ppm (CH-O), δ_H 10.19 ppm (s, NH), δ_C 187.46 ppm (C=S). Assignments were performed based on COSY and HSQC experiments.

***In vitro* cytotoxic activity**

The newly synthesized compounds were evaluated for their *in vitro* cytotoxic activity against human breast (MCF-7), liver (HepG2) and colon (HCT 116) cancer cell lines. The clinically used drug doxorubicin, one of the most effective anticancer agents, was used as the reference drug in the current study. The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of the three tested human cell lines. The data were expressed as the IC_{50} values, which corresponds to the concentration required for 50% inhibition of cell lines viability. The obtained IC_{50} values are presented in Table 1 indicating the *in vitro* anticancer activity of the tested compounds compared to the reference drug. It was found that, in the negative control, solvent has no effect on the cells as the surviving fraction is 1.00. The bisbiphenylsulfone **8** carrying the biologically active thiourea moiety with IC_{50} values (6.93, 4.0 µg/mL) is nearly as active as doxorubicin with IC_{50} values (5.40, 2.97 µg/mL) as reference drug against both breast and liver cancer cell lines. On the other hand, compound **8** exhibited a moderate activity with IC_{50} value (11.50 µg/mL) against colon cancer cell line compared to doxorubicin. Compounds **3**, **4**, **9**, **10** and **11** showed weaker activity than the positive control. In an attempt to correlate the activity of **8** with its unique structural features among the other tested compounds it was noticed that: two free hydroxyl groups, two thiourea moieties and the molecular symmetry are major features in **8** rather than all the other members of the tested compounds. More *in vitro* and *in vivo* biological evaluation are required in order to explore the possibility of using this promising compound in practice.

CONCLUSION

The objective of the present study was to semi-synthesize and investigate the anticancer activity of some novel sulfonamide and bis-biphenylsulfone carrying the biologically active thiourea moieties. Compounds **8** is nearly as active as doxorubicin as reference drug against breast and liver cancer cell line, while it was exhibited a moderate activity against colon cancer cell line. In addition, compounds **3**, **4**, **9**, **10** and **11** revealed weak activity.

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