Dapson in Heterocyclic Chemistry Part VI: Synthesis and Molecular Docking of Some Novel Sulfonebiscompounds of Expected Anticancer Activity

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Key words
- thiazole
- acrylamide
- thiophene
- benzothiophene
- anticancer activity

Abstract

To discover new bioactive lead compounds for medicinal purposes, herein, sulfone biscompounds bearing dihydrothiazoles (3–9, 14, 15), acrylamide (11), thiazolidinones (12, 13, 20), thiophenes (16, 17) and benzothiophene (19) were prepared and tested for their anticancer activity. The structures of the products were confirmed from elemental analysis as well as spectral data. All the synthesized compounds showed remarkable anticancer activity against human breast cancer cell line especially, compound (3) with IC_{50} value 23.02 µM which was better than that of Doxorubicin by three folds. In order to elucidate the mechanism of action of their cytotoxic activity molecular docking on the active sites of farnesyl transferase and arginine methyl transferase was performed for all synthesized compounds and good results were obtained.

received 26.06.2012
accepted 23.07.2012

Bibliography
DOI http://dx.doi.org/10.1055/s-0032-1323660
Published online: September 21, 2012
Arzneimittelforschung 2012; 62: 497–507

ISSN 0004-4172

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Introduction

Diarylsulfones is a class of compounds which have received an interest as biologically active agents especially in anticancer and antiviral activities [1–6]. The diarylsulfone derivative I showed good activity as anti HIV-1compared to Nevirapine [7,8] (**Fig. 1**). Moreover, Allantodaopsone II, a diarylsulfone derivative exhibited a remarkable anticancer effect as arginine methyl transferase inhibitor [9] (**Fig. 1**). In addition, thiophene and thiazole derivatives are known to possess interesting biological properties that showed anticancer [10–12], and antimicrobial activities [13,14].

Thiazole derivatives constituting sulfone have shown activity as anticancer moiety [15,16]. Compound III showed a good α-pyrolyl hydroxylase inhibiton with IC_{50} value 0.072 µM [15] while, compound IV exhibited its activity through p13 kinase p11α inhibition [16] (**Fig. 1**). In addition, the chemistry of acrylamide, acetamide, thiophene and benzothiophene system has received an increasing interest because of its biological significance. Many derivatives of this system showed anti- inflammatory, antibacterial [17], antifungal [18] and anticancer activities [19–23]. On the other hand, cyanoacetamides are highly reactive compounds. The carbonyl and the cyano functions of these compounds are suitably situated to enable reaction with common reagents to form a variety of heterocyclic compounds. Also, the active methylene of cyanoacetamide can take part in a variety of condensation and substitution reactions. Moreover, cyanoacetamides and their related heterocyclic derivatives have generated great attention due to their interesting biological, therapeutic value and pharmaceutical activities such as anticancer agents [24].

Therefore, it was aimed in the present investigation and as a continuation to a previous work [25–28] to synthesize and characterize a new series of biologically active sulfone derivatives carrying the corresponding dihydrothiazole, acrylamide, acetamide, thiophene and benzothiophene derivative to evaluate their anticancer activity.

Materials and Methods

Chemistry

General methods

All chemicals used in this study were purchased from Aldrich and Fluka. Melting points (°C, uncorrected) were determined in open capillaries on a Gallenkemp melting point apparatus (Sanyo Gallenkemp, Southborough, UK) and were uncorrected. Precoated silica gel plates (silica gel 0.25 mm, 60 G F254; Merck, Germany) were used for thin layer chromatography, dichloromethane/

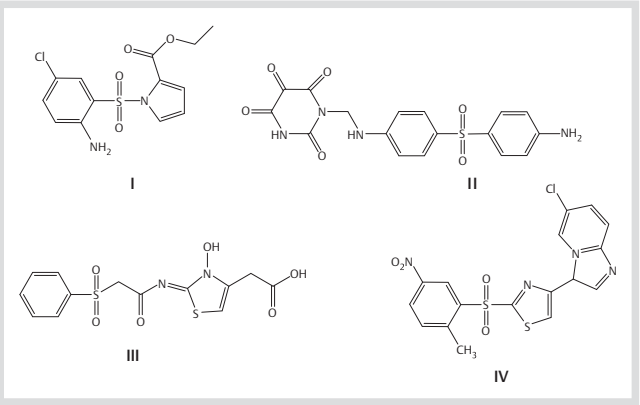

Fig. 1 Biologically active diarylsulfone derivatives.

methanol (9.5:0.5) mixture was used as a developing solvent system and the spots were visualized by ultraviolet light and/or iodine. Infra red spectra were recorded in KBr discs using IR-470 Shimadzu spectrometer (Shimadzu, Tokyo, Japan). NMR spectra (in DMSO-d6) were recorded on Bruker AC-300 Ultra Shield NMR spectrometer (Bruker, Flawil, Switzerland, δ ppm) at 300 MHz using TMS as internal Standard and peak multiplicities are designed as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Elemental analyses were performed on Carlo Erba 1108 Elemental Analyzer (Heraeus, Hanau, Germany). All analyses were done in Medicinal, Aromatic and Poisonous Plants Research Center (MAPPRC), College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

Synthesis

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-cyanoacetamid) (Compound 2): A mixture of Dapson 1 (2.48 g, 0.01 mol.) was fused with excess ethyl cyanoacetate (10 mL) at 220 °C in an oil bath for 2 h. Excess ethyl cyanoacetate was evaporated under vacuum. The solid product remained was triturated with diethylether (100 mL) then filtered. The solid obtained was crystallized from ethanol to give 2.

General procedure for synthesis of compounds (3–9): To a suspension of compound 2 (3.82 g, 0.01 mol.) in ethanol (50 mL), finally divided sulfur (0.64 g, 0.02 mol.), triethylamine (5 drops), isothiocyanate derivatives (0.02 mol.) and dimethylformamide (10 mL) were added. The reaction mixture was stirred at 60 °C for 6 h, then left to cool at room temperature. The separated products were filtered, washed with ethanol, dried and crystallized from dioxane to give 3–9, respectively.

(2E,2′E)-N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-cyano-3-mercapto-3-(phenylamino)acrylamide) (Compound 11): To a cold suspension of finally divided KOH (1.12 g, 0.02 mol.) in dry DMF (20 mL), the cyanoacetamide derivative 2 (3.82 g, 0.01 mol.), followed by phenyl isothiocyanate (2.7 g, 0.02 mol.), were added. The mixture was stirred at room temperature over night then poured into ice-water and acidified with 0.1 N HCl to a pH 3–4. The resulting precipitate was filtered off, dried and crystallized from aqueous ethanol to give compound 11.

(2E,2′E)-N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)acetamide) (Compound 12): To a cold suspension of finally divided KOH (1.12 g, 0.02 mol.) in dry DMF (50 mL), the cyanoacetamide derivative 2 (3.82 g, 0.01 mol.), followed by phenyl isothiocyanate (2.7 g, 0.02 mol.), were added. The mixture was stirred at room temperature for 12 h, then cooled again to 0 °C, treated with chloroacetyl chloride (2.26 g, 0.02 mol.), and left to stand at room temperature for 24 h. The reaction mixture was poured into ice water. The obtained solid was crystallized from DMF/EtOH to give compound 12.

General procedure for synthesis of compounds (13–15): To compound 11 (6.53 g, 0.01 mol.) in DMF (30 mL) and ethyl chloroacetate (1.45 g, 0.02 mol.) or chloroacetone (1.84 g, 0.02 mol.) or phenacyl chloride (3.08 g, 0.02 mol.) was added. The reaction mixture was heated under reflux for 6 h, then cooled and neutralized with saturated sodium acetate solution. The resulting precipitate was filtered off, dried and crystallized from dioxane to give compound 13–15, respectively.

General procedure for synthesis of compounds (16 and 17): To compound 11 (6.53 g, 0.01 mol.) in DMF (30 mL), chloroacetone (1.84 g, 0.02 mol.) or phenacyl chloride (3.08 g, 0.02 mol.) and triethylamine (0.5 mL) were added. The reaction mixture was refluxed for 9 h, then cooled and neutralized with saturated sodium acetate solution. The solid obtained was crystallized from dioxane to give 16 and 17, respectively.

(4,4′-sulfonylbis(4,1-phenylene))bis(2-amino-4,5,6,7-tetrahydrobenzo [b]thiophene-3-carboxamide) (Compound 19): To compound 2 (3.82 g, 0.01 mol.) in absolute ethanol (50 mL), morpholine (1.74 g, 0.02 mol.), cyclohexanone (1.96 g, 0.02 mol.), and sulfur (0.64 g, 0.02 mol.) were added. The reaction mixture was refluxed for 6 h. The obtained solid was crystallized from dioxane to give 19.

(2E,2′E)-N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-(4-oxothiazolidin-2-ylidene)acetamide) (Compound 20): A mixture of compound 2 (3.82 g, 0.01 mol.) and 2-sulfanylacetic acid (1.84 g, 0.02 mol.) in acetic acid (50 mL) was refluxed for 12 h. The obtained solid was crystallized from ethanol to give 20.

Molecular docking

All the molecular modeling studies were carried out on an Intel Pentium 1.6 GHz processor, 512 MB memory with Windows XP operating system using Molecular Operating Environment (MOE, 10.2008) software. All the minimizations were performed with MOE until a RMSD gradient of 0.05 kcal $mol^{-1}A^{\circ-1}$ with MMFF94X forcefield and the partial charges were automatically calculated. The X-ray crystallographic structure of franesyl transferase and arginine methyl transferase (PRMT1) complexes with their ligands (PDB ID: 3E3O, 3Q7E) were obtained from the protein data bank. The enzymes were prepared for docking studies where: (i) Ligand molecule was removed from the enzyme active site. (ii) Hydrogen atoms were added to the structure with their standard geometry. (iii) MOE Alpha Site Finder was used for the active sites search in the enzyme structure and dummy atoms were created from the obtained alpha spheres. (iv) The obtained model was then used in predicting the ligand enzymes interactions at the active site.

Biological screening

In vitro antitumor activity

Human tumor breast cell line (MCF7) was used in this study. The cytotoxic activity was measured in vitro for the newly synthe-

sized compounds using the Sulfo-Rhodamine-B stain (SRB) assay using the method of Skehan et al. [29]. The in vitro anticancer screening was done by the pharmacology unit at the National Cancer Institute, Cairo University.

Cells were plated in 96-multiwell plate (104 cells/well) for 24 h before treatment with the compound(s) to allow attachment of cell to the wall of the plate. Test compounds were dissolved in dimethylsulfoxide. Different concentrations of the compound under test (10, 25, 50, and 100 µM) were added to the cell monolayer. Triplicate wells were prepared for each individual concentration. Monolayer cells were incubated with the compound(s) 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% (wt/vol) SRB dissolved in 1% acetic acid. Excess unbound dye was removed by 4 washes with 1% acetic acid and attached stain was recovered with Trise-EDTA buffer. Color intensity was measured in an 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. The molar concentration required for 50% inhibition of cell viability (IC_{50}) was calculated and compared to the reference drug Doxorubicin (CAS, 25316-40-9). The surviving fractions were expressed as means ± standard error.

Results

Chemistry

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-cyanoacetamid) (Compound 2): Yield 92%, m.p. 137.5 °C. IR: $\upsilon_{max.}$/cm^{-1} 3448, 3363 (2NH), 3062 (CH arom.), 2960, 2931 (CH aliph.), 2256 (C≡N), 1701 (2 C=O),1342, 1180 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 4.0 (s, 4H, $2CH_2$), 7.4–7.9 (m, 8H, Ar-H), 10.7 (s, 2H, 2NH exchangeable). ^{13}C-NMR (DMSO-d_6): 24.4(2), 115.6(2), 119.2(2), 119.3(2), 128.1(2), 129.2(2), 137.8(2), 142.7(2), 162.2(2). Anal. Calcd. for $C_{18}H_{14}N_4O_4S$ (382.39): C, 56.54; H, 3.69; N, 14.65. Found: C, 56.81; H, 3.84; N, 14.29.

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxamide) (Compound 3): Yield 81%, m.p. 130 °C. IR:$\upsilon_{max.}$/cm^{-1} 3448, 3320, 3260 (NH, NH_2), 1662 (2 C=O),1290 (2 C=S), 1393, 1177 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 6.9 (s, 4H, $2NH_2$, exch.), 7.0–7.9 (m, 18H, Ar-H), 8.5 (s, 2H, 2NH, exch.). *Anal.Calcd*. for $C_{32}H_{24}N_6O_4S_5$ (716.90): C, 53.61; H, 3.37; N, 11.72. Found: C, 53.82; H, 3.23; N, 12.09.

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(4-amino-2-thioxo-3-p-tolyl-2,3-dihydrothiazole-5-carboxamide) (Compound 4): Yield 76%, m.p. 105.8 °C. IR:$\upsilon_{max.}$/cm^{-1} 3410, 3375, 3232 (NH, NH_2), 3070 (CH arom.), 2930, 2866 (CH aliph.), 1654 (2 C=O), 1285 (2 C=S), 1319, 1199 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 2.3 (s, 6H, 2 CH_3), 4.5 (s, 4H, $2NH_2$, exch.), 6.6–7.9 (m, 16H, Ar-H), 10.9 (s, 2H, 2 NH, exch.). ^{13}C-NMR (DMSO-d_6): 20.4 (2), 67.0 (2), 123.0 (4), 126.7 (4), 128.2 (4), 129.6 (4), 130.1 (2), 133.7 (2), 135.2 (2), 142.1 (2), 154.8 (2), 162.2 (2), 186.9 (2). *Anal.Calcd.* for $C_{34}H_{28}N_6O_4S_5$ (744.95): C, 54.82; H, 3.79; N, 11.28. Found: C, 55.10; H, 3.55; N, 11.03.

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(4-amino-3-(4-methoxyphenyl)-2-thioxo-2,3-dihydrothiazole-5-carboxamide) (Compound 5): Yield 86%, m.p. 217.7 °C. IR:$\upsilon_{max.}$/cm^{-1} 3483, 3380, 3371 (NH, NH_2), 1680 (2 C=O), 1249 (2 C=S), 1400, 1145 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 3.8 (s, 6H, 2 OCH_3), 6.6 (s, 4H, $2NH_2$, exch.), 6.8–7.8 (m, 16H, Ar-H), 10.9 (s, 2H, 2 NH, exch.). ^{13}C-NMR (DMSO-d_6): 55.1 (2), 87.8 (2), 113.8 (4), 123.3 (4), 124.4 (2), 125.3 (4), 129.7 (4), 130.1 (2), 143.1 (2), 155.9 (2), 158.3 (2), 162.2 (2), 189.3 (2). *Anal.Calcd.* for $C_{34}H_{28}N_6O_6S_5$ (776.94): C, 52.56; H, 3.63; N, 10.82. Found: C, 52.34; H, 3.86; N, 10.57.

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(4-amino-3-(4-nitrophenyl)-2-thioxo-2,3-dihydrothiazole-5-carboxamide) (Compound 6): Yield 71%, m.p. 165.1 °C. IR:$\upsilon_{max.}$/cm^{-1} 3480, 3310, 3290 (NH, NH_2), 3090 (CH arom.), 1660 (2 C=O), 1203 (2 C=S), 1377, 1149 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 4.5 (s, 4H, $2NH_2$, exch.), 6.6–8.1 (m, 16H, Ar-H), 11.6 (s, 2H, 2 NH, exch.). ^{13}C-NMR (DMSO-d_6, D_2O): 67.1 (2), 123.8 (4), 124.6 (4), 126.3 (4), 128.4 (4), 129.2 (2), 142.9 (2), 144.0 (2), 145.1 (2), 161.3 (2), 162.2(2), 187.6 (2). *Anal.Calcd.* for $C_{32}H_{22}N_8O_8S_5$ (806.89): C, 47.63; H, 2.75; N, 13.89. Found: C, 47.89; H, 3.11; N, 13.50.

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(4-amino-3-(4-chlorophenyl)-2-thioxo-2,3-dihydrothiazole-5-carboxamide) (Compound 7): Yield 91%, m.p. 122.7 °C. IR:$\upsilon_{max.}$/cm^{-1} 3464, 3236, 3109 (NH, NH_2), 3051 (CH arom.), 1654 (2 C=O), 1280 (2 C=S), 1377, 1145 (SO_2), 821 (C-Cl). ^{1}H-NMR (DMSO-d_6, D_2O): δ 4.5 (s, 4H, $2NH_2$, exch.), 6.6–7.9 (m, 16H, Ar-H), 11.1 (s, 2H, 2 NH, exch.). ^{13}C-NMR (DMSO-d_6): 67.3 (2), 123.0 (4), 124.2 (4), 125.8 (4), 128.5 (4), 129.2 (4), 136.0 (2), 137.4 (2), 138.4 (2), 153.2 (2), 162.2 (2), 187.6 (2). *Anal.Calcd.* for $C_{32}H_{22}Cl_2N_6O_4S_5$ (785.79): C, 48.91; H, 2.82; N, 10.70. Found: C, 49.02; H, 2.56; N, 10.99.

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(4-amino-3-(4-bromophenyl)-2-thioxo-2,3-dihydrothiazole-5-carboxamide) (Compound 8): Yield 78%, m.p. 105.8 °C. IR:$\upsilon_{max.}$/cm^{-1} 3464, 3363, 3236 (NH, NH_2), 3100 (CH arom.), 1659 (2 C=O), 1284 (2 C=S), 1377, 1199 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 4.5 (s, 4H, $2NH_2$, exch.), 6.6–7.9 (m, 16H, Ar-H), 11.1 (s, 2H, 2 NH, exch.). ^{13}C-NMR (DMSO-d_6): 67.4 (2), 113.0 (2), 125.0 (4), 128.4 (4), 129.2 (4), 130.5 (4), 131.4 (2), 137.8 (2), 140.4 (2), 162.3 (2), 179.3 (2), 187.6 (2). *Anal.Calcd.* for $C_{32}H_{22}Br_2N_6O_4S_5$ (874.69): C, 43.94; H, 2.54; N, 9.61. Found: C, 44.27; H, 2.30; N, 9.28.

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(4-amino-3-(4-iodophenyl)-2-thioxo-2,3-dihydrothiazole-5-carboxamide) (Compound 9): Yield 69%, m.p. 148.1 °C. IR:$\upsilon_{max.}$/cm^{-1} 3367, 3224, 3120 (NH, NH_2), 3093 (CH arom.), 1654 (2 C=O), 1290 (2 C=S), 1392, 1195 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 4.5 (s, 4H, $2NH_2$, exch.), 6.6–7.9 (m, 16H, Ar-H), 11.1 (s, 2H, 2 NH, exch.). ^{13}C-NMR (DMSO-d_6): 67.4 (2), 88.9 (2), 123.6 (4), 128.6 (4), 129.2 (4), 135.7 (2), 136.2 (2), 137.3 (4), 140.1 (2), 158.6 (2), 162.2 (2), 187.3 (2). *Anal.Calcd.* for $C_{32}H_{22}I_2N_6O_4S_5$ (968.69): C, 39.68; H, 2.29; N, 8.68. Found: C, 39.40; H, 2.41; N, 8.33.

(2E,2′E)-N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-cyano-3-mercapto-3-(phenylamino)acrylamide) (Compound 11): Yield 86%, m.p. 162.6–168 °C. IR:$\upsilon_{max.}$/cm^{-1} 3448, 3380 (4 NH), 2187 (2 C≡N), 1654 (2 C=O), 1315, 1149 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 2.7 (s, 2H, 2SH), 7.0–7.9 (m, 18H, Ar-H), 9.8, 10.2 (2 s, 4H, 4 NH, exch.). ^{13}C-NMR (DMSO-d_6): 73.3 (2), 113.1 (2), 118.4 (4), 119.3 (2), 122.9 (4), 128.3 (4), 129.7 (4), 137.7 (2), 139.0 (2), 139.4 (2), 162.2 (2), 179.5 (2). *Anal.Calcd.* for $C_{32}H_{24}N_6O_4S_3$ (652.77): C, 58.88; H, 3.71; N, 12.87. Found: C, 59.02; H, 3.96; N, 12.50.

(2E,2′E)-N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)acetamide) (Compound 12): Yield 62%, m.p. 193.2 °C. IR:$\upsilon_{max.}$/cm^{-1} 3387 (2 NH), 3059 (CH arom.), 2194 (2 C≡N), 1730, 1660 (4 C=O), 1365, 1149 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 4.2 (s, 4H, 2 CH_2), 6.5–7.9 (m, 18H, Ar-H), 10.8 (s, 2H, 2 NH, exch.). ^{13}C-NMR (DMSO-d_6): 78.3 (2), 85.6 (2), 113.2 (4), 117.7 (2), 119.4 (2), 123.5 (4), 128.9 (4), 129.8 (4), 139.2 (2), 142.8 (2), 148.1 (2), 163.5 (2), 173.3 (2), 193.9 (2). *Anal.Calcd.* for $C_{36}H_{24}N_6O_6S_3$ (732.81): C, 59.00; H, 3.30; N, 11.47. Found: C, 59.32; H, 3.13; N, 11.29.

(2E,2′E)-N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-cyano-2-(4-oxo-3-phenylthiazolin-2-ylidene)acetamide) (Compound 13): Yield 86%, m.p. 162.7 °C. IR:$\upsilon_{max.}$/cm^{-1} 3375 (2 NH), 2195 (2 C≡N), 1732, 1650 (4 C=O), 1390, 1188 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 3.9 (s, 4H, 2 CH_2 thiazole), 7.0–7.9 (m, 18H, Ar-H), 10.2 (s, 2H, 2 NH, exch.). ^{13}C-NMR (DMSO-d_6): 32.8 (2), 62.9 (2), 119.2 (2), 120.6 (4), 121.5 (4), 124.1 (2), 128.9 (4), 129.4 (4), 130.4 (2), 135.2 (2), 148.1 (2), 162.2 (2), 170.3 (2), 173.3(2). *Anal. Calcd.* for $C_{36}H_{24}N_6O_6S_3$ (732.81): C, 59.00; H, 3.30; N, 11.47. Found: C, 59.09; H, 3.21; N, 11.51.

(2E,2′E)-N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-cyano-2-(4-methyl-3-phenylthiazol-2(3H)-ylidene)acetamide) (Compound 14): Yield 69%, m.p. 89.8 °C. IR:$\upsilon_{max.}$/cm^{-1} 3448 (2 NH), 2187 (2 C≡N), 1654 (2 C=O), 1400, 1149 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 1.8 (s, 6H, 2 CH_3), 6.6 (s, 2H, 2CH thiazoles), 7.0–7.9 (m, 18H, Ar-H), 10.5 (s, 2H, 2 NH, exch.). *Anal.Calcd.* for $C_{38}H_{28}N_6O_4S_3$ (728.86): C, 62.62; H, 3.87; N, 11.53. Found: C, 62.91; H, 3.49; N, 11.22.

(2E,2′E)-N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-cyano-2-(3,4-diphenylthiazol-2(3H)-ylidene)acetamide) (Compound 15): Yield 78%, m.p. 78.8 °C. IR:$\upsilon_{max.}$/cm^{-1} 3356, 3232 (2 NH),3055 (CH arom.), 2179 (2 C≡N), 1670 (2 C=O), 1357, 1145 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 6.6 (s, 2H, 2 CH thiazole), 7.0–7.9 (m, 28H, Ar-H), 8.4 (s, 2H, 2 NH, exch.). ^{13}C-NMR (DMSO-d_6): 79.1 (2), 112.8 (2), 113.0 (4), 119.2 (4), 122.8 (4), 126.2 (4), 127.8 (2), 128.9 (4), 129.8 (4), 130.7 (4), 134.3. (2), 136.7 (2), 137.8 (2), 139.2 (2), 141.7 (2), 162.2 (2), 174.2 (2). *Anal.Calcd.* for $C_{48}H_{32}N_6O_4S_3$ (853.00): C, 67.59; H, 3.78; N, 9.85. Found: C, 68.00; H, 3.42; N, 9.49.

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(5-acetyl-4-amino-2-(phenylamino)thiophene-3-carboxamide) (Compound 16): Yield 63%, m.p. 92.4 °C. IR:$\upsilon_{max.}$/cm^{-1} 3448, 3370, 3290 (NH, NH_2), 1670, 1649 (4 C=O), 1390, 1145 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 2.7 (s, 6H, 2 $COCH_3$), 5.9 (s, 4H, 2 NH_2, exch.). 6.8–7.9 (m, 18H, Ar-H), 10.5 (s, 2H, 2 NHCO, exch.), 10.6 (s, 2H, 2NHPh, exch.). ^{13}C-NMR (DMSO-d_6,): 30.7 (2), 104.5 (2), 119.1 (4), 120.4 (2), 124.5 (4), 128.4 (4), 128.7 (4), 129.1 (2), 137.4 (2), 138.8 (2), 147.3 (2), 152.6 (2), 162.2 (2), 168.7 (2), 195.4 (2). *Anal.Calcd.* for $C_{38}H_{32}N_6O_6S_3$ (764.89): C, 59.67; H, 4.22; N, 10.99. Found: C, 59.60; H, 4.19; N, 10.71.

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(4-amino-5-benzoyl-2-(phenylamino)thiophene-3-carboxamide) (Compound 17): Yield 67%, m.p. 102.2 °C. IR:$\upsilon_{max.}$/cm^{-1} 3433, 3394, 3200 (NH, NH_2), 1690, 1655 (4 C=O), 1315, 1145 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 6.1 (s, 4H, 2 NH_2, exch.). 7.1–7.9 (m, 28H, Ar-H), 10.5 (s, 4H, 4 NH, exch.). ^{13}C-NMR (DMSO-d_6): 96.8 (2), 103.8 (2), 112.9 (4), 120.9 (2), 121.5 (4), 128.5 (4), 128.7 (4), 129.9 (4), 130.0 (4), 134.3 (2), 135.6 (2), 137.9 (2), 138.3 (2), 139.9 (2), 146.2 (2), 162.7 (2), 166.4 (2), 188.1 (2) *Anal.Calcd.* for $C_{48}H_{36}N_6O_6S_3$ (889.03): C, 64.85; H, 4.08; N, 9.45. Found: C, 65.04; H, 3.89; N, 9.16.

N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-amino-4,5,6,7-tetrahydrobenzo [b]thiophene-3-carboxamide) (Compound 19): Yield 66%, m.p. 190.9 °C. IR:$\upsilon_{max.}$/cm^{-1} 3448, 3380, 3310 (NH, NH_2), 1680 (2 C=O), 1388, 1145 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 1.7–2.6 (m, 16H, 8 CH_2 cyclo), 6.6 (s, 4H, 2 NH_2, exch.), 6.9–7.9 (m, 8H, Ar-H), 9.3 (s, 2H, 2 NH, exch.). ^{13}C-NMR (DMSO-d_6): 22.4 (2), 22.7 (2), 23.9 (2), 25.5 (2), 112.9 (2), 119.2 (4), 128.4 (2), 129.0 (4), 136.0 (2), 136.5 (2), 141.2 (2), 162.8 (2). 163.4 (2). *Anal.Calcd.* for $C_{30}H_{30}N_4O_4S_3$ (606.78): C, 59.38; H, 4.98; N, 9.23. Found: C, 59.03; H, 5.11; N, 9.06.

(2E,2′E)-N,N′-(4,4′-sulfonylbis(4,1-phenylene))bis(2-(4-oxothiazolidin-2-ylidene)acetamide) (Compound 20): Yield 80%, m.p. 182.8 °C. IR:$\upsilon_{max.}$/cm^{-1} 3325, 3201(4NH), 3100 (CH arom.), 2960, 2870 (CH aliph.), 1705, 1680 (4 C=O), 1346, 1153 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O): δ 3.9 (s, 4H, 2 CH_2), 4.2 (s, 2H, 2 CH thiazolidinone), 7.1–7.9 (m, 8H, Ar-H), 10.3, 10.7 (2s, 4H, 4 NH, exch.). ^{13}C-NMR (DMSO-d_6): 38.9 (2), 90.6 (2), 119.3 (4), 128.5 (4), 136.0 (2), 143.6 (2), 161.9 (2), 169.1 (2), 171.9 (2). *Anal.*

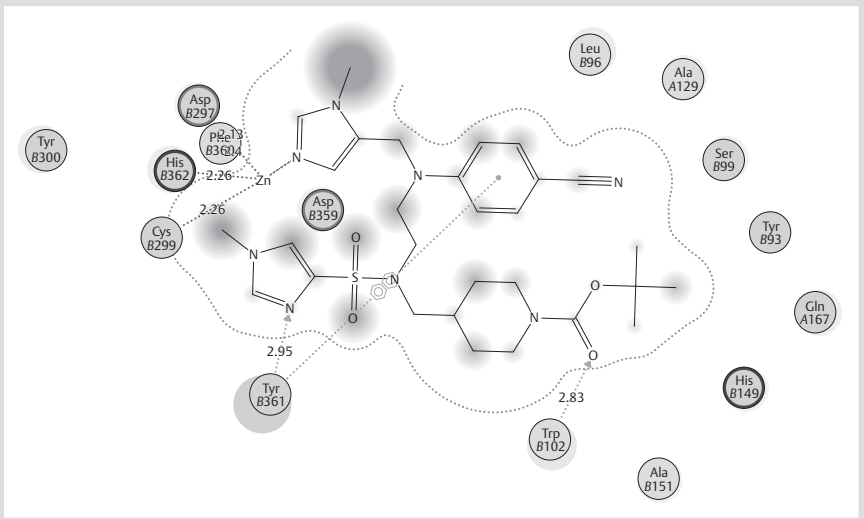

Fig. 2 Co-crystallized sulfone ligand on the active site of farnesyl transferase.

Calcd. for $C_{22}H_{18}N_4O_6S_3$ (530.60): C, 49.80; H, 3.42; N, 10.56. Found: C, 50.06; H, 3.18; N, 10.22.

Molecular Docking

Molecular docking on the active site of farnesyl transferase (FT)

The protein data bank file (PDB: 3E30) was selected for this purpose. The file contains farnesyl transferase enzyme co-crystallized with a sulfone ligand. All docking procedures were achieved by MOE (Molecular Operating Environment) software 10.2008 provided by chemical computing group, Canada. Docking on the active site of farnesyl transferase enzyme was performed for all synthesized compounds.

Docking protocol was verified by redocking of the co-crystallized ligand in the vicinity of the active site of the enzyme with energy score (S) = −25.6345 Kcal/mol and root mean standard deviation (RMSD) = 2.8268 (▶ **Fig. 2**). The sulfone ligand interacts with the active site of farnesyl transferase by 4 interactions: Try B361 with a hydrogen bond of 2.95 A° and arene-arene interaction, Trp B102 with a hydrogen bond of 2.83 and with Zn by the lone pair of imidazole nitrogen. All synthesized compounds were fit to the active site of farnesyl transferase enzyme with good energy scores (S) suggesting activity as farnesyl transferase inhibitors. Energy scores (S) and amino acid interactions for the synthesized compounds were listed in ▶ **Table 1**. Compound 11 gave the best energy score (S) = −36.8099 and interacted with Arg B202 with a hydrogen bond of 2.64 A°, Asp B352 with a hydrogen bond of 1.4 A° and with Zn through its carboxamido group (▶ **Fig. 3**). 3D interaction of compound **3**

Table 1 Binding scores and amino acid interactions of the docked compounds on the active site of farnesyl transferase (FT).

Compound No.	S Kcal/Mol	Amino acid interactions	H bond length A°	Interaction with Zn
2	−22.2685	Leu B295, Lys B294	3.37, 2.76	No interaction
3	−29.4698	Ser B99, Asp B297 Asp B352	3.30, 2.4 2.8	C=O
4	−35.6889	His B245, Arg B291 Asp B452	2.61, 3.05 1.45	C=O
5	−30.746	Lys B294	2.69	C=O
6	−20.4074	Lys A164, Tyr B301 Lys B356	2.89, 2.57 2.44	No interaction
7	−36.6898	Arg B357	1.48–1.48	C=O
8	−28.5758	Lys B294	2.82	No interaction
9	−23.3689	Lys B294, Arg B291 Lys B356, Lys B363	2.87, 2.77 2.93, 3.11	No interaction
11	−36.8099	Arg B202, Asp B352	2.64, 1.4	C=O
12	−33.2105	Tyr A168, Ser B99 Arg B291	2.65, 2.91 3.30	CN
13	−27.7094	Arg B291, Gln A167	2.69, 2.80	CN
14	−30.7510	Arg B202	3.62	C=O
15	−36.6799	Lys B356, Ser B99	2.79, 2.93	No interaction
16	−37.5820	Lys B356	2.42	No interaction
17	−36.3035	Lys B356	2.58	No interaction
19	−27.9411	Arg B291, Tyr A168 Tyr B251	2.67, 2,92 3.02	No interaction
20	−33.5881	Lys A164, Ser B99	2.54, 1.87–2.63	C=O

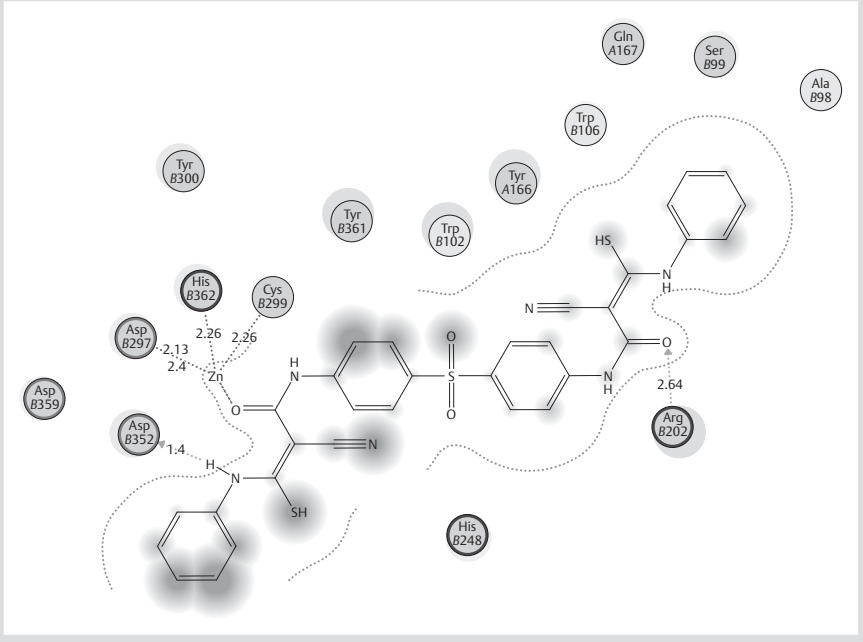

Fig. 3 Compound 11 on the active site of farnesyl transferase.

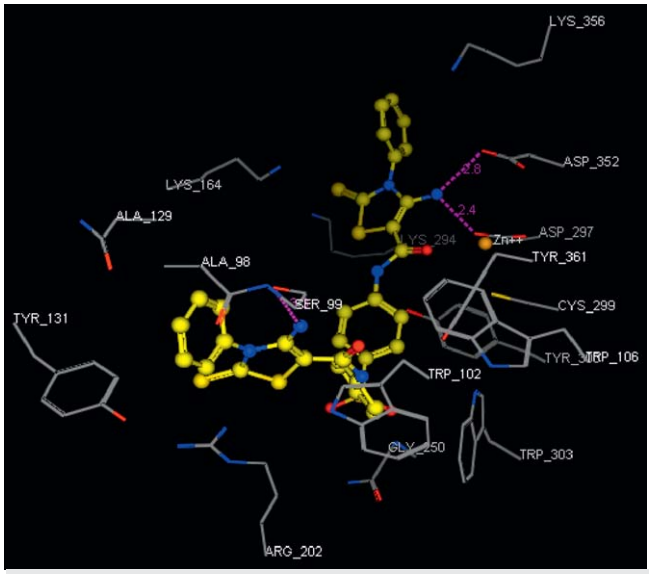

Fig. 4 Compound 3 on the active site of farnesyl transferase.

with the amino acid of active site of the enzyme is illustrated in (**Fig. 4**).

Molecular docking on the active site of arginine methyl transferase (PRMT1)

The protein data bank file (PDB: 3Q7E) was selected for this purpose. The file contains arginine methyl transferase co-crystallized with its ligand, S-adenosyl methionine. All docking procedures were achieved by MOE (Molecular Operating Environment) software 10.2008 provided by chemical computing group, Canada. Docking on the active site of arginine methyl transferase enzyme was performed for all synthesized compounds.

Docking protocol was verified by redocking of the co-crystallized ligand in the vicinity of the active site of the enzyme with energy score (S) = −18.5932 Kcal/mol and root mean standard deviation (RMSD) = 0.3523. The ligand interacts with the active site of arginine methyl transferase by 5 interactions: Val 128 with a hydrogen bond of 3.00 A°, Arg 54 with a hydrogen bond of 2.64, Gly 78 with a hydrogen bond of 1.81 A° and Glu 100 with 2 hydrogen bonds of 181, 186 A° (**Fig. 5**). All synthesized compounds were fit to the active site of arginine methyl transferase enzyme with good energy scores (S) suggesting activity as arginine methyl transferase inhibitors for most of the synthesized compounds. Energy scores (S) and amino acid interactions for the synthesized compounds were listed in **Table 2**. Compound 17 gave the best energy score (S) = -33.0593 and interacted with His 45 with a hydrogen bond of 2.66 A°, Lys 127 with a hydrogen bond of 2.68 A°, Glu 130 with a hydrogen bond of 1.27 A° and Arg 327 & His 161 by arene cation interactions (**Fig. 6**). 3D interaction of compound **3** with the amino acid of active site of the enzyme is illustrated in **Fig. 7**.

Biological screening

In vitro antitumor activity

The newly synthesized compounds were evaluated for their in vitro cytotoxic activity against human breast cancer cell line, MCF7. Doxorubicin which is one of the most effective anticancer agents was used as the reference drug in this study. The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of breast cancer cell line

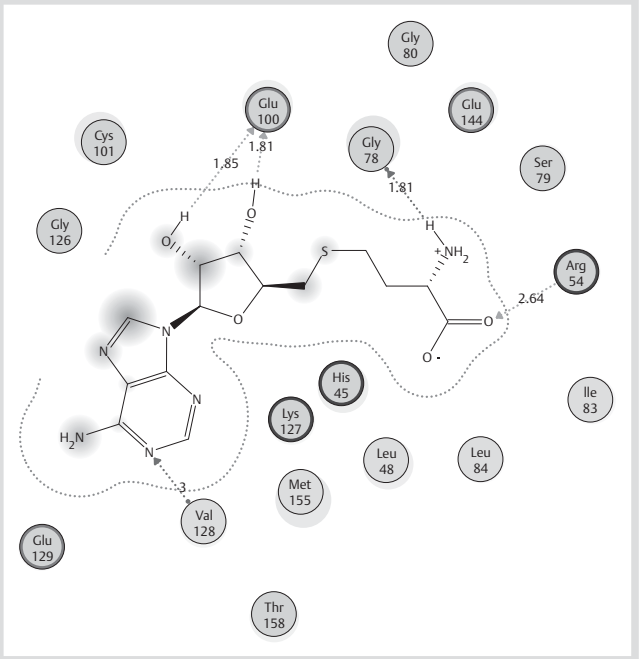

Fig. 5 Co-crystallized S-adenosyl methionine ligand on the active site of arginine methyl transferase (PRMT1).

Table 2 Binding scores and amino acid interactions of the docked compounds on the active site of arginine methyl transferase (PRMT1).

Compound No.	S Kcal/Mol	Amino acid interactions	H bond length A°
2	−20.0584	Lys 127, His 293	2.65, 2.81
3	−22.9402	Lys 127	2.46
4	−14.2954	Thr 158, Glu 100	2.75, 2.15–2.48
5	−18.2714	Glu 130, Lys 127	1.41, 2.47
6	−23.0610	Arg 327, Lys 127	2.89, 1.27
7	−16.0863	Arg 327	3.20
8	−25.5443	Lys 127	2.44
9	−18.6599	Lys 127, Arg 327	2.45, 2.47
11	−21.7302	Glu 130, Lys 127 Arg 327	1.34, 2.52 2.31
12	−25.2873	Lys 127, Arg 327	2.68, 3.14
13	−21.1864	Asn 157, Lys 127 Arg 327	2.68, 2.74 2.92
14	−23.3643	Arg 327	2.96–2.32
15	−18.4392	His 45, Thr 185	2.85, 3.11
16	−20.8016	Glu 100, Arg 327	1.81, 2.69–2.89
17	−33.0593	Glu 130, His 45 Lys 127	1.27, 2.66 2.68
19	−18.1701	Gly 78, Glu 100	1.77, 1.96
20	−20.3841	Lys 127, His 45	2.78, 1.90

(MCF7). The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability. **Table 3** shows the in vitro cytotoxic activity of the synthesized compounds where all compounds exhibited significant activity compared to the reference drug.

Discussion

Chemistry

The synthetic procedures adopted to obtain the target compounds are depicted in **Fig. 8–11**. N,N′-(4,4′-sulfonylbis(4,1-

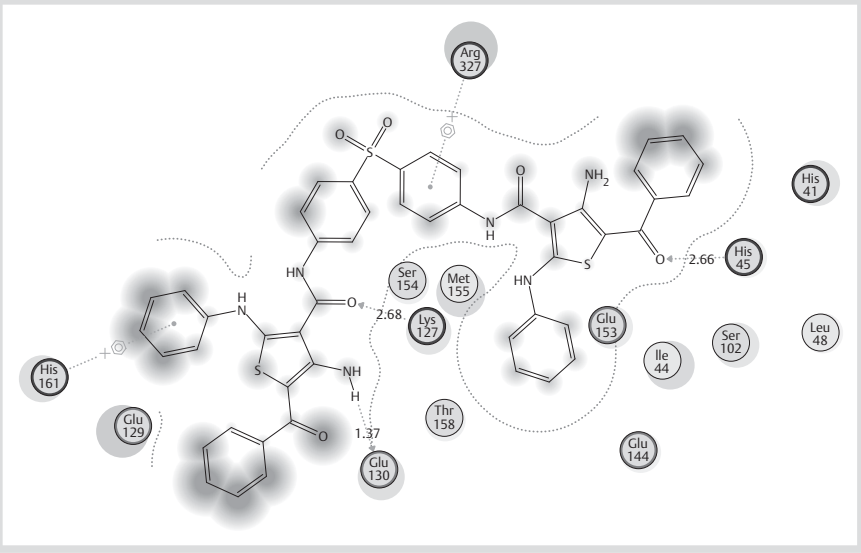

Fig. 6 Compound 17 on the active site of arginine methyl transferase (PRMT1).

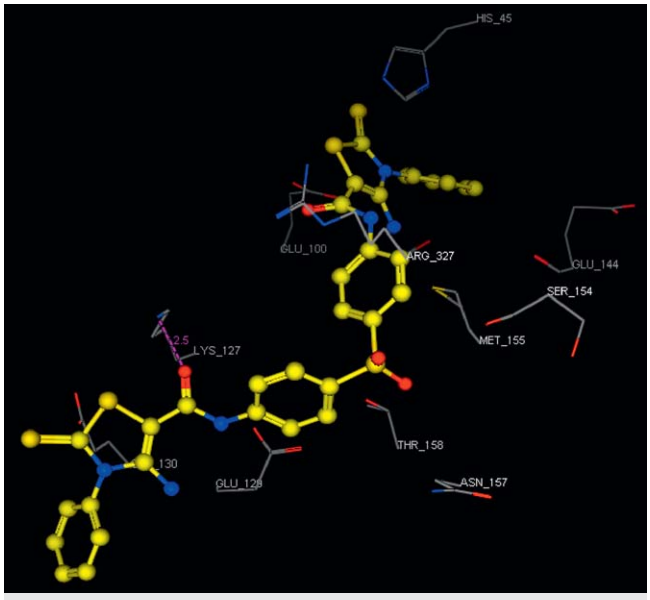

Fig. 7 Compound 3 on the active site of arginine methyl transferase (PRMT1).

phenylene))bis(2-cyanoacetamid) 2 was prepared via reaction of Dapson 1 with ethyl cyanoacetate under condition of fusion (**Fig. 8**). Compound 2 was characterized by the presence of absorption band at 2256 cm^{-1} for (2 C≡N), and a strong absorption band at 1701 cm^{-1} for (2 C=O). ^{1}H-NMR spectrum in (DMSO-d_6) revealed signals at 4.0 ppm represents CH_2 protons and 10.7 ppm corresponding to NH groups. Also, compounds 3–9 were obtained by reacting compound 2 with sulfur and isothiocyanate derivatives. The IR spectra of compounds 3–9, exhibited the absence of (C≡N) band & presence of characteristic bands for NH_2, SO_2 and C=S groups. ^{1}H-NMR spectrum of 3 in (DMSO-d_6) exhibited signals at 6.9 ppm due to NH_2 groups and 8.5 ppm corresponding to NH groups. ^{1}H-NMR spectrum of 4 in (DMSO-d_6) exhibited signals at 2.3 ppm due to CH_3 groups, 4.5 ppm corresponding to NH_2 groups. ^{1}H-NMR spectrum of 5 in (DMSO-d_6) revealed signal at 3.8 ppm corresponding to OCH_3 groups. IR spectrum for compound 6 showed the characteristic bands for NH_2 and C=S groups. ^{1}H-NMR spectrum of 6 in (DMSO-d_6) revealed a singlet signal at 4.5 ppm for NH_2 which was exchanged by D_2O. Also, the IR spectra for compounds 7–9 showed the corresponding bands for NH_2, C=S and SO_2 groups. ^{1}H-NMR spectra for compounds 7–9 revealed signals corresponding to the presence of NH_2 groups.

The synthesis of (2E,2′E)-N,N′-(4,4′-sulfonylbis(4,1-pheneylene)-bis(2-cyano-3-mercapto-3-(phenylamino)acrylamide 11 and (2E,2′E)-N,N′-(4,4′-sulfonylbis(4,1-phenylene)-bis(2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)acetamide 12 were achieved. Treatment of acetamide 2 with phenyl isothiocyanate in dry dimethylformamide in the presence of equivalent amount of potassium hydroxide produced the potassium salt 10, which acidification of such potassium salt 10 liberated the acrylamide derivative 11, whereas reaction with chloroacetyl chloride in dry dimethylformamide to afford thiazolidinone derivative 12. The structures of compounds 11 and 12 were proved on the basis of elemental analyses and spectral data. Thus, IR spectrum of 11 exhibited characteristic band at 3448 cm^{-1} (4 NH), 2187 cm^{-1} (2 C≡N) and 1645 cm^{-1} for (2 C=O). ^{1}H-NMR spectrum of 11 revealed signals at 2.7 ppm for SH groups and 10.2 ppm for NH groups. IR spectrum of 12 showed bands at 3387 cm^{-1} (2 NH), 2194 cm^{-1} (2 C≡N) and 1730, 1660 cm^{-1} for (4 C=O). ^{1}H-NMR spectrum of 12 revealed signals at 4.2 ppm corresponding to CH_2 groups and 10.8 ppm due to NH groups (**Fig. 9**).

The reactivity of the acetamide derivative 2 towards isothiocyanate was investigated. Thus, when compound 2 was left to react with phenyl isothiocyanate in the presence of dilute solution of potassium hydroxide at room temperature and ethyl chloroacetate was added, the corresponding thiazolidinone derivative 13 was obtained as a clean cut product in good yield (**Fig. 10**). Compound 13 was proved on the basis of analytical and spectral data. Thus, IR spectrum of 13 showed band at 3375 cm^{-1} (2 NH), 2195 cm^{-1} (2 C≡N) and 1732, 1650 cm^{-1} for (4 C=O). ^{1}H-NMR spectrum of 13 revealed signals at 3.9 ppm for CH_2 groups, 10.2 ppm to NH groups.

Similarly, the novel phenylthiazole 14 was synthesized by reaction of 2 with phenyl isothiocyanate in the presence of potassium hydroxide at room temperature and chloroacetone was added, the corresponding phenylthiazole derivative 14 was obtained as a clean cut product in a good yield. Probably the reaction mechanism is assumed to proceed via initial alkylation

Table 3 In vitro anticancer screening of the synthesized compounds against human breast cell line (MCF7).

Comp NO.	Compound concentration (μM)				IC_{50} (μM)
	10 μM	25 μM	50 μM	100 μM	
	Surviving fraction (Mean ± S.E.)*				
Doxorubicin	0.721 ± 0.02	0.546 ± 0.02	0.461 ± 0.01	0.494 ± 0.03	71.80
2	0.727 ± 0.134	0.427 ± 0.055	0.307 ± 0.029	0.317 ± 0.021	46.57
3	0.390 ± 0.043	0.320 ± 0.037	0.166 ± 0.640	0.273 ± 0.156	23.02
4	0.851 ± 0.188	0.521 ± 0.062	0.412 ± 0.016	0.351 ± 0.016	57.67
5	0.821 ± 0.068	0.564 ± 0.092	0.301 ± 0.061	0.300 ± 0.046	51.07
6	0.444 ± 0.010	0.310 ± 0.064	0.342 ± 0.085	0.289 ± 0.071	32.19
7	0.582 ± 0.108	0.277 ± 0.085	0.247 ± 0.066	0.297 ± 0.033	33.67
8	0.715 ± 0.064	0.407 ± 0.056	0.286 ± 0.060	0.277 ± 0.047	42.71
9	0.458 ± 0.099	0.344 ± 0.112	0.271 ± 0.007	0.300 ± 0.034	31.59
11	0.623 ± 0.120	0.419 ± 0.206	0.251 ± 0.054	0.332 ± 0.044	41.87
12	0.818 ± 0.071	0.418 ± 0.088	0.233 ± 0.010	0.225 ± 0.041	42.00
13	0.873 ± 0.083	0.358 ± 0.197	0.280 ± 0.084	0.238 ± 0.086	44.15
14	0.502 ± 0.007	0.434 ± 0.027	0.255 ± 0.045	0.410 ± 0.028	41.57
15	0.746 ± 0.096	0.292 ± 0.075	0.233 ± 0.083	0.221 ± 0.050	37.02
16	0.634 ± 0.184	0.454 ± 0.046	0.301 ± 0.040	0.298 ± 0.097	43.36
17	0.637 ± 0.098	0.491 ± 0.081	0.419 ± 0.052	0.406 ± 0.057	56.34
19	0.425 ± 0.056	0.269 ± 0.094	0.321 ± 0.076	0.435 ± 0.040	33.34
20	0.793 ± 0.055	0.454 ± 0.097	0.292 ± 0.008	0.332 ± 0.050	49.37

*Each value is the mean of 3 values ± Standard Error

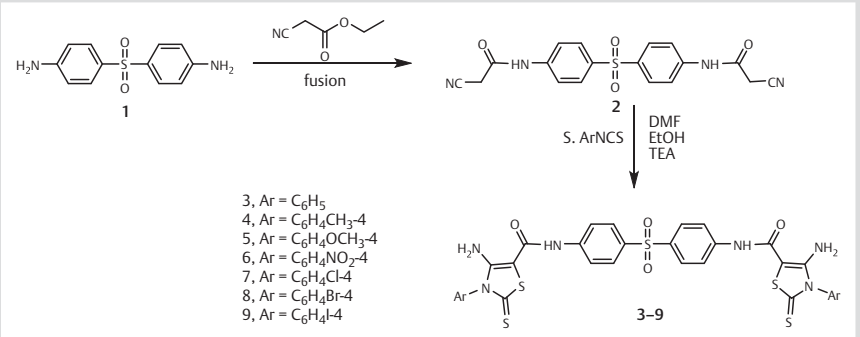

Fig. 8 Synthetic pathways for compounds 2–9.

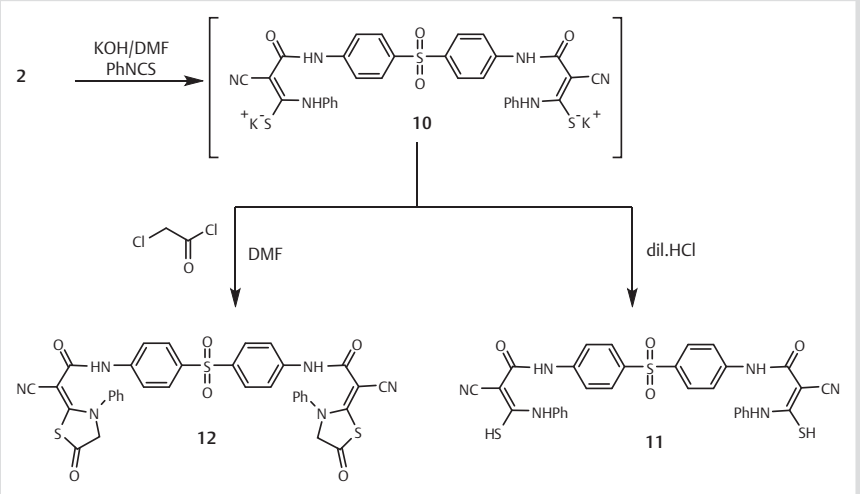

Fig. 9 Synthetic pathways for compounds 11 and 12.

followed by in situ heterocyclization through nucleophilic addition of secondary amino group to carbonyl group of chloroacetone to yield the cyclic product 14. Also, the diphenylthiazole derivative 15 was obtained by the same conditions of preparing compound 14 but using phenacyl chloride instead of chloroacetone. The structure of compound 14 and 15 were established on the basis of elemental and spectral data. Thus, IR spectrum of compound 14 exhibited bands at 3448 cm^{-1} (2 NH), 2187 cm^{-1} (2 C≡N), 1654 cm^{-1} (2 C=O). ^{1}H-NMR spectrum of 14 revealed signals at 1.8 ppm for $2CH_3$ groups and 6.6 ppm corresponding to 2CH of thiazoles. IR spectrum of compound 15 exhibited bands at 3356, 3232 cm^{-1} (2 NH), 2179 cm^{-1} (2 C≡N), 1670 cm^{-1} (2 C=O). ^{1}H-NMR spectrum of 15 revealed signals at 6.6 ppm

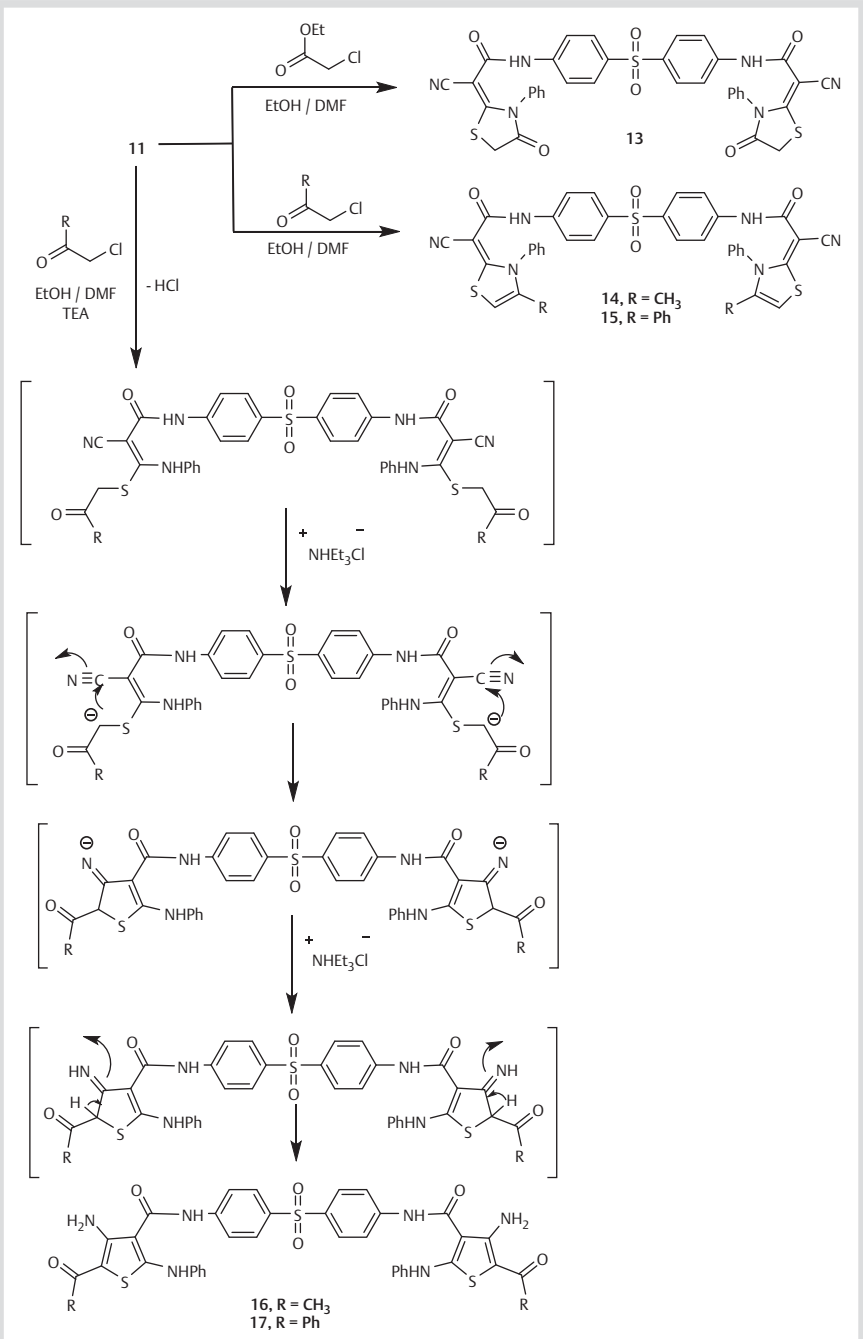

Fig. 10 Synthetic pathways for compounds 13–17.

corresponding to 2CH of thiazoles and 8.4 ppm corresponding to 2NH groups.

In continuation of our work on the synthesis of biologically interesting heterocyclic molecules containing thiophene moiety [25–28], several thiophene derivatives have been synthesized with a view to evaluate their anticancer activities. Thus, refluxing of 11 in DMF/EtOH containing a catalytic amount of triethylamine, chloroacetone and/or phenacyl chloride revealed formation of the thiophene derivatives 16 and 17, respectively. The IR spectra of compounds 16 and 17 were characterized by the disappearance of C≡N groups band and the appearance of NH_2 and C=O bands. In addition, the ^{1}H-NMR spectrum of 16 in (DMSO-d_6) showed 3 singlet signals at 2.7, 10.5 and 10.6 ppm due to $COCH_3$, NHCO and NHPh protons, respectively.

On the other hand, the tetrahydrobenzothiophene derivative 19 was obtained by the reaction of 2 with cyclohexanone and sulfur in a mixture of DMF/EtOH containing a catalytic amount of morpholine. The reaction may be explained via intermediate 18 (**Fig. 11**). The structure of compound 19 was established on the basis of its elemental analysis and spectral data; its IR spectrum showed the presence of bands at 3448, 3380, 3310 cm^{-1} (NH, NH_2), 1680 cm^{-1} (2 C=O) and 1388, 1149 cm^{-1} (SO_2). ^{1}H-NMR spectrum of 19 in (DMSO-d_6) displayed a multiplet at 1.7–2.6 ppm corresponding to tetrahydrobenzene moieties. Moreover, ^{13}C-NMR spectrum revealed signals at 22.4, 22.7, 23.9 and 25.5 ppm due to tetrahydrobenzene nucleus.

Finally, reaction of compound 2 with 2-sulfanylacetic acid afforded the thiazolidinone derivative 20 (**Fig. 11**). Compound 20 was characterized by the presence of a strong absorption band at 1705 cm^{-1} in the IR spectrum, specific for the thiazolidinone ring. Another piece of evidence for cyclization, in the ^{1}H-NMR spectrum is the presence of a singlet signal, equivalent

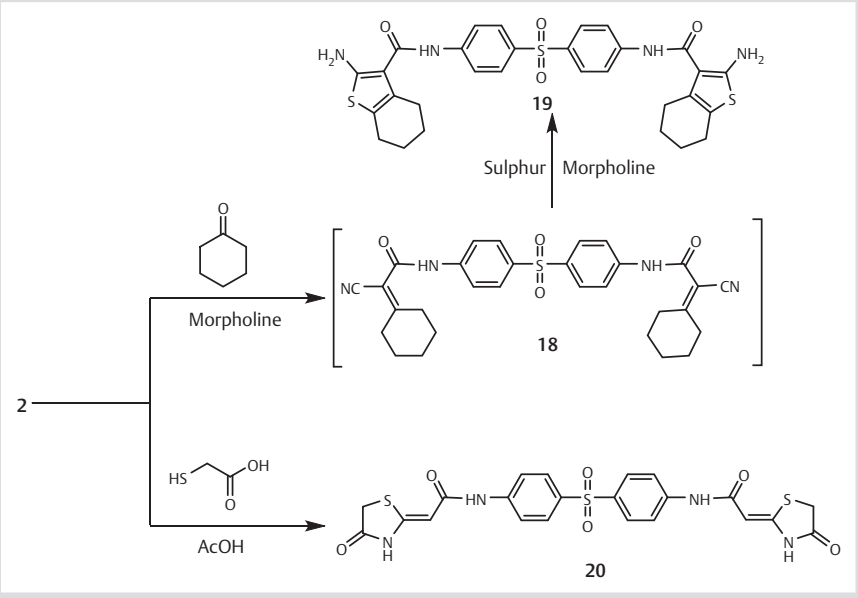

Fig. 11 Synthetic pathways for compounds 18–20.

to 2 protons at 3.9 ppm which represents the C-5 protons of thiazolidinone nucleus. ^{13}C-NMR spectrum of compound 20 showed signals at 169.1 and 90.6 ppm due to C-4 and C-5 of the thiazolidinone nucleus, respectively.

Molecular Docking

Advances in molecular biology over the past decade have identified a number of novel targets for cancer therapy. One such target is the enzyme farnesyl protein transferase (FT), which catalyses a key step in the addition of an aliphatic isoprenoid side chain to a number of proteins. A novel class of antineoplastic agents, the farnesyl transferase inhibitors (FTIs), have recently been developed to specifically inhibit FT. These inhibitors were designed to target Ras, a G-protein with 4 isoforms (H-, N- and K-RasA/K-RasB) mutated in a large number of cancers, which requires prenylation for functioning [30]. Despite uncertainty about the true target of FTIs, these agents demonstrate anticancer activity as single agents and in combination with standard cytotoxic chemotherapy [31–33]. In addition, FTIs synergize with gamma irradiation, and may have a role in chemoprevention [34–36].

On the other hand, Methylation at arginine residues is of interest because it can affect gene transcription, or signal transduction by modulating protein-protein interactions [37]. In mammalian cells methylation of arginine residues is catalyzed by a family of at least 9 protein methyl transferases (PRMTs, E.C. 2.1.1.125) [38]. Arginine methyl transferase (PRMT1) is thought to contribute to as much as 85% of all cellular PRMT activity and its inhibition may lead to good antitumor activity [39].

Upon the preceding, the present investigation is concerned with the synthesis of novel anticancer agents and trying to elucidate their mechanism of action by performing molecular docking on the active sites of farnesyl transferase (FT) and arginine methyl transferase (PRMT1).

The trial in the present investigation to predict an assumption on the mechanism of action of the synthesized compounds was conducted through molecular docking on the active site of 2 enzymes based on the similarities between the synthesized compounds and the enzyme inhibitors of these enzymes.

The good energy scores (S) for all synthesized compounds as well as the good amino acid interactions shown on the active sites of both farnesyl transferase enzyme and arginine methyltransferase enzyme may provide a tool to predict the possibility of their cytotoxic compounds as inhibitors for these 2 enzymes. However, no defined relationship between the biological activity and the docking results could be identified suggesting more investigation to be conducted in order to specify their mechanism of action.

Biological screening

In vitro antitumor activity

All the synthesized compounds showed better cytotoxic activity than Doxorubicin especially the thiazolidinone derivative 3 which showed IC_{50} value 23.02 µM. Upon substitution on the phenyl rings of compound 3 with several electron donating and electron withdrawing groups the activity drops. However, substitution with electron withdrawing groups did not decrease the activity in the same way substitution with electron donating group did. This was clearly illustrated by the values of IC_{50} of the thiazolidinone derivatives 6 and 9 with IC_{50} values of 32.19 µM and 31.59 µM, respectively. In these 2 derivatives, substitution of the phenyl rings was with NO_2 in case of compound 6 and I in case of compound 9. On the other hand, the IC_{50} values for the thiazolidinone derivatives in which the substitution on the phenyl rings was with electron donating groups were much higher indicating less activity. This was clearly shown in the thiazolidinone derivatives 4 and 5 with IC_{50} values of 57.67 µM and 51.07 µM, respectively. In these 2 derivatives, substitution of the phenyl rings was with CH_3 in case of compound 4 and OCH_3 in case of compound 5.

Compounds 11–20 showed cytotoxic activity with IC_{50} in the range of 33.34–56.35 µM with cytotoxic activity better than that of Doxorubicin. The cyclohexyl thiazole derivative 19 was with the best IC_{50} = 33.34 µM among these compounds while the (phenylamino)thiophene-3-carboxamide derivative 17 showed the highest IC_{50} = 56.35 µM among these compounds.

The promising results of cytotoxic activity of the synthesized compounds especially compound 3 urge more investigations for their mechanism of action. The trial in the present investigation to predict an assumption on the mechanism of action of the synthesized compounds was conducted through molecular docking on the active site of 2 enzymes based on the similarities between

the synthesized compounds and the enzyme inhibitors of these enzymes.

Acknowledgements

The authors are grateful to the sponsorship of the College of Pharmacy Research Centre and the Deanship of the Scientific Research, King Saud University, Riyadh, Saudi Arabia.

Conflict of Interest

The authors declare no conflict of interest.

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