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SYNTHESIS AND MOLECULAR DOCKING OF SOME NOVEL ANTICANCER SULFONAMIDES CARRYING A BIOLOGICALLY ACTIVE PYRROLE AND PYRROLOPYRIMIDINE MOIETIES

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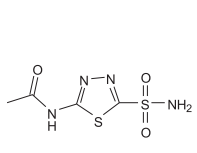
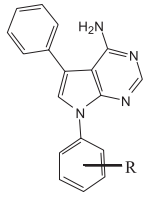
Abstract: A novel series of pyrroles and pyrrolopyrimdines carrying a biologically active sulfonamide moiety have been synthesized. The structures were confirmed by elemental analyses and spectral data. All the target compounds were subjected to *in vitro* cytotoxic screening on breast cancer cell line (MCF-7). Most of the synthesized compounds showed good activity as cytotoxic agents with better IC_{50} than doxorubicin as a reference drug. In order to suggest a mechanism of action for their activity, molecular docking on the active site of human c-Src was performed for all synthesized compounds.

Keywords: sulfonamide derivatives, anticancer activity

Nitrogen heterocyclic compounds are of special interest because they constitute an important class of natural and synthetic products, many of which exhibit useful biological activities. Pyrrole and fused pyrrole compounds such as pyrrolopyrimidine derivatives exhibit a broad spectrum of biological activities such as antimicrobial (1), analgesic (2), anti-inflammatory (3), antiviral (4) and anticancer activity (5–7). The potential use of aromatic/heterocylic sulfonamides as carbonic anhydrase (CA) inhibitors has been little explored to date in the treatment of cancer. Acetazolamide (CAS 59- 66- 5) **I** was reported as a strong inhibitor of several carbonic anhydrase isozymes (8). It acts as a potential modulator of anticancer therapies in combination with different cytotoxic agents (alkylating agents, nuclueoside analogs, etc.). Also, 5,7-diphenylpyrrolo[2,3-d]pyrimidines **II** were described as potent inhibitors of the tyrosine kinase C-Src, which is now considered as an attractive target of cancer therapy (9). In addition, it was reported that pyrrolopyrimidine U101033 (phase III clinical trials for ischemic brain injuries; have not yet CAS number) [(9-(2-morpholinyl)indole monohydrochloride hydrate] efficiently protected against hydroxy radical-induced lipid peroxidation that occurs deeply within the membrane bilayer (10). Due to our interest in the development of novel anticancer agents, in this study, we report the synthesis of some novel pyrrole and pyrrolopyrimidine derivatives containing a biologically active sulfonamide moiety as analogs to **I** and **II**, respectively, hoping that these new compounds might show significant anticancer activity.



I



II

EXPERIMENTAL

Chemistry

Melting points were determined in open capillaries on a Gallenkamp melting point apparatus (Sanyo Gallenkamp, Southborough, UK) and are uncorrected. Pre-coated silica gel plates (silica gel, 60 F_{254}; Merck, Germany) were used for thin layer chromatography, dichloromethane/methanol (9.5 : 0.5, v/v) mixture was used as a developing solvent system and the spots were visualized by ultraviolet light and/or iodine. Infra-red spectra were recorded

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in KBr discs using IR-470 Shimadzu spectrometer (Shimadzu, Tokyo, Japan). NMR spectra in DMSO-d_6 were recorded on Bruker Ac-500 ultra shield NMR spectrometer (Bruker, Flawil, Switzerland) at 500 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 compounds were within ± 0.4% of the theoretical values.

4-[2-(4-Bromophenyl)-2-oxoethylamino]benzenesulfonamide (3)

A mixture of sulfanilamide **1** (1.72 g, 0.01 mol) and 4-bromophenacylbromide **2** (2.77 g, 0.01 mol) was refluxed in N,N'-dimethylformamide (20 mL) in the presence of catalytic amount of triethylamine for 6 h. The solid obtained was filtered and recrystallized from ethanol to give **3**. Yield 89%, m.p. 232.6°C, IR: (ν_{max}, cm^{-1}): 3358, 3255 (NH, NH_2), 3100 (CH arom.), 2970, 2863 (CH aliph.), 1685 (C=O), 1381, 1157 (SO_2).^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 4.7 (s, 2H, CH_2), 6.6 (s, 1H, NH, D_2O exchangeable), 6.7, 7.5 (2d, 4H, Ar-H, AB system, J = 7.1 Hz), 7.8, 8.0 (2d, 4H, Ar-H, AB system, J = 6.9 Hz). ^{13}C-NMR (DMSO-d_6, δ, ppm): 49.4, 111.4 (2), 127.1, 127.7, 129.9 (2), 130.7 (2), 131.8 (2), 133.9, 150.8, 195.3. Analysis: calcd. for $C_{14}H_{13}BrN_2O_3S$ (369.23): C, 45.54; H, 3.55; N, 7.59%; found: C, 45.54; H, 3.31; N, 7.24%.

4-[2-Amino-4-(4-bromophenyl)-3-cyano-1*H*-pyrrol-1-yl]benzenesulfonamide (5)

A mixture of compound **3** (3.69 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) in ethanol (20 mL) containing sodium ethoxide (0.5 g) was refluxed for 8 h. The reaction mixture was cooled and acidified with dil. HCl. The solid obtained was filtered and recrystallized from dioxane to give **5**. Yield 78%, m.p. 221.2°C, IR: (ν_{max}, cm^{-1}): 3419, 3344, 3238 (NH_2), 3095 (CH arom.), 2187 (C=N), 1635 (C=N), 1342, 1176 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 6.1 (s, 2H, NH_2, D_2O exchangeable), 7.0 (s, 1H, CH pyrrole), 7.5–7.9 (m, 10H, Ar-H + SO_2NH_2).^{13}C-NMR (DMSO-d_6, δ, ppm): 70.5, 113.5, 117.5, 119.5, 121.3 (2), 125.2, 127.3, 131.2 (2), 131.6 (2), 132.3 (2), 139.5, 142.9, 148.5. Analysis: calcd. for $C_{17}H_{13}BrN_4O_2S$ (417.28): C, 48.93; H, 3.14; N, 13.43%; found: C, 48.71; H, 3.50; N, 13.16.%

4-[4-Amino-5-(4-bromophenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl]benzenesulfonamide (6)

A solution of compound **5** (4.17 g, 0.01 mol) in formamide (20 mL) was refluxed for 8 h. The reaction mixture was cooled and then poured onto ice/cold water. The formed residue was recrystallized from dioxane to give **6**. Yield 75%, m.p. > 350°C, IR: (ν_{max}, cm^{-1}): 3470, 3380, 3217 (NH_2), 3100 (CH arom.), 1620 (C=N), 1381, 1159 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 6.5 (s, 2H, NH_2, D_2O exchangeable), 7.2 (s, 1H, CH pyrrole), 7.4–8.0 (m, 10H, Ar-H + SO_2NH_2), 8.6 (s, 1H, CH pyrimidine).^{13}C-NMR (DMSO-d_6, δ, ppm): 100.9, 116.8, 120.4, 122.5, 123.2, 124.3, 126.7, 127.0, 128.5, 130.5, 131.7, 132.9, 139.9, 141.3, 152.6, 157.6, 160.2, 162.9. Analysis: calcd. for $C_{18}H_{14}BrN_5O_2S$ (444.31): C, 48.66; H, 3.18; N, 15.76%; found: C, 48.41; H, 3.46; N, 15.98%.

General procedure for synthesis of compounds 7a–m

A mixture of **5** (4.17 g, 0.01 mol) and aromatic aldehydes (0.01 mol.) in glacial acetic acid (20 mL) was refluxed for 4 h. The reaction mixture was cooled, filtered and the obtained solid was recrystallized from dioxane to give **7a**–**m**, respectively.

4-[4-(4-Bromophenyl)-3-cyano-2-(4-methylbenzylideneamino)-1*H*-pyrrol-1-yl]benzenesulfonamide (7a)

Yield 68%, m.p. 277.3°C, IR: (ν_{max}, cm^{-1}): 3363, 3269 (NH_2), 3100 (CH arom.), 2970, 2816 (CH aliph.), 2202 (C=N), 1600 (C=N), 1328, 1166 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 2.4 (s, 3H, CH_3), 7.3 (s, 1H, CH pyrrole), 7.4–7.9 (m, 14H, Ar-H + SO_2NH_2), 9.0 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 21.2, 78.7, 116.8, 119.4, 120.6, 124.0, 125.6, 126.5, 127.9, 129.2 (2), 129.6 (2), 129.7 (2), 131.3, 131.8, 132.4, 133.9 (2), 139.4, 143.0, 145.2, 147.0, 163.4. Analysis: calcd. for $C_{25}H_{19}BrN_4O_2S$ (518.04): C, 57.81; H, 3.69; N, 10.79%; found: C, 57.50; H, 3.88; N, 10.49%.

4-[4-(4-Bromophenyl)-3-cyano-2-(4-hydroxybenzylideneamino)-1*H*-pyrrol-1-yl]benzenesulfonamide (7b)

Yield 82%, m.p. 194.3°C, IR: ν_{max}, cm^{-1}): 3410 (OH), 3356, 3270 (NH_2), 3095 (CH arom.), 2966, 2846 (CH aliph.), 2208 (C=N), 1595 (C=N), 1346, 1161 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 6.9 (s, 1H, CH pyrrole), 7.0–8.0 (m, 14H, Ar-H + SO_2NH_2), 8.9 (s, 1H, N=CH), 10.5 (s, 1H, OH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 78.2, 117.0, 117.6, 118.8, 119..5, 120.5, 121.3 (2), 125.5, 126.5, 127.3, 128.3 (2), 131.4 (2), 131.8 (2), 132.3 (2), 139.5, 142.8, 148.5, 162.1, 163.1. Analysis:

calcd. for $C_{24}H_{17}BrN_4O_3S$ (521.38): C, 55.29; H, 3.29; N, 10.75%. found: C, 55.50; H, 3.10; N, 10.66%.

4-[4-(4-Bromophenyl)-3-cyano-2-(4-fluorobenzylideneamino)-1*H*-pyrrol-1-yl]benzenesulfonamide (7c)

Yield 80%, m.p. 142.9°C, IR: (ν_{max}, cm^{-1} 3300, 3270 (NH_2), 3055 (CH arom.), 2971, 2836 (CH aliph.), 2210 (C=N), 1598 (C=N), 1372, 1165 (SO_2).^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 7.3(s, 1H, CH pyrrole), 7.4–7.9 (m, 14H, Ar-H + SO_2NH_2), 9.1 (s, 1H, N=CH).^{13}C-NMR (DMSO-d_6, δ, ppm): 78.9, 116.4 (2), 116.7, 119.7, 124.1, 125.2 (2), 126.5, 127.1, 127.3 (2), 127.8, 128.0 (2), 131.9 (2), 132.3 (2), 139.5, 143.1, 146.6, 162.2, 165.8. Analysis: calcd. for $C_{24}H_{16}BrFN_4O_2S$ (522.01): C, 55.08; H, 3.08; N, 10.70%; found: C, 55.25; H, 3.31; N, 10.59%.

4-[4-(4-Bromophenyl)-3-cyano-2-(2-methoxybenzylideneamino)-1*H*-pyrrol-1-yl]benzenesulfonamide (7d)

Yield 56%, m.p. 137.6°C, IR: (ν_{max}, cm^{-1}): 3280, 3263 (NH_2), 3074 (CH arom.), 2941, 2839 (CH aliph.), 2212 (C=N), 1597 (C=N), 1340, 1163 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 3.9 (s, 3H, OCH_3), 7.0 (s, 1H, CH pyrrole), 7.2–7.9 (m, 14H, Ar-H + SO_2NH_2), 9.2 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 56.0, 110.2, 112.6, 116.8 (2), 119.8, 120.9, 122.7, 123.0 (2), 124.4, 128.0, 129.6 (2), 131.8 (2), 132.3, 134.7, 136.6, 136.7, 139.4, 143.0, 147.3, 160.0, 161.4. Analysis: calcd. for $C_{25}H_{19}BrN_4O_3S$ (535.41): C, 56.08; H, 3.58; N, 10.46%; found: C, 56.26; H, 3.31; N, 10.71%.

4-[4-(4-Bromophenyl)-3-cyano-2-(4-methoxybenzylideneamino)-1*H*-pyrrol-1-yl]benzenesulfonamide (7e)

Yield 66%, m.p. 141.2°C, IR: (ν_{max}, cm^{-1}): 3338, 3259 (NH_2), 3100 (CH arom.), 2970, 2860 (CH aliph.), 2212 (C=N), 1593 (C=N), 1370, 1166 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 3.8 (s, 3H, OCH_3), 7.1 (s, 1H, CH pyrrole), 7.2–7.9 (m, 14H, Ar-H + SO_2NH_2), 9.0 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 56.0, 78.3, 114.6 (2), 116.9, 119.1, 120.5, 123.9 (2), 125.6, 126.5, 127.7, 127.9 (2), 129.6 (2), 131.2 (2), 131.8 (2), 139.5, 142.9, 147.5, 162.9, 164.1. Analysis: calcd. for $C_{25}H_{19}BrN_4O_3S$ (535.41): C, 56.08; H, 3.58; N, 10.46%; found: C, 56.30; H, 3.36; N, 10.68%.

4-[2-(Benzo[d][1,3]dioxol-5-ylmethyleneamino)-4-(4-bromophenyl)-3-cyano-1*H*-pyrrol-1-yl]benzenesulfonamide (7f)

Yield 66%, m.p. 111.9°C, IR: (ν_{max}, cm^{-1}): 3346, 3261 (NH_2), 3100 (CH arom.), 2920, 2860 (CH aliph.), 2210 (C=N), 1587 (C=N), 1340, 1165 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 6.1 (s, 2H, CH_2), 7.0 (s, 1H, CH pyrrole), 7.1–7.9 (m, 13H, Ar-H + SO_2NH_2), 8.9 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 102.2, 106.2, 108.6, 116.8, 119.2, 120.5, 123.9, 124.4 (2), 124.8, 126.5, 127.9, 128.5, 129.6 (2), 131.4 (2), 131.8 (2), 139.4, 143.0, 148.3, 151.6, 152.7, 162.5. Analysis: calcd. for $C_{25}H_{17}BrN_4O_4S$ (549.39): C, 54.65; H, 3.12; N, 10.20%; found: C, 54.91; H, 3.39; N, 10.46%.

4-[4-(4-Bromophenyl)-3-cyano-2-(4-(dimethylamino)benzylideneamino)-1*H*-pyrrol-1-yl]benzenesulfonamide (7g)

Yield 76%, m.p. 99.7°C, IR: (ν_{max}, cm^{-1}): 3300, 3246 (NH_2), 3100 (CH arom.), 2920, 2870 (CH aliph.), 2206 (C=N), 1593 (C=N), 1373, 1165 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 3.0 (s, 6H, $2CH_3$), 6.7 (s, 1H, CH pyrrole), 7.0–7.9 (m, 14H, Ar-H + SO_2NH_2), 9.6 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 41.1 (2), 111.5, 115.1 (2), 117.3, 119.4, 120.4, 124.4 (2), 125.5, 126.6, 127.3, 127.9 (2), 131.5 (2), 132.3 (2), 134.3 (2), 139.7, 142.1, 148.7, 153.3, 162.7. Analysis: calcd. for $C_{26}H_{22}BrN_5O_2S$ (548.45): C, 56.94; H, 4.04; N, 12.77%; found: C, 56.68; H, 4,36; N, 12.55%.

4-[4-(4-Bromophenyl)-3-cyano-2-(4-nitrobenzylideneamino)-1*H*-pyrrol-1-yl]benzenesulfonamide (7h)

Yield 85%, m.p. 318.5°C, IR: (ν_{max}, cm^{-1}): 3373, 3269 (NH_2), 3100 (CH arom.), 2910, 2860 (CH aliph.), 2214 (C=N), 1593 (C=N), 1398, 1165 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 7.5 (s, 1H, CH pyrrole), 7.7–8.0 (m, 14H, Ar-H + SO_2NH_2), 9.2 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 79.7, 116.4, 120.8 (2), 124.2 (2), 124.7, 125.8 (2), 126.6, 128.0 (2), 130.6 (2), 131.0 (2), 131.9 (2), 139.2, 140.4, 143.3, 145.3, 149.4, 160.6. Analysis: calcd. for $C_{24}H_{16}BrN_5O_2S$ (549.01): C, 52.37; H, 2.93; N, 12.72%; found: C, 52.10; H, 2.66; N, 12.44%.

4-[4-(4-Bromophenyl)-3-cyano-2-(2,4-dinitrobenzylideneamino)-1*H*-pyrrol-1-yl]benzenesulfonamide (7i)

Yield 77%, m.p. 210.2°C, IR: (ν_{max}, cm^{-1}): 3300, 3211 (NH_2), 3095 (CH arom.), 2930, 2860 (CH aliph.), 2218 (C=N), 1583 (C=N), 1346, 1165 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 6.9 (s, 1H, CH pyrrole), 7.1–7.9 (m, 13H, Ar-H + SO_2NH_2), 10.3 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 104.4,

119.7, 120.6, 123.6, 126.6, 127.6 (2), 128.5, 129.0, 129.5 (2), 131.5 (2), 131.9, 132.2, 132.4 (2), 134.4, 134.8, 146.0, 148.9, 149.5, 151.5, 156.0. Analysis: calcd. for $C_{24}H_{15}BrN_6O_6S$ (595.38): C, 48.42; H, 2.54; N, 14.12%; found: C, 48.76; H, 2.26; N, 14.51%.

4-[4-(4-Bromophenyl)-2-(4-chlorobenzylideneamino)-3-cyano-1*H*-pyrrol-1-yl]benzenesulfonamide (7j)

Yield 79%, m.p. 164.6°C, IR: (ν_{max}, cm^{-1}): 3305, 3255 (NH_2), 3095 (CH arom.), 2910, 2861 (CH aliph.), 2212 (C=N), 1593 (C=N), 1338, 1165 (SO_2), 719 (C-Cl). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 7.0 (s, 1H, CH pyrrole), 7.4–7.9 (m, 14H, Ar-H + SO_2NH_2), 9.1 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 79.1, 116.6, 119.9, 120.7, 124.3 (2), 125.7, 126.6, 127.8 (2), 129.3 (2), 131.2 (2), 131.9 (2), 133.8, 134.7 (2), 137.5, 139.3, 143.1, 146.3, 162.0. Analysis: calcd. for $C_{24}H_{16}BrClN_4O_2S$ (537.98): C, 53.40; H, 2.99; N, 10.38%; found: C, 53.67; H, 2.68; N, 10.76%.

4-[4-(4-Bromophenyl)-3-cyano-2-(2,4-dichlorobenzylideneamino)-1*H*-pyrrol-1-yl]benzenesulfonamide (7k)

Yield 86%, m.p. 115.6°C, IR: (ν_{max}, cm^{-1}): 3346, 3265 (NH_2), 3088 (CH arom.), 2926, 2836 (CH aliph.), 2216 (C=N), 1581 (C=N), 1379, 1166 (SO_2), 719, 825 (2 C-Cl). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 7.1 (s, 1H, CH pyrrole), 7.2–7.9 (m, 13H, Ar-H + SO_2NH_2), 10.2 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 79.6, 120.6, 125.7, 125.9, 126.5 (2), 127.3, 128.2, 129.2, 130.6 (2), 131.0 (2), 132.4, 133.6, 136.3, 137.1 (2), 139.7 (2), 144.9, 145.3, 145.5, 156.8. Analysis: calcd. for $C_{24}H_{15}BrCl_2N_4O_2S$ (574.27): C, 50.19; H, 2.63; N, 9.76%; found: C, 50.47; H, 2.37; N, 9.50%.

4-[4-(4-Bromophenyl)-3-cyano-2-[(2-methoxynaphthalen-1-yl)methylene-amino]-1*H*-pyrrol-1-yl]benzenesulfonamide (7l)

Yield 65%, m.p. 278.2°C, IR: (ν_{max}, cm^{-1}): 3346, 3255 (NH_2), 3074 (CH arom.), 2971, 2842 (CH aliph.), 2210 (C=N), 1624 (C=N), 1371, 1151 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 4.0 (s, 3H, OCH_3), 7.4 (s, 1H, CH pyrrole), 7.5–8.0 (m, 16H, Ar-H + SO_2NH_2), 9.9 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 57.1, 104.3, 113.5, 114.5, 117.0, 117.6, 119.6, 120.0 (2), 120.5, 124.3, 125.1, 126.4, 126.5, 128.1 (2), 128.5, 128.7, 130.8 (2), 131.5, 131.8 (2), 136.2, 139.7, 143.5, 148. 4, 160.1, 161.5. Analysis: calcd. for $C_{29}H_{21}BrN_4O_3S$ (584.05): C, 59.49; H, 3.62; N, 9.57%; found: C, 59.21; H, 3.91.37; N, 9.81%.

4-[4-(4-Bromophenyl)-3-cyano-2-[(4-methoxynaphthalen-1-yl)methylene-amino]-1*H*-pyrrol-1-yl]benzenesulfonamide (7m)

Yield 73%, m.p. 181.2°C, IR: (ν_{max}, cm^{-1}): 3327, 3310 (NH_2), 3100 (CH arom.), 2955, 2846 (CH aliph.), 2208 (C=N), 1590 (C=N), 1370, 1157 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 4.0 (s, 3H, OCH_3), 7.1–8.0 (m, 16H, Ar-H + SO_2NH_2), 8.9 (s, 1H, CH pyrrole), 9.5 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 56.2, 104.0, 104.7, 117.2, 119.2, 120.5, 122.0, 122.3 (2), 122.5, 124.0, 124.2, 124.6, 124.8, 125.9, 126.1, 126.5, 127.9 (2), 131.5 (2), 134.5 (2), 139.6, 140.3, 143.2, 148.1, 159.1, 160.1. Analysis: calcd. for $C_{29}H_{21}BrN_4O_3S$ (585.47): C, 59.49; H, 3.62; N, 9.57%; found: C, 59.70; H, 3.41.37; N, 9.19%.

4-[5-(4-Bromophenyl)-4-oxo-3,4-dihydropyrrolo[2,3-d]pyrimidin-7-yl]benzenesulfonamide (8)

A solution of compound **5** (4.17 g, 0.01 mol.) in formic acid (20 mL) was refluxed for 6 h. The reaction mixture was poured onto ice/water and the solid obtained was recrystallized from dioxane to give **8**. Yield 81%, m.p. 313.7°C, IR: (ν_{max}, cm^{-1}): 3320, 3236, 3156 (NH, NH_2), 3094 (CH arom.), 1683 (C=O), 1591 (C=N), 1386, 1161 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 7.5 (s, 1H, CH pyrrole), 7.6–8.0 (m, 10H, Ar-H + SO_2NH_2), 8.1 (s, 1H, CH pyrimidine), 12.3 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 106.3, 119.7, 120.3, 121.5 (2), 124.4, 126.7, 127.9 (2), 130.8 (2), 132.3 (2), 141.1, 142.2, 145.0, 148.2, 158.4. Analysis: calcd. for $C_{18}H_{13}BrN_4O_3S$ (445.29): C, 48.55; H, 2.94; N, 12.58%; found: C, 48.30; H, 2.65; N, 12.84%.

***N*-[4-(4-bromophenyl)-3-cyano-1-(4-sulfamoylphenyl)-1*H*-pyrrol-2-yl]-2,2,2-trifluoroacetamide (9)**

A solution of compound **5** (4.17 g, 0.01 mol.) in trifluoroacetic anhydride (15 mL) was refluxed for 20 h. The solid obtained was recrystallized from ethanol to give **9**. Yield 69%, m.p. 206.5°C, IR: (ν_{max}, cm^{-1}): 3309, 3291 (NH_2), 3100 (CH arom.), 2202 (C=N), 1681 (C=O), 1610 (C=N), 1336, 1151 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 7.1 (s, 1H, CH pyrrole), 7.2–8.4 (m, 10H, Ar-H + SO_2NH_2), 13.8 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 118.6, 119.4, 120.2, 123.8, 124.1, 124.5, 124.9, 126.5, 126.8, 127.1 (2), 130.3, 130.5, 131.0, 131.5, 131.7, 138.9, 147.7, 159.9. Analysis: calcd. for $C_{19}H_{12}BrF_3N_4O_3S$ (513.29): C, 44.46; H, 2.36; N, 10.92%; found: C, 44.12; H, 2.71; N, 10.66%.

***N*-[4-(4-bromophenyl)-3-cyano-1-(4-sulfamoylphenyl)-1*H*-pyrrol-2-yl]acetamide (10)**

A solution of compound **5** (4.17 g, 0.01 mol.) in acetic anhydride (20 mL) was refluxed for 5 min. The reaction mixture was concentrated and the solid separated was recrystallized from ethanol to give **10**. Yield 81%, m.p. 113.0°C, IR: (ν_{max}, cm^{-1}): 3389, 3344, 3238 (NH, NH_2), 3095 (CH arom.), 2981, 2862 (CH aliph.), 2189 (C=N), 1685 (C=O), 1635 (C=N), 1340, 1163 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 2.0 (s, 3H, $COCH_3$), 6.1 (s, 1H, CH pyrrole), 7.0–8.0 (m, 10H, Ar-H + SO_2NH_2), 10.2 (s, 1H, NH, D_2O exchangeable) . ^{13}C-NMR (DMSO-d_6, δ, ppm): 22.3, 113.5, 117.5, 119.5, 121.3, 123.0, 124.8, 125.8, 127.8, 131.3 (2), 132.3 (2), 134.3 (2), 139.2, 142.9, 148.5, 170.0. Analysis: calcd. for $C_{19}H_{15}BrN_4O_3S$ (459.32): C, 49.68; H, 3.29; N, 12.20%; found: C, 49.36; H, 3.51; N, 12.56%.

***N*-acetyl-N-[4-(4-bromophenyl)-3-cyano-1-(4-sulfamoylphenyl)-1*H*-pyrrol-2-yl]acet-amide (11)**

A solution of compound **5** (4.17 g, 0.01 mol.) in acetic anhydride (20 mL) was refluxed for 24 h. The reaction mixture was concentrated and the solid obtained was recrystallized from dioxane to give **11**. Yield 59%, m.p. 142.8°C, IR: (ν_{max}, cm^{-1}): 3495, 3122 (NH_2), 3055 (CH arom.), 2920, 2862 (CH aliph.), 2227 (C=N), 1734, 1718 (2 C=O), 1593 (C=N), 1369, 1161 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 2.4 (s, 6H, $2COCH_3$), 7.4 (s, 1H, CH pyrrole), 7.5–8.1 (m, 10H, Ar-H + SO_2NH_2). ^{13}C-NMR (DMSO-d_6, δ, ppm): 21.0 (2), 113.9, 120.4, 120.8, 120.9, 121.8 (2), 124.9, 125.3, 128.8 (2), 129.5 (2), 133.5 (2), 139.5, 140.1, 146.5, 171.8 (2). Analysis: calcd. for $C_{21}H_{17}BrN_4O_4S$ (501.35): C, 50.31; H, 3.42; N, 11.18%; found: C, 50.63; H, 3.12; N, 11.41%.

***N*-[4-(4-bromophenyl)-3-cyano-1-(4-sulfamoylphenyl)-1*H*-pyrrol-2-yl]-2-chloroacetamide (13)**

A solution of compound **5** (4.17 g, 0.01 mol.) in chloroacetylchloride (20 mL) was refluxed for 1 h. The reaction mixture was poured onto ice/water and the solid obtained was recrystallized from dioxane to give **13**. Yield 80%, m.p. 154.4°C, IR: (ν_{max}, cm^{-1}): 3470, 3380, 3210 (NH, NH_2), 3100 (CH arom.), 2956, 2817 (CH aliph.), 2223 (C=N), 1707 (C=O), 1627 (C=N), 1388, 1149 (SO_2), 725 (C-Cl). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 4.2 (s, 2H, CH_2), 7.4 (s, 1H, CH pyrrole), 7.5–7.9 (m, 10H, Ar-H + SO_2NH_2), 8.2 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 42.4, 89.5, 114.7, 119.4, 121.3, 124.9 (2), 125.1, 128.5, 129.3, 130.5, 131.1, 131.4, 132.3, 133.1, 138.8, 142.6, 149.7, 166.8. Analysis: calcd. for $C_{19}H_{14}BrClN_4O_3S$ (493.76): C, 46.22; H, 2.86; N, 11.35%; found: C, 46.52; H, 2.67; N, 11.14%.

***N*-[4-(4-bromophenyl)-3-cyano-1-(4-sulfamoylphenyl)-1*H*-pyrrol-2-yl]-2-chloro-*N*-(2-chloroacetyl)acetamide (14)**

A solution of compound **5** (4.17 g, 0.01 mol) in chloroacetylchloride (20 mL) was refluxed for 16 h. The solid obtained was recrystallized from acetic acid to give **14**. Yield 64%, m.p. 359.2°C, IR: (ν_{max}, cm^{-1}): 3253, 3190 (NH_2), 3088 (CH arom.), 2944, 2865 (CH aliph.), 2223 (C=N), 1720, 1705 (2 C=O), 1591 (C=N), 1388, 1174 (SO_2), 727 (C-Cl). ^{1}H-NMR (DMSO-d_6, D_2O, δ, ppm): 4.2 (s, 4H, 2 CH_2), 7.3 (s, 1H, CH pyrrole), 7.4–8.0 (m, 10H, Ar-H + SO_2NH_2). ^{13}C-NMR (DMSO-d_6, δ, ppm): 42.1, 42.8, 89.7, 114.6, 119.4, 120.6, 123.3 (2), 124.8, 125.1, 125.8, 127.8 (2), 129.1 (2), 131.0, 131.9, 133.0, 138.2, 140.5, 165.2, 166.8. Analysis: calcd. for $C_{21}H_{15}BrCl_2N_4O_4S$ (570.24): C, 44.23; H, 2.65; N, 9.83%; found: C, 44.51; H, 2.36; N, 10.19%.

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 $mol^{-1}Å^{-1}$ with MMFF94X force field and the partial charges were automatically calculated. The X-ray crystallographic structure of c-Src complex with its ligand (PDB ID: 1YOL) was obtained from the protein data bank. The enzyme was 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 (Table 1).

***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 synthesized compounds using the sulfo-rhodamine-B stain (SRB) assay using the method of Skehan et al. (11). 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

(10^4 cells/well) for 24 h before treatment with the compound(s) to allow attachment of cell to the wall of the plate. The tested compounds were dissolved in dimethyl sulfoxide. 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% (w/v) SRB dissolved in 1% acetic acid. An 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 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 the means ± standard error and the results are given in Table 2.

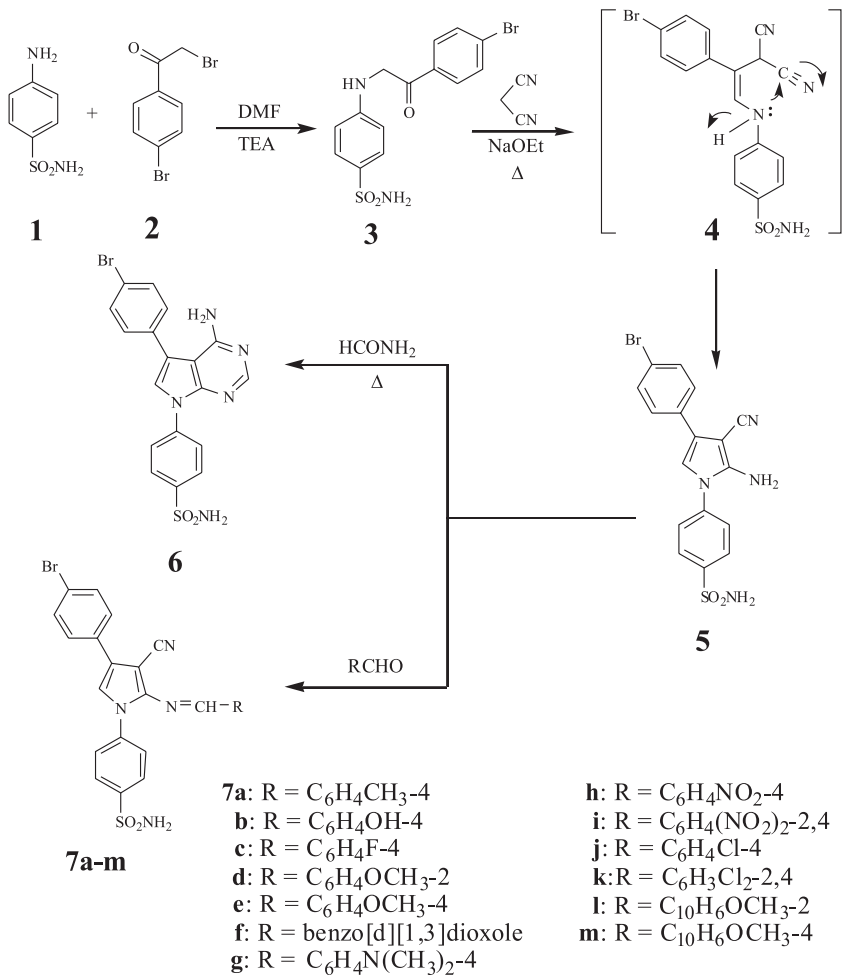
RESULTS AND DISCUSSION

Chemistry

The synthesized compounds were designed with the aim of exploring their anticancer activity. In this investigation, a novel series of bromopyrroles **5**, **7a–m**, **9–11**, **13**, **14** and bromopyrrolopyrimidines **6**, **8** having a biologically active sulfonamide moieties were synthesized to evaluate their *in vitro* anticancer activity. Thus, interaction of sulfanilamide **1** with 4-

Table 1. Binding scores and amino acid interactions of the docked compounds on the active site of c-Src.

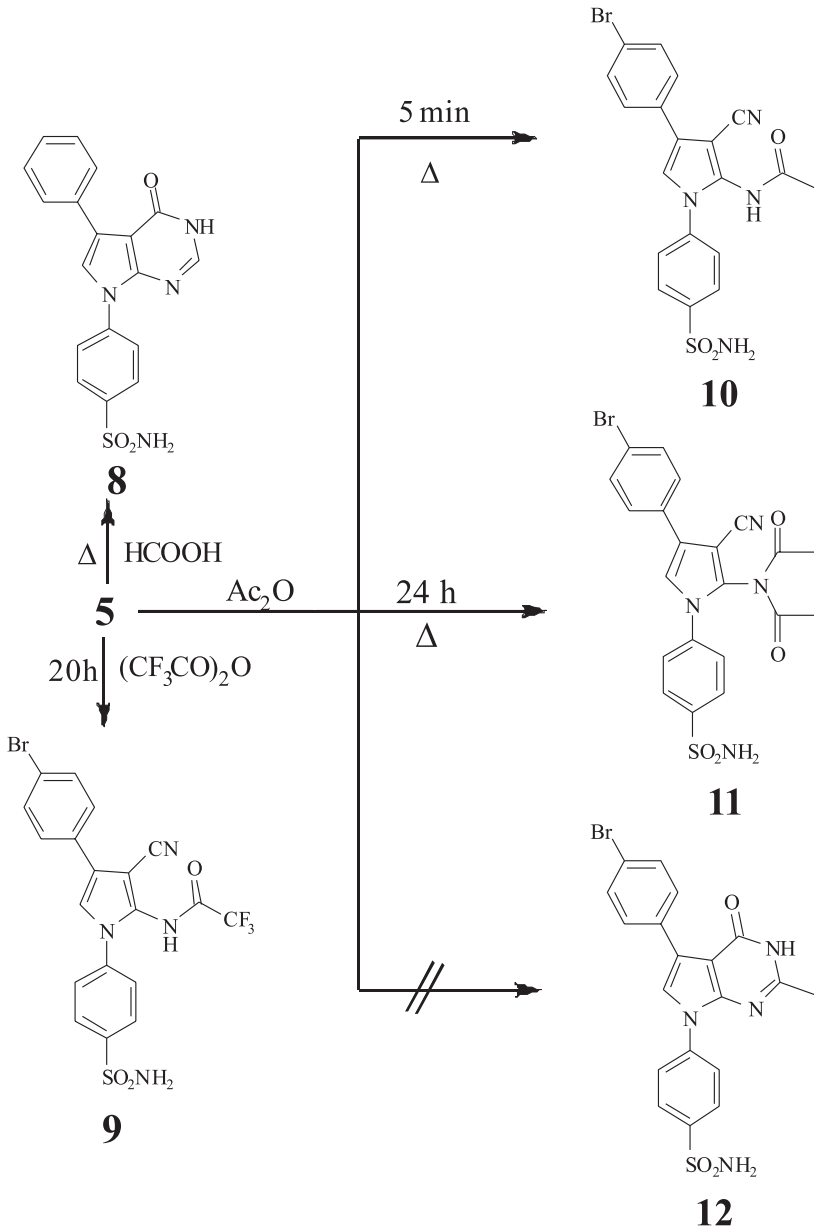
Compd. No.	S Kcal/mol	Amino acid interactions	Interacting groups	H bond length Å
5	–13.6201	Asp 350, Met 343 Ser 347	NH_2 N pyrimidine	3.22, 2.22 3.09
6	–16.1961	Glu 341, Met 343 Asp 350, Ser 347	NH_2, N pyrimidine SO_2NH_2, SO_2NH_2	1.94, 2.89 1.42, 3.02
7a	–17.7147	Glu 312, Asp 436 Asp 350	SO_2NH_2, SO_2NH_2 CN	2.43, 201 3.74
7b	–9.3848	Met 343, Asp 350 Ser 347	OH, SO_2NH_2 SO_2	2.89, 1.98 3.47
7c	–10.4441	Asp 350	SO_2	3.04
7d	–14.8247	Glu 281, Asp 350 Asp 350	OCH_3, SO_2NH_2	3.49, 1.67 3.32
7e	–11.6741	Asp 350	SO_2NH_2	2.34–1.80
7f	–12.3196	Asp 350	SO_2NH_2	3.01
7g	–20.4112	Asp 350	N=C	3.11
7h	–17.8049	Glu 312, Asp 406	SO_2NH_2, SO_2NH_2	2.14, 2.15
7i	–15.5585	Asp 350	CN	3.74
7j	–13.7170	Met 343	SO_2, SO_2NH_2	3.25, 2.01
7k	–19.0188	Asp 350	SO_2NH_2	2.40
7l	–22.8663	Gly 281	SO_2NH_2	3.28, 3.15
7m	–10.4936	Asp 350	SO_2NH_2	1.78
8	–3.1180	Asp 350, Ser 347	SO_2NH_2, SO_2NH_2	1.40, 1.97
9	–11.6900	Asp 350, Asp 406 Glu 312	SO_2NH_2, SO_2NH_2 SO_2NH_2	3.48, 3.05 2.16
10	–16.0731	Asp 350	SO_2NH_2	1.52
11	–10.0602	Asp 350	SO_2NH_2	2.51
13	–13.0866	Ala 382	C=O	2.43
14	–12.9995	Asp 350	SO_2NH_2	1.57



Scheme 1. Formation of pyrrolo and pyrrolopyrimidine derivatives **5**–**7a**–**m**

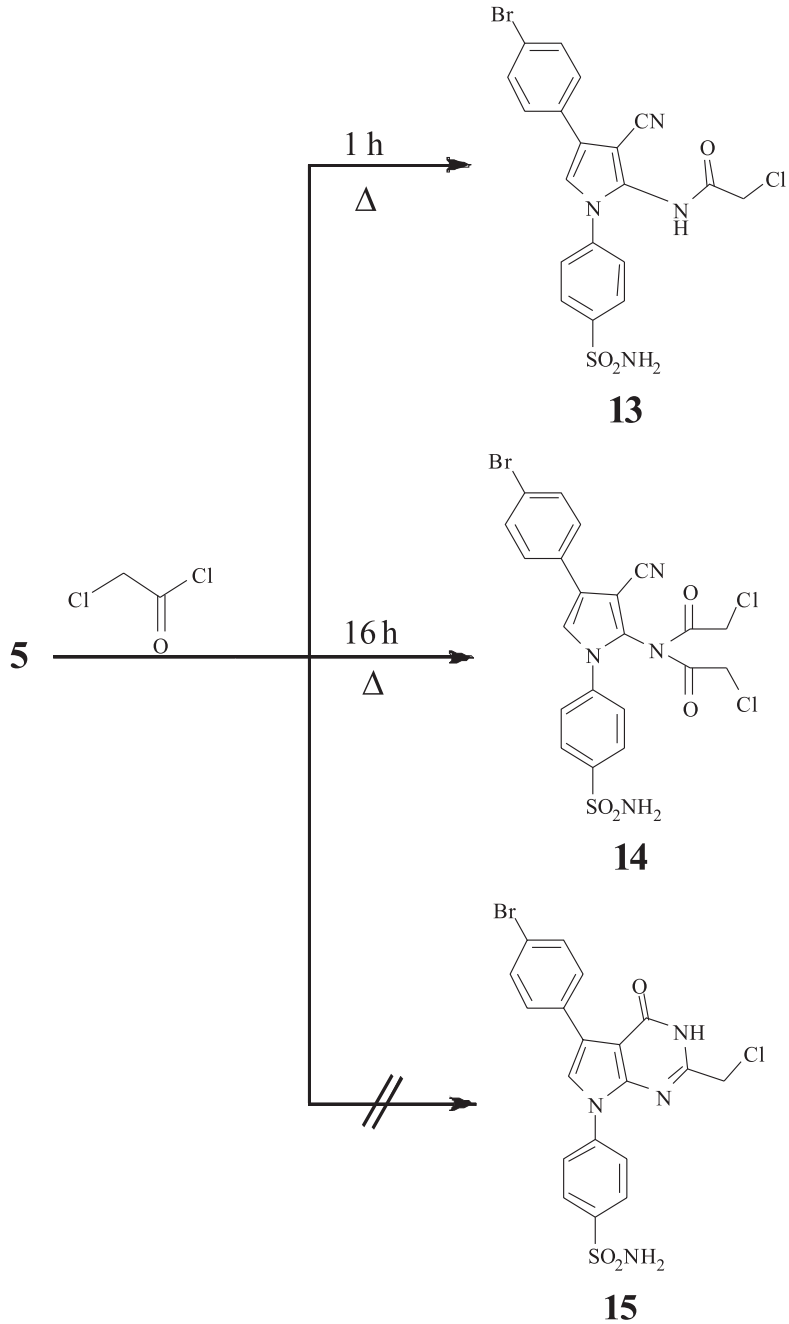
bromophenacyl bromide **2** in DMF containing a catalytic amount of triethylamine gave 4-(2-(4-bromophenyl)-2-oxoethyl-amino)benzene-sulfonamide **3**, which upon interaction with malononitrile in refluxing ethanol containing sodium ethoxide furnished the strategic starting material, pyrrole-2-amino-3-carbonitrile **5** (Scheme 1). The formation of compound **5** proceeded *via* initial formation of the intermediate **4** followed by intramolecular cyclization to give **5**. The structure of compound **3** was verified by elemental analysis and spectral data. The IR spectrum of compound **3** showed the presence of the characteristic bands for (NH, NH_2), (C=O) and (SO_2). Also, ^{1}H-NMR spectrum indicated the presence of a singlet at 4.7 ppm, which could be assigned to CH_2 group. The IR spectrum of compound **5** exhibited bands for (NH_2), (C=N) and (SO_2) groups. In addition, ^{1}H-NMR spectrum of compound **5** revealed signals at 6.1 ppm due to NH_2 group and 7.9 ppm for SO_2NH_2 group.

Interaction of compound **5** with formamide caused cyclization to give pyrrolopyrimidine derivative **6** (Scheme 1). Its IR spectrum showed the absence of (C=N) band, which confirms the cyclization and formation of pyrrolopyrimidine system **6**. In addition, the behavior of compound **5** towards carbonyl compounds was studied. Thus, the reaction of compound **5** with aromatic aldehydes in acetic acid yielded Schiff's bases **7a**–**m**. The structures of compounds **7a**–**m** were confirmed by elemental analyses, IR, ^{1}H-NMR and ^{13}C-NMR spectra. The IR spectra of compounds **7a**–**m** revealed the presence of (C=N) band. Also, ^{1}H-NMR spectra showed the presence of singlet for (N=CH) group.



Scheme 2. Formation of new pyrrolo and pyrrolopyrimidine derivatives **8**–**11**

Refluxing compound **5** in formic acid caused cyclization *via* elimination of water to give the pyrrolopyrimidine derivative **8** (Scheme 2). Its IR spectrum exhibited the absence of (C=N) band, which confirms the cyclization and formation of pyrrolopyrimidine system **8**. The reactivity of compound **5** towards acid anhydride in different time of reflux was observed. Thus, reaction of compound **5** with acetic anhydride for 5 min furnished the monoacetyl derivative **10**. On the other hand, when compound **5** was reacted with acetic anhydride for long time (24 h), the corresponding diacetyl derivative **11** was obtained instead of the cyclic system pyrrolopyrimidine derivative **12** on the basis of elemental analysis and IR spectrum, which showed the presence of (C=N) band. When compound **5** was reacted with trifluoroacetic anhydride for long time (20 h), the corresponding monoacetyl derivative **9** was obtained, on the basis of elemental analysis and IR spectrum, which showed the presence of (C=N)



Scheme 3. Formation of some novel pyrrole derivatives **13** and **14**

band. ^{1}H-NMR spectrum of **11** showed singlet at 2.4 ppm for two acetyl groups.

On the other hand, when compound **5** was reacted with chloroacetylchloride for short time (1 h), the corresponding monoacetylchloride derivative **13** was obtained while, applying the same reaction for long time (16 h), the corresponding diacetylchloride derivative **14** was obtained in a good yield rather than the cyclic pyrrolopyrimidine derivative **15**, based on the elemental analyses and spectral data. The IR spectrum of compound **13** showed the presence of (C=N), (C=O) and (C-Cl) bands. ^{1}H-

Table 2. *In vitro* anticancer screening of the synthesized compounds against human breast cancer cell line (MCF7).

Compound	Compound concentration (μM)				IC_{50} (μM)
	10 μM	25 μM	50 μM	100 μM	
	Surviving fraction (mean ± SE)*				
Doxorubicin	0.314 ± 0.032	0.309 ± 0.016	0.251 ± 0.023	0.266 ± 0.032	8.02
5	0.327 ± 0.121	0.273 ± 0.043	0.233 ± 0.011	0.255 ± 0.020	7.56
6	0.340 ± 0.090	0.294 ± 0.021	0.246 ± 0.110	0.256 ± 0.002	7.56
7a	0.275 ± 0.113	0.265 ± 0.005	0.323 ± 0.010	0.349 ± 0.032	6.74
7b	0.301 ± 0.121	0.244 ± 0.055	0.236 ± 0.001	0.238 ± 0.012	7.01
7c	0.300 ± 0.090	0.247 ± 0.035	0.238 ± 0.023	0.311 ± 0.066	7.34
7d	0.345 ± 0.133	0.262 ± 0.100	0.313 ± 0.043	0.319 ± 0.065	7.84
7e	0.234 ± 0.033	0.225 ± 0.111	0.248 ± 0.015	0.279 ± 0.076	6.47
7f	0.256 ± 0.067	0.362 ± 0.021	0.345 ± 0.034	0.235 ± 0.041	7.90
7g	0.252 ± 0.084	0.265 ± 0.142	0.231 ± 0.101	0.264 ± 0.102	6.46
7h	0.338 ± 0.066	0.261 ± 0.031	0.234 ± 0.116	0.263 ± 0.131	7.56
7i	0.235 ± 0.019	0.228 ± 0.008	0.261 ± 0.032	0.256 ± 0.056	6.46
7j	0.273 ± 0.191	0.205 ± 0.018	0.237 ± 0.011	0.251 ± 0.007	6.74
7k	0.331 ± 0.012	0.310 ± 0.110	0.295 ± 0.044	0.299 ± 0.033	8.15
7l	0.334 ± 0.061	0.319 ± 0.029	0.287 ± 0.017	0.289 ± 0.049	6.70
7m	0.391 ± 0.028	0.300 ± 0.015	0.299 ± 0.006	0.311 ± 0.112	8.45
8	0.273 ± 0.004	0.315 ± 0.017	0.276 ± 0.003	0.287 ± 0.001	6.74
9	0.361 ± 0.011	0.379 ± 0.089	0.298 ± 0.042	0.321 ± 0.058	7.84
10	0.353 ± 0.071	0.323 ± 0.006	0.273 ± 0.027	0.222 ± 0.010	7.56
11	0.288 ± 0.055	0.229 ± 0.091	0.240 ± 0.042	0.242 ± 0.080	6.74
13	0.324 ± 0.010	0.340 ± 0.021	0.294 ± 0.069	0.316 ± 0.049	7.29
14	0.332 ± 0.023	0.273 ± 0.011	0.285 ± 0.048	0.234 ± 0.052	7.29

* Each value is the mean of three values ± standard error (SE)

NMR spectrum of **13** revealed the presence of a singlet at 4.2 ppm assigned for CH_2 group. The IR spectrum of **14** revealed the presence of (C=N) at 2223 cm^{-1} and 2C=O at 1720 and 1705 cm^{-1}. The ^{1}H-NMR spectrum of **14** exhibited singlet at 4.2 ppm due to two CH_2 groups (Scheme 3).

Molecular docking

Several classes of inhibitors are currently used to inhibit the activity of c-Src in a number of cell types. However, they often show poor selectivity within the c-Src family, which in mammals comprises at least eight members involved in many key functions of the cell (12). Recently, it has been shown that c-Src inhibitors of the pyrrolopyrimidine class exhibit a powerful inhibitory activity and a several-fold greater selectivity for c-Src against most tyrosine kinases (13–15). suggesting that c-Src can be activated downstream of receptor activator of NF-κB (RANK) (16), a member of the tumor necrosis factor (TNF) receptor superfamily that is involved in cell differentiation, function, and survival (17–19).

In order to realize the aim of the present investigations, the authors have performed molecular docking of the synthesized compounds on the active sites of c-Src, which may provide an understanding of their effect as antitumor agents. The protein data bank file (PDB ID:1YOL) was selected for this purpose. The file contains c-Src enzyme co-crystallized with a pyrrolopyrimidine 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 c-Src enzyme was performed for all synthesized compounds. Docking protocol was verified by redocking of the co-crystal-

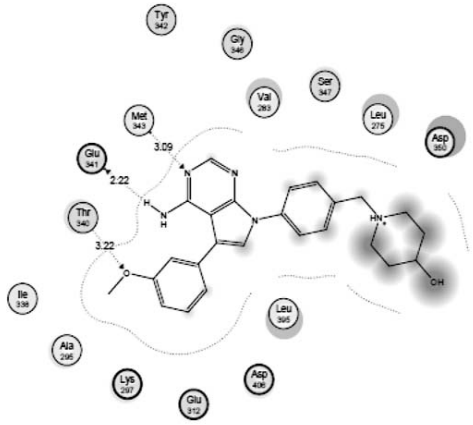


Figure 1. Pyrrolopyrimidine ligand on the active site of c-Src enzyme

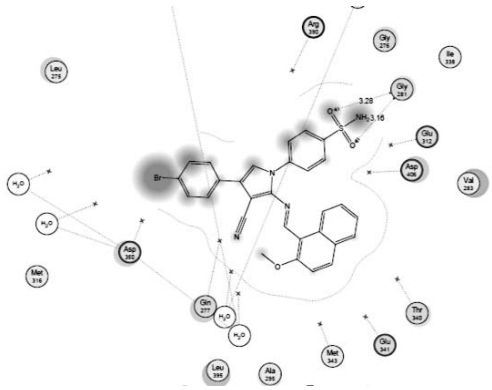


Figure 3. Compound **7l** on the active site of c-Src enzyme

lized ligand in the vicinity of the active site of the enzyme with energy score (S) = –22.6799 Kcal/ mol and root mean standard deviation (RMSD) = 0.8205 (Fig. 1). The ligand interacts with the active site amino acids by three interactions: with Met 343 with hydrogen bond of 3.09 Å, with Glu 341 with hydrogen bond of 2.22 Å and with Thr 340 with hydrogen bond of 3.22 Å.

All the synthesized compounds were docked on the active site of the enzyme showing good fitting. The energy score (S) as well as amino acid interactions of the synthesized compounds are listed in Table 1.

The best energy scores were exhibited by compounds **7g** and **7l** with S = –20.4112 and –22.8663 Kcal/ mol, respectively. Figures 2 and 3 describe the amino acid interactions with compounds **7g** and **7l**, respectively.

In vitro antitumor activity

The newly synthesized compounds were evaluated for their *in vitro* cytotoxic activity against

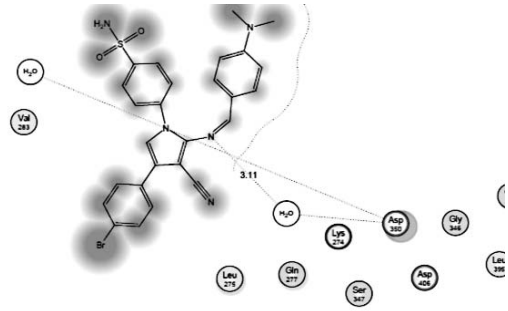


Figure 2. Compound **7g** on the active site of c-Src enzyme

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 (MCF7). The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability. *In vitro* cytotoxic activity of the synthesized compounds compared to the reference drug is presented in Table 2.

The strategic starting material – pyrrole derivative **5** – showed IC_{50} value 7.65 µM which did not change upon cyclization to the amino pyrrolopyrimidine derivative **6**. However, the formation of several Schiff's bases **7a**–**m** dramatically influenced the activity, especially for compounds **7a**, **7e**, **7g**, **7i**, **7j**, and **7l**, with IC_{50} values of 6.74, 6.47, 6.46, 6.46, 6.74 and 6.70 µM, respectively. On the other hand, the pyrrolopyrimidine derivative **8** showed good IC_{50} value of 6.74 µM. In case of the trifluoroacetyl derivative **9**, the IC_{50} value was 7.84 µM while the monoacetyl pyrrolo derivative **10** showed IC_{50} value of 7.56 µM, which was better for the diacetyl analogue **11** with IC_{50} value of 6.74 µM. The IC_{50} values of 7.29 µM were observed for the mono and dichloroacetyl derivatives **13** and **14**, respectively. Finally, all the synthesized compounds showed better IC_{50} than doxorubicin except compounds **7k** and **7m** with IC_{50} values of 8.15 and 8.45 µM, respectively. Compounds **7g** and **7l** showed both good IC_{50} of 6.46 and 6.70 µM and also good docking score of –20.4112 and –22.8663 Kcal/mol, suggesting good candidates for c-Src inhibitors.

CONCLUSION

The objective of the present study was to synthesize and investigate the anticancer activity of some novel pyrrolo and pyrrolopyrimidine deriva-

tives carrying the biologically active sulfonamide moieties. Most of the synthesized compounds showed good activity with better IC_{50} than doxorubicin as reference drug, especially compounds **7a**, **7e**, **7g**, **7i**, **7j**, **8** and **11**. Also, compounds **5**, **6**, **7b–d**, **7f**, **7h**, **7l**, **9**, **10**, **13**, **14** are nearly as active as doxorubicin as positive control, while compounds **7k** and **7m** showed activity lower than doxorubicin.

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