Acta Poloniae Pharmaceutica – Drug Research, Vol. 72 No. 1 pp. 79–87, 2015 ISSN 0001-6837
Polish Pharmaceutical Society

CYTOTOXIC ACTIVITY OF SOME NOVEL SULFONAMIDE DERIVATIVES

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Abstract: The versatile synthons 2-chloro-*N*-(4-sulfamoylphenyl)acetamides **1a,b** were used as a key intermediates for the synthesis of sulfonamide derivatives with adamantyl **2**, indene **3**, morpholinophenyl **4**, pipronyl **5**, benzothiazole **6–8**, pyrazole **9**, thiadiazole **10**, **11**, quinoline **12**, isoquinoline **13**, thiazoles **14–19**, acrylamides **20–24** and benzochromene **25** moieties *via* reaction with several nitrogen nucleophiles. The newly synthesized compounds were screened *in vitro* for their anticancer activity against breast cancer (MDA-MB-231) and colon cancer (HT-29) cell lines. Compound **17** was found to be the most potent against breast cancer cell lines with IC_{50} value 66.6 μM compared with the reference drug 5-fluorouracil with IC_{50} value 77.28 μM.

Keywords: synthesis, sulfonamides, anticancer activity

Although there has been great progress in the development of treatment and prevention for cancer, it still remains an enormous threat to people's health in the 21st century, representing the second primary cause of death in the world (1). In the past years, considerable efforts have been made to develop innovative strategies for finding safe and effective methods of treating this disease. With the increasing understanding of the biological process involved in cancer cell survival and the discovering of new targets, more and more novel chemical therapeutic drugs have been designed for treatment of cancer. Sulfonamides have attracted great interest over many years due to their broad bioactivities (2–4). The heterocyclic compounds are very important part of medicinal chemistry, among them it is worth to pay attention on derivatives of adamantyl, morpholine, piperonyl, benzothiazole, pyrazole, thiadiazole, quinoline and isoquinoline. They have a broad spectrum of pharmacological activities like anticancer (5–9), antibacterial (10–12) and antifungal activity (13–15). Moreover, it was also reported that acrylamides and chromenes have an interesting anticancer activity against different cell lines (16–19). Generally, it seems that a sulfonamide group combined with acetamide having different type of aryl, heteroaryl as well as alkyl substituents exhibited a wide range of pharmacological applications. In our earlier work, we also showed that compounds containing short amine fragments exhibit anticancer activity (20–22). It has been known that aryl/heteroaryl sulfonamides may act as anticancer agents through a variety of mechanisms such as: cell cycle perturbation in the G1 phase, disruption of microtubule assembly, angiogenesis inhibition, and functional suppression of the transcriptional activator NF-Y. Moreover, following an extensive evaluation, numerous sulfonamides were found to act as carbonic anhydrase (CA) inhibitiors (23–26). The most prominent mechanism was the inhibition of carbonic anhydrase isozymes (CAs) (27). In light of this information and in continuation of our interest in the biologically active heterocyclic compounds, we have decided to continue the study on the antiproliferative activity of some newer sulfonamide moiety bearing aryl amines, acetamide, acrylamide and chromene derivatives.

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EXPERIMENTAL

Chemistry

Melting points (°C, uncorrected) were determined in open capillaries on a Gallenkemp melting point apparatus (Sanyo Gallenkemp, Southborough, UK). Pre-coated silica gel plates (silica gel 0.25 mm, 60 GF-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. IR spectra were recorded in KBr discs using IR-470 Shimadzu spectrometer (Shimadzu, Tokyo, Japan). NMR spectra in DMSO-d_6 were recorded on Bruker Ac-500 UltraShield NMR spectrometer (Bruker, Flawil, Switzerland, δ, ppm) at 500 MHz, using TMS as an internal standard. Elemental analyses were performed on Carlo Erba 1108 Elemental Analyzer (Heraeus, Hanau, Germany). For all compounds they were within ± 0.4% of the theoretical values. All chemicals were commercially supplied from Sigma-Aldrich, USA.

General procedure for the synthesis of sulfonamides (2–13)

A mixture of compound **1a** (2.489 g, 0.01 mol) and required amines, namely: adamantylamine, 5-aminoindanone, 4-morpholinobenzamine, piperonylamine, 2-amino-6-fluorobenzothiazole, 2-amino-6-ethoxybenzothiazole, 2-amino-5,6-dimethyl-benzothiazole, 2-amino-1-ethylpyrazole, 2-amino-5-ethylthiadiazole, 2-amino-5-thioethylthiadiazole, 3-aminoquinoline and 2-aminoisoquinoline (0.01 mol) in dimethylformamide (20 mL) containing 3 drops of triethylamine was refluxed for 17 h. The reaction mixture was collected and poured onto ice/water. The obtained solid was recrystallized from dioxane to give derivatives **2**–**13**, respectively.

2-(Adamant-2-ylamino)-*N*-(4-sulfamoylphenyl)acetamide(2)

Yield 89%, m.p. 244.5°C. IR (KBr, cm^{-1}): 3425, 3310, 3278 (NH, NH_2), 3068 (CH arom.), 2976, 2881 (CH aliph.), 1684 (C=O), 1383, 1160 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.5–2.0 (m, 12H, $6CH_2$, adamantyl), 1.59–1.67 (m, 4H, CH adamantyl), 3.5 (s, 2H, CH_2CO), 7.2 (s, 1H, NHCH$_2$, D_2O-exchangeable), 7.7–7.9 (m, 4H, Ar-H), 10.2 (s, 1H, NH-Ph, D_2O-exchangeable), 11.1 (s, 2H, SO_2NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 28.6 (3), 36.1 (3), 40.1 (3), 44.4, 50.2, 118.5 (2), 126.8 (2), 138.4, 141.2, 171.7 (C=O). Analysis: calcd. for $C_{18}H_{25}N_3O_3S$ (363.47): C, 59.48; H, 6.93; N, 11.56%; found: C, 59.12; H, 6.68; N, 11.23%.

2-(2,3-Dihydro-1*H*-inden-5-ylamino-*N*-(4-sulfamoylphenyl)acetamide(3)

Yield 79%, m.p. 188.9°C. IR (KBr, cm^{-1}): 3391, 3362, 3212 (NH, NH_2), 3072 (CH arom.), 1681 (C=O), 1378, 1156 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.9–2.0 (m, 2H, CH_2-CH_2-CH_2, cyclopentyl), 2.6–2.8 (m, 4H, $2CH_2$ cyclopentyl), 3.9 (s, 2H, CH_2CO), 5.9 (s, 1H, NHCH$_2$, D_2O-exchangeable), 6.4–7.8 (m, 9H, Ar-H + SO_2NH_2), 10.2 (s, 1H, NHCO, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 25.1, 32.5 (2), 47.9, 110.8, 115.3, 124.3 (2), 126.8 (2), 131.6, 136.4, 138.4, 141.6, 144.3, 146.9, 171.2 (C=O). Analysis: calcd. for $C_{17}H_{19}N_3O_3S$ (345.41): C, 59.11; H, 5.54; N, 12.17%; found: C, 59.32; H, 5.22; N, 12.50%.

2-(4-Morpholinophenylamino)-*N*-(4-sulfamoylphenyl)acetamide (4)

Yield 77%, m.p. 222.8°C. IR (KBr, cm^{-1}): 3406, 3385, 3261 (NH, NH_2), 3099 (CH arom.), 2962, 2909 (CH aliph.), 1378, 1161 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.0–3.7 (m, 8H, $4CH_2$, morpholino), 4.3 (d, 2H, CH_2CO, J = 7.0 Hz), 6.8 (s, 1H, NHCH$_2$, D_2O-exchangeable), 7.0–7.9 (m, 10H, Ar-H + SO_2NH_2, 11.1 (s, 1H, NHCO, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 48.5 (2), 57.0, 66.1 (2), 115.0 (2), 117.4 (2), 120.2 (2), 126.8 (2), 138.8, 140.4, 141.4, 143.3, 171.2 (C=O). Analysis: calcd. for $C_{18}H_{22}N_4O_4S$ (390.46): C, 55.37; H, 5.68; N, 14.35%; found: C, 55.62; H, 5.33; N, 14.16%.

2-(Benzo[d][1,3]dioxol-5-ylmethylamino)-*N*-(4-sulfamoylphenyl)acetamide (5)

Yield 91%, m.p. 263.7°C. IR (KBr, cm^{-1}): 3386, 3318, 3256 (NH, NH_2), 3100 (CH arom.), 2991, 2868 (CH aliph.), 1386, 1156 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.9 (s, 2H, CH_2CO), 4.1 (s, 2H, CH_2NH), 6.0 (s, 2H, OCH_2O), 6.9–7.9 (m, 9H, Ar-H + SO_2NH_2), 9.6 (s, 1H, NHCH$_2$, D_2O-exchangeable), 11.2 (s, 1H, NHCO, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 47.2, 49.7, 100.8, 110.4, 118.9, 124.4, 124.8 (2), 126.6 (2), 126.7, 139.0, 141.0, 147.3, 147.8, 164.2. Analysis: calcd. for $C_{16}H_{17}N_3O_5S$ (363.39): C, 52.88; H, 4.72; N, 11.56%; found: C, 52.56; H, 4.48; N, 11.21%.

2-(6-Fluorobenzo[d]thiazol-2-ylamino)-*N*-(4-sulfamoylphenyl)acetamide (6)

Yield 68%, m.p. 207.6°C; IR (KBr, cm^{-1}): 3410, 3368, 3271 (NH, NH_2), 3081 (CH arom.), 2936, 2836 (CH aliph.), 1688 (C=O), 1612 (C=N), 1383, 1160 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.2 (s, 2H, CH_2CO), 7.0–8.0 (m, 9H, Ar-H + SO_2NH_2), 8.5 (s, 1H, NHCH$_2$, D_2O-exchangeable), 10.7 (s, 1H,

NHCO, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 64.6, 107.1, 114.6, 117.3 (2), 118.6, 120.1, 124.8 (2), 130.8, 131.7, 146.2, 154.6, 163.6, 168.4 (C=O). Analysis: calcd. for $C_{15}H_{13}FN_4O_3S_2$ (380.42): C, 47.36; H, 3.44; N, 14.73%; found: C, 47.16; H, 3.19; N, 14.46%.

2-(6-Ethoxybenzo[d]thiazol-2-ylamino)-*N*-(4-sulfamoylphenyl)acetamide (7)

Yield 59%, m.p. 144.2°C. IR (KBr, cm^{-1}): 3425, 3390, 3278 (NH, NH_2), 3077 (CH arom.), 2981, 2876 (CH aliph.), 1662 (C=O), 1628 (C=N), 1365, 1160 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.3 (t, 3H, CH_3), 4.0 (s, 2H, CH_2CO), 4.1 (q, 2H, CH_2), 6.8–8.1 (m, 9H, Ar-H + SO_2NH_2), 8.6 (s, 1H, NHCH$_2$, D_2O-exchangeable), 10.4 (s, 1H, NHCO, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 14.7, 60.9, 63.7, 105.5, 113.5, 118.1 (2), 119.1, 121.4, 126.7 (2), 132.0, 132.9, 146.8, 153.6, 164.8, 169.9. Analysis: calcd. for $C_{17}H_{18}N_4O_4S_2$ (406.48): C, 50.23; H, 4.46; N, 13.78%; found: C, 50.49; H, 4.18; N, 13.48%.

2-(5,6-Dimethylbenzo[d]thiazol-2-ylamino)-*N*-(4-sulfamoylphenyl)acetamide (8)

Yield 73%, m.p. 147.1°C. IR (KBr, cm^{-1}): 3410, 3376, 3312 (NH, NH_2), 3092 (CH arom.), 2936, 2872 (CH aliph.), 1689 (C=O), 1618 (C=N), 1382, 1155 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.3 (s, 6H, $2CH_3$), 4.1 (s, 2H, CH_2), 7.1–8.1 (m, 8H, Ar-H + SO_2NH_2), 9.9 (s, 1H, NH, D_2O-exchangeable), 10.6 (s, 1H, NHCO, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 19.2, 19.6, 60.8, 118.7, 119.1, 121.1, 121.5 (2), 126.7 (2), 128.0, 129.2, 133.6, 138.6, 151.9, 165.9, 170.0. Analysis: calcd. for $C_{17}H_{18}N_4O_3S_2$ (390.48): C, 52.29; H, 4.65; N, 14.35%; found: C, 52.61; H, 4.39; N, 14.55%.

2-(1-Ethyl-1*H*-pyrazol-5-ylamino)-*N*-(4-sulfamoylphenyl)acetamide (9)

Yield 64%, m.p. 238.7°C. IR (KBr, cm^{-1}): 3368, 3290, 3186 (NH, NH_2), 3075 (CH arom.), 2978, 2912 (CH aliph.), 1694 (C=O), 1599 (C=N), 1378, 1156 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.3 (t, 3H, CH_3), 3.9 (q, 2H, CH_2), 4.0 (s, 2H, CH_2CO), 6.6–8.1 (m, 8H, Ar-H + 2 CH pyrazole + SO_2NH_2), 10.5 (s, 1H, NH, D_2O-exchangeable), 10.7 (s, 1H, NHCO, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 14.2, 49.1, 56.8, 94.6, 119.7 (2), 126.6 (2), 139.0, 141.4, 142.6, 150.8, 163.7. Analysis: calcd. for $C_{13}H_{17}N_5O_3S$ (323.37): C, 48.28; H, 5.30; N, 21.66%; found: C, 48.09; H, 5.63; N, 21.42%.

2-(5-Ethyl-1,3,4-thiadiazol-2-ylamino)-*N*-(4-sulfamoylphenyl)acetamide (10)

Yield 68%, m.p. 128.4°C. IR (KBr, cm^{-1}): 3388, 3266, 3214 (NH, NH_2), 3100 (CH arom.), 2984, 2836 (CH aliph.), 1678 (C=O), 1619 (C=N), 1377, 1161 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.1 (t, 3H, CH_3), 2.9 (d, 2H, CH$_2$NH, J = 6.9 Hz), 5.4 (s, 1H, NH, D_2O-exchangeable), 7.0–7.9 (m, 6H, Ar-H + SO_2NH_2), 10.7 (s, 1H, NHCO, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 13.7, 24.4, 53.1, 120.6 (2), 126.7 (2), 138.8, 141.3, 162.2, 164.2, 165.5. Analysis: calcd. for $C_{12}H_{15}N_5O_3S_2$ (341.41): C, 42.22; H, 4.43; N, 20.51%; found: C, 42.46; H, 4.11; N, 20.19%.

2-(5-(Ethylthio)-1,3,4-thiadiazol-2-ylamino)-*N*-(4-sulfamoylphenyl)acetamide (11)

Yield 74%, m.p. 154.1°C. IR (KBr, cm^{-1}): 3441, 3377, 3189 (NH, NH_2), 3086 (CH arom.), 2976, 2880 (CH aliph.), 1666 (C=O), 1627 (C=N), 1388, 1160 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3), 3.1 (q, 2H, CH_2), 4.1 (s, 2H, CH_2), 7.0–8.0 (m, 6H, Ar-H + SO_2NH_2), 8.9 (s, 1H, NH, D_2O-exchangeable), 10.6 (s, 1H, NHCO, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 14.3, 28.2, 55.6, 119.1 (2), 126.7 (2), 138.6, 140.9, 160.1, 166.6, 169.9. Analysis: calcd. for $C_{12}H_{15}N_5O_3S_3$ (373.47): C, 38.59; H, 4.05; N, 18.75%; found: C, 38.29; H, 4.27; N, 18.51%.

2-(Quinolin-3-ylamino)-*N*-(4-sulfamoylphenyl)acetamide (12)

Yield 59%, m.p. 144.1°C. IR (KBr, cm^{-1}): 3328, 3291, 3191 (NH, NH_2), 3056 (CH arom.), 2967, 2871 (CH aliph.), 1696 (C=O), 1619 (C=N), 1378, 1154 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.1 (d, 2H, CH_2, J = 6.8 Hz), 6.6 (s, 1H, NH, D_2O-exchangeable), 7.0–7.9 (m, 11H, Ar-H + SO_2NH_2), 8.2 (s, 1H, N=CH quinoline), 10.5 (s, 1H, NHCO, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 60.8, 123.8 (2), 124.2, 125.4, 126.9, 127.6, 128.4 (2), 129.2, 129.6, 136.3, 138.5, 141.6, 142.0, 143.4, 169.7. Analysis: calcd. for $C_{17}H_{16}N_4O_3S$ (356.40): C, 57.29; H, 4.52; N, 15.72%; found: C, 57.48; H, 4.21; N, 15.50%.

2-(Isoquinolin-3-ylamino)-*N*-(4-sulfamoylphenyl)acetamide (13)

Yield 61%, m.p. 180.7°C. IR (KBr, cm^{-1}): 3406, 3366, 3218 (NH, NH_2), 3062 (CH arom.), 2968, 2866 (CH aliph.), 1677 (C=O), 1611 (C=N), 1376, 1161 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.0 (s, 3H, CH_2), 6.6–8.6 (m, 12H, Ar-H + SO_2NH_2), 9.1 (s, 1H, NH, D_2O-exchangeable), 11.8 (s, 1H, NHCO, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 58.1, 96.6, 124.3 (3), 126.0 (3), 126.6 (2),

130.8, 138.8 (2), 143.4, 155.2, 157.3, 169.0. Analysis: calcd. for $C_{17}H_{16}N_4O_3S$ (356.40): C, 57.29; H, 4.52; N, 15.72%; found: C, 56.91; H, 4.75; N, 15.40%.

General procedure for the synthesis of 4-amino-*N*-(4-sulfamoylphenyl)-2-thioxo-3-substituted phenyl-2,3-dihydrothiazole-5-carboxamides (14–19)

To a solution of **1b** (2.39 g; 0.01 mol) in absolute ethanol (30 mL) and dimethylformamide (10 mL) containing triethylamine (1 mL), the isothiocyanate derivatives (0.01 mol) together with elemental sulfur (0.32 g; 0.01 mol) were added. The reaction mixture was refluxed for 5 h, and poured onto ice/water. The obtained solid was crystallized from dioxane to give **14**–**19**, respectively.

4-Amino-*N*-(4-sulfamoylphenyl)-2-thioxo-3-*p*-tolyl-2,3-dihydrothiazole-5-carboxamide (14)

Yield 66%, m.p. 117.7°C. IR (KBr, cm^{-1}): 3368, 3305, 3226 (NH, NH_2), 2981, 2848 (CH aliph.), 1687 (C=O), 1378, 1160 (SO_2), 1276 (C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.2 (s, 3H, CH_3), 6.5 (s, 2H, NH_2, D_2O-exchangeable), 6.7–7.9 (m, 10H, Ar-H + SO_2NH_2), 10.6 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 23.2, 81.6, 122.6 (2), 127.6 (2), 128.6 (2), 130.8 (2), 133.6 (2), 139.7, 144.1, 160.6, 165.4, 178.4. Analysis: calcd. for $C_{17}H_{16}N_4O_3S_3$ (420.53): C, 48.55; H, 3.83; N, 13.32%; found: C, 48.29; H, 3.52; N, 13.62%.

4-Amino-3-(4-methoxyphenyl)-*N*-(4-sulfamoylphenyl)-2-thioxo-2,3-dihydrothiazole-5-carboxamide (15)

Yield 66%, m.p. 139.7°C. IR (KBr, cm^{-1}): 3385, 3315, 3271 (NH, NH_2), 3095 (CH arom.), 2961, 2861 (CH aliph.), 1681 (C=O), 1388, 1156 (SO_2), 1276 (C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.8 (s, 3H, OCH_3), 6.6 (s, 2H, NH_2, D_2O-exchangeable), 6.7–8.0 (m, 10H, Ar-H + SO_2NH_2), 10.9 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 54.2, 79.2, 113.6 (2), 123.7 (2), 124.3, 125.6 (2), 126.0 (2), 133.2, 140.6, 155.7, 158.6, 166.7, 189.6. Analysis: calcd. for $C_{17}H_{16}N_4O_4S_3$ (436.53): C, 46.77; H, 3.69; N, 12.83%; found: C, 46.48; H, 3.42; N, 12.49%.

4-Amino-3-(4-fluorophenyl)-*N*-(4-sulfamoylphenyl)-2-thioxo-2,3-dihydrothiazole-5-carboxamide (16)

Yield 81%, m.p. 196.8°C. IR (KBr, cm^{-1}): 3410, 3391, 3246 (NH, NH_2), 3100 (CH arom.), 1672 (C=O), 1376, 1152 (SO_2), 1269 (C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.4 (s, 2H, NH_2, D_2O-exchangeable), 7.0–8.1 (m, 10H, Ar-H + SO_2NH_2), 11.2 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 76.1, 114.6 (2), 122.7 (2), 128.4 (2), 129.6 (2), 131.1, 137.8, 141.2, 157.0, 160.2, 165.5, 187.4. Analysis: calcd. for $C_{16}H_{13}FN_4O_3S_3$ (424.49): C, 45.27; H, 3.09; N, 13.20%; found: C, 45.53; H, 3.28; N, 13.46%.

4-Amino-3-(4-nitrophenyl)-*N*-(4-sulfamoylphenyl)-2-thioxo-2,3-dihydrothiazole-5-carboxamide (17)

Yield 78%, m.p. 175.3°C. IR (KBr, cm^{-1}): 3284, 3220, 3186 (NH, NH_2), 3066 (CH arom.), 1654 (C=O), 1508, 1307 (NO_2), 1379, 1198 (SO_2), 1203 (C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.7 (s, 2H, NH_2, D_2O-exchangeable), 6.9–7.9 (m, 10H, Ar-H + SO_2NH_2), 10.9 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 77.4, 120.7 (2), 123.6 (2), 126.4 (2), 128.1 (2), 133.7, 141.4, 142.6, 145.0, 158.2, 162.7, 190.1. Analysis: calcd. for $C_{16}H_{13}N_5O_5S_3$ (451.50): C, 42.56; H, 2.90; N, 15.51%; found: C, 42.31; H, 2.60; N, 15.74%.

4-Amino-3-(4-bromophenyl)-*N*-(4-sulfamoylphenyl)-2-thioxo-2,3-dihydrothiazole-5-carboxamide (18)

Yield 71%, m.p. 290.9°C. IR (KBr, cm^{-1}): 3376, 3212, 3186 (NH, NH_2), 3056 (CH arom.), 1676 (C=O), 1376, 1165 (SO_2), 1218 (C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.2 (s, 2H, NH_2, D_2O-exchangeable), 7.2–8.0 (m, 10H, Ar-H + SO_2NH_2), 10.8 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 72.3, 120.6, 122.7 (2), 126.8 (2), 127.4 (2), 130.6 (2), 133.7, 136.1, 138.8, 156.7, 162.9, 186.8. Analysis: calcd. for $C_{16}H_{13}BrN_4O_3S_3$ (485.40): C, 39.59; H, 2.70; N, 11.54%; found: C, 39.81; H, 2.96; N, 11.36%.

4-Amino-3-(4-iodophenyl)-*N*-(4-sulfamoylphenyl)-2-thioxo-2,3-dihydrothiazole-5-carboxamide (19)

Yield 69%, m.p. 272.2°C. IR (KBr, cm^{-1}): 3385, 3318, 3190 (NH, NH_2), 3076 (CH arom.), 1684 (C=O), 1394, 1161 (SO_2), 1254 (C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.5 (s, 2H, NH_2, D_2O-exchangeable), 7.0–8.1 (m, 10H, Ar-H + SO_2NH_2), 10.6 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 74.3, 91.6, 120.4 (2), 128.7 (2), 129.6 (2), 131.3, 133.6, 139.1 (2), 141.4, 157.6, 164.2, 189.6. Analysis: calcd. for $C_{16}H_{13}IN_4O_3S_3$ (532.40): C, 36.10; H, 2.46; N, 10.52%; found: C, 36.41; H, 2.70; N, 10.19%.

General procedure for the synthesis of 2-cyano-3-(4-substituted phenyl)-*N*-(4-sulfamoylphenyl)acrylamides (20-24)

A mixture of **1b** (2.39 g; 0.01 mol) and aromatic aldehydes (0.01 mol) in ethanol (20 mL) containing 3 drops of piperidine was refluxed for 8 h. The obtained solid was crystallized from ethanol to give **20**–**24**, respectively.

2-Cyano-3-(4-fluorophenyl)-*N*-(4-sulfamoylphenyl)acrylamide (20)

Yield 83%; m.p. 265.9°C. IR (KBr, cm^{-1}): 3337, 3310, 3290 (NH, NH_2), 3065 (CH arom.), 2966, 2876 (CH aliph.), 2205 (C≡N), 1685 (C=O), 1396, 1184 (SO_2): ^{1}H-NMR in (DMSO-d_6, δ, ppm): 7.0–8.1 (m, 10H, Ar-H + SO_2NH_2), 8.3 (s,1H, CH), 10.9 (s, 1H, NH, D_2O- exchangeable). ^{13}C-NMR in (DMSO-d_6, δ, ppm): 105.6, 114.3 (2), 114.9, 122.6 (2) 126.7 (2), 127.8 (2), 129.9, 130.8, 133.7, 152.6, 163.1, 164.9. Analysis: calcd. for $C_{16}H_{12}FN_3O_3S$ (345.35): C, 55.65; H, 3.50; N, 12.17%; found: C, 55.38; H, 3.22; N, 12.51%.

3-(3-Bromophenyl)-2-cyano-*N*-(4-sulfamoylphenyl)acrylamide (21)

Yield 86%, m.p. 167.2°C. IR (KBr, cm^{-1}): 3412, 3391, 3212 (NH, NH_2), 3095 (CH arom.), 2971, 2836 (CH aliph.), 2218 (C≡N), 1685 (C=O), 1328, 1155 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 7.0–7.9 (m, 10H, Ar-H + SO_2NH_2), 8.9 (s, 1H, CH), 10.6 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 109.0, 115.8, 121.1 (2), 126.2, 126.5, 127.3 (2), 130.3, 130.8, 131.8, 137.5, 138.3, 141.3, 152.6, 170.3. Analysis: calcd. for $C_{16}H_{12}BrN_3O_3S$ (406.25): C, 47.30; H, 2.98; N, 10.34%; found: C, 47.62; H, 2.66; N, 10.12%.

3-(4-Bromophenyl)-2-cyano-*N*-(4-sulfamoylphenyl)acrylamide (22)

Yield 80%, m.p. 233.3°C. IR (KBr, cm^{-1}): 3390, 3309, 3287 (NH, NH_2), 3100 (CH arom.), 2992, 2920 (CH aliph.), 2219 (C≡N), 1689 (C=O), 1336, 1156 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 7.0–7.9 (m, 10H, Ar-H + SO_2NH_2), 8.4 (s, 1H, CH), 11.2 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 108.2, 115.1, 119.8 (2), 121.7, 128.4 (2), 129.6 (2), 130.7 (2), 133.8, 136.7, 140.8, 155.1, 164.6. Analysis: calcd. for $C_{16}H_{12}BrN_3O_3S$ (406.25): C, 47.30; H, 2.98; N, 10.34%; found: C, 47.07; H, 2.66; N, 10.59%.

2-Cyano-3-(3-methoxynaphthalen-2-yl)-*N*-(4-sulfamoylphenyl)acrylamide (23)

Yield 69%, m.p. 104.5°C. IR (KBr, cm^{-1}): 3364, 3310, 3206 (NH, NH_2), 3066 (CH arom.), 2980, 2942 (CH aliph.), 2212 (C≡N), 1652 (C=O), 1376, 1156 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 4.0 (s, 3H, OCH_3), 7.0–8.0 (m, 12H, Ar-H + SO_2NH_2), 9.1 (s, 1H, CH), 10.7 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 56.2, 109.7, 110.2, 115.4, 121.2 (2), 123.3, 126.5 (3), 127.3 (2), 127.9, 128.5, 129.7, 133.8, 137.9, 139.3, 155.8, 160.5, 164.0. Analysis: calcd. for $C_{21}H_{17}N_3O_4S$ (407.44): C, 61.90; H, 4.21; N, 10.31%; found: C, 61.59; H, 4.44; N, 10.02%.

2-Cyano-5-(4-dimethylamino)phenyl)-*N*-(4-sulfamoylphenyl)penta-2,4-dienamide (24)

Yield 59%, m.p. 240.2°C. IR (KBr, cm^{-1}): 3360, 3315, 3272 (NH, NH_2), 3091 (CH arom.), 2946, 2860 (CH aliph.), 2212 (C≡N), 1676 (C=O), 1377, 1156 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.0 (s, 6H, $N(CH_3)_2$), 6.6, 6.9 (2d, 2H, CH=CH, J =7.0, 7.1 Hz), 7.5 (s, 1H, CH, J =7.2 Hz), 7.7–8.0 (m, 10H, Ar-H + SO_2NH_2), 10.3 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 40.1 (2), 96.7, 112.4 (2), 115.8, 122.1 (2), 122.8, 126.4, 126.8 (2), 129.3 (2), 130.6, 131.0, 138.9, 141.5, 149.7, 164.2. Analysis: calcd. for $C_{20}H_{20}N_4O_3S$ (396.46): C, 60.59; H, 5.08; N, 14.13%; found: C, 60.92; H, 5.30; N, 14.41%.

3-Oxo-*N*-(4-sulfamoylphenyl)-3*H*-benzo[f]chromone-2-carboxamide (25)

Yield 79%, m.p. 287.1°C. IR (KBr, cm^{-1}): 3343, 3309, 3275 (NH, NH_2), 3076 (CH arom.), 1700, 1673 (2C=O), 1374, 1184 (SO_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 7.4–8.1 (m, 12H, Ar-H + SO_2NH_2), 8.5 (s, 1H, CH), 10.3 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 116.3, 116.9, 118.2, 120.7 (2), 121.4, 122.6, 125.2, 127.3 (2), 128.2 (2), 131.7 (2), 135.7 (2), 142.6, 154.8, 168.9, 172.0. Analysis: calcd. for $C_{20}H_{14}N_2O_5S$ (394.40): C, 60.91; H, 3.58; N, 7.10%; found: C, 60.64; H, 3.29; N, 7.33%.

***In vitro* antiproliferative activity**

Antiproliferative activity *in vitro* was measured by the cell growth inhibition assay. The general *in vitro* anticancer evaluation of the synthesized compounds was conducted by using WST-1 reagent for determination of IC_{50} for each compound. Results are given in Table 1.

WST-1 cell proliferation assay

MDA-MB-231 breast cancer and HT-29 colon cancer cell lines were purchased from the American Type Culture Collection. Cells were maintained in RPMI 1640 (Sigma), supplemented with 10% FBS

Table 1. *In vitro* antiproliferative activity of the novel synthesized compounds against breast (MDA-MB-231) and colon (HT-29) cancer cell lines.

Compd. No.	MDA-MB-231 IC_{50} (μM)[a]	HT-29 IC_{50} (μM)[a]
1b	NA[b]	49.22 ± 0.02
2	NA	109.94 ± 0.01
3	147 ± 0.3	NA
4	NA	NA
5	NA	NA
6	NA	96.61 ± 0.085
7	NA	NA
8	171.76 ± 0.7	45.62 ± 0.04
9	NA	NA
10	NA	NA
11	221.53 ± 0.08	NA
12	271.67 ± 0.03	NA
13	184.82 ± 0.08	NA
14	NA	NA
15	NA	NA
16	NA	NA
17	66.6 ± 0.04	NA
18	NA	77.96 ± 0.01
19	139.4 ± 0.2	74.46 ± 0.09
20	NA	60.84
21	NA	NA
22	NA	NA
23	236.78 ± 0.11	NA
24	85.31 ± 0.02	131.86 ± 0.018
5-Fluorouracil	77.28 ± 0.2	10.23 ± 0.09

[a] IC_{50}: Concentration of the synthesized compounds (μM) producing 50% cell growth inhibition after 48 h of compound exposure, as determined by the WST-1 assay. Each experiment was run at least three times, and the results are presented as average values ± standard deviation. [b] Activity is above 150 μM.

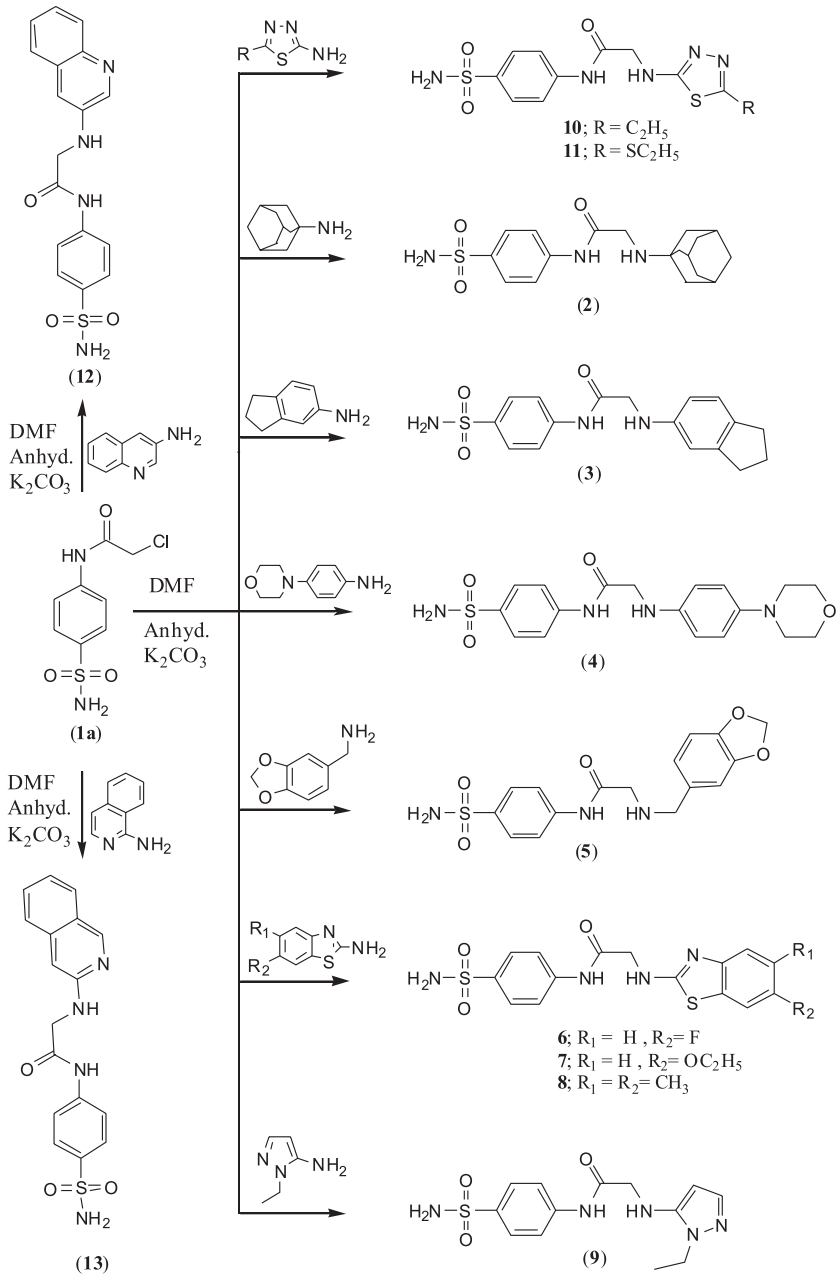
(Lonza), 100 IU/mL penicillin, 100 μg/mL streptomycin and 2 mmol/L L-glutamine (Sigma). Cells were seeded into 96-well plates at 0.4 × 104/well and incubated overnight. The medium was replaced with fresh one containing the desired concentrations of the synthesized compounds. After 48 h, 10 μL of the WST-1 reagent was added to each well and the plates were re-incubated for 4 h at 37°C. The amount of formazan was quantified using ELISA reader at 450 nm (28, 29).

RESULTS AND DISCUSSION

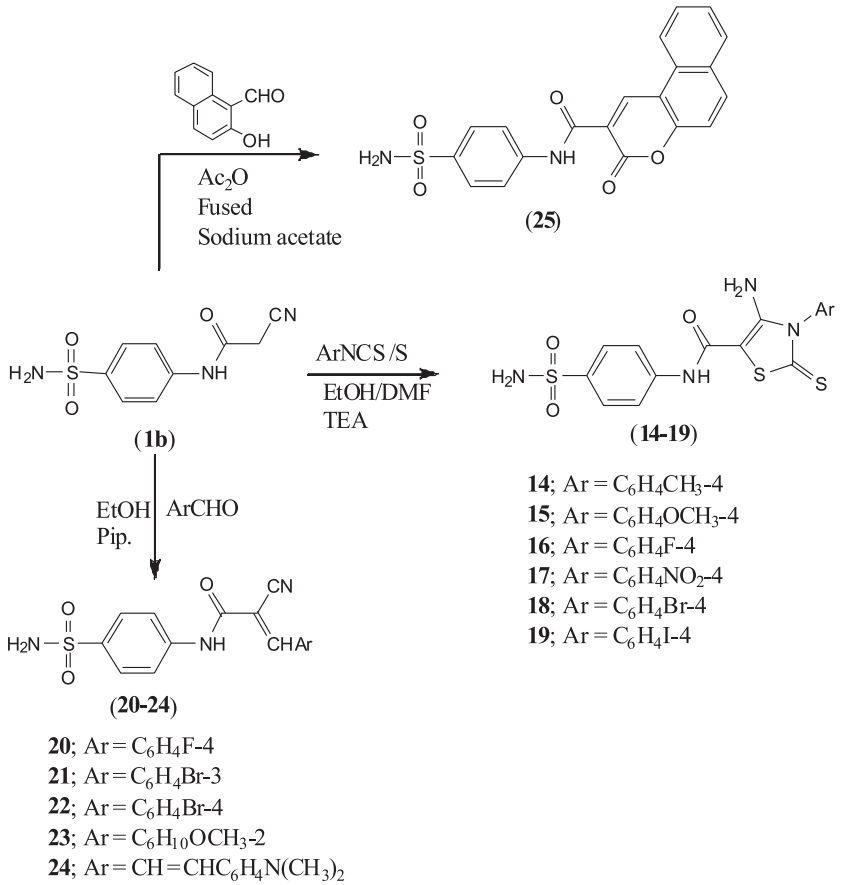
Chemistry

The starting material – 2-chloro-*N*-(4-sulfamoylphenyl) acetamide **1a** was prepared according to the reported method (29) and converted to the corresponding acetamide derivatives **2–13** by reaction with different amines such as adamantylamine, 5-aminoindanone, 4-morpholino-benzeneamine, piperonylamine, 2-aminobenzothiophenes, 2-amino-1-ethylpyrazole, 2-amino-5-ethyl-1,3,4-thiadiazole, 3-aminoquinoline and 2-aminoisoquinoline (Scheme 1). The structures of compounds **2–13** were established on the basis of microanalysis and spectral data. The IR spectra showed the presence of characteristic bands for (NH, NH_2), (CH aromatic), (CH aliphatic), (C=O), (SO_2). ^{1}H-NMR spectra of **2–13** revealed signals around 3.5–4.9 ppm assigned to CH_2CO group. In addition, interaction of 2-cyano-*N*-(4-sulfamoylphenyl)acetamide **1b** (23) with elemental sulfur and arylisothiocyanate yielded

the corresponding thiazole derivatives **15**–**19**, respectively (Scheme 2). The formation of the later products took place in accordance with a reported reaction (26). The structures of compounds **15**–**19** were supported on the basis of elemental analysis, IR, ^{1}H-NMR and ^{13}C-NMR spectral data. IR spectra revealed the absence of C≡N band and the presence of the characteristic bands for NH, NH_2, C=O, and C=S. ^{1}H-NMR spectra showed a singlet at around 6.2–6.7 ppm assigned to (NH_2) group. ^{13}C-NMR spectra exhibited a singlet at 178.4–190.1 ppm assigned to (C=S) group. On the other hand, reaction of **1b** with aromatic aldehydes gave the corresponding acrylamide derivatives **20**–**24**. Analytical and spectral data were in agreement with the proposed structures. The IR spectra of compounds **20**–**24** exhibited characteristic bands for NH, C≡N, C=O and SO_2 groups, while ^{1}H-NMR spectra showed the



Scheme 1. Synthesis of novel sulfonamide derivatives (**2**–**13**)



Scheme 2. Synthesis of novel sulfonamide derivatives (**14**–**25**)

disappearance of CH_2 group and the presence of a new peak at 10.3–11.2 ppm assigned to NH group. Furthermore, Perkin reaction was carried out by reaction of **1b** with 2-hydroxy-1-naphthaldelyde in acetic anhydride in the presence of fused sodium acetate and yielded the corresponding benzochromene-2-one derivative **25**. The reaction went in analogy with the reported method (10). The IR spectrum of **25** exhibited the absence of C≡N band and the presence of 2 C=O bands. ^{1}H-NMR spectrum of **25** showed a singlet at 8.5 ppm assigned to CH chromene group and 10.3 ppm due to NH group consistent with the proposed structure.

In-vitro antiproliferative activity

Antiproliferative activity of all the synthesized compounds was assessed against breast cancer (MDA-MB-231) and colon cancer (HT-29) cell lines. The results of antiproliferative activity indicated that sulfonamide **17** carrying 2,3-dihydrothiazole with free amino group at 4-position, 4-nitrophenyl at 3-position and thioxo at 2-position was found to exert the most powerful effect on MDA-MB-231 with IC_{50} of 66.6 µM compared with that of the positive control – 5-fluorouracil (IC_{50} = 77.28 µM). Also, the sulfonamide **24** containing 2-cyano-5-(4-*N*,*N*-dimethylphenylamino)penta-2,4-dienamide was slightly less active than 5-fluorouracil as reference drug against MDA-MB-231 (IC_{50} = 85.31 µM). On the other hand, sulfonamides having cyano and acetamide groups **1b** and 5,6-dimethylbenzothiazole with acetamide moiety **8** were found to be the most active compounds against HT-29 with IC_{50} values of 49.22 and 45.62 µM, respectively, but less active than 5-fluorouracil. In addition, compounds **18**–**20** exhibited a moderate activity with IC_{50} values 77.96, 74.46 and 60.84 µM against HT-29, while, compounds **3**–**7**, **9**–**16** and **21**–**23** showed no activity (Table 1).

CONCLUSION

The objective of the present study was to synthesize and investigate the antiproliferative activity of some novel sulfonamide derivatives carrying the biologically active acetamide, dihydrothiazole, acrylamide and benzochromene moieties. Compound **17** was found to be the most potent against breast cancer cell lines compared with the reference drug – 5-fluorouracil. Also, compound **24** is nearly as active as 5-fluorouracil. In addition, compounds **1b** and **8** exhibited a moderate activity against colon cancer cell line but less active than the positive control.

Acknowledgments

The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for its funding of this research through the Research Group Project no. GP-VPP-302.

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Received: 13. 11 2013