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) inhibitors (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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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, piperonyl 5, benzothiazole 6–8, pyrazole 9, thiadiazole 10, 11, quinoline 12, isoquinoline 13, thiazole 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 IC50 value 66.6 µM compared with the reference drug 5-fluorouracil with IC50 value 77.28 µM.

Keywords: synthesis, sulfonamides, anticancer activity

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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-d6 were recorded on Bruker Ac-500 UltraShield NMR spectrometer (Bruker, Flawil, Switzerland, 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-aminooindanone, 4-morpholinobenzamine, piperonylamine, 2-amino-6-fluorobenzothiazole, 2-amino-5-thioethylthiadiazole, 3-ethoxybenzothiazole, 2-amino-1-ethylpyrazole, 2-amino-5-ethoxyindanone, 4-morpholinobenzamine, piperonylaminophenol, 4.3 (d, 2H, CH2CO, J = 7.0 Hz), 6.8 (s, 1H, NHCH3, D2O-exchangeable), 7.0–7.9 (m, 10H, Ar-H) 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, NH2), 3068 (CH aril), 2976, 2881 (CH aliph.), 1684 (C=O), 1383, 1160 (SO2). 1H-NMR (DMSO-d6, δ, ppm): 1.5–2.0 (m, 12H, 6CH2, adamantyl), 1.59–1.67 (m, 4H, CH2, D2O-exchangeable), 3.5 (s, 2H, CH2CO), 7.2 (s, 1H, NHCH3, D2O-exchangeable), 7.7–7.9 (m, 4H, Ar-H), 10.2 (s, 1H, NHPh, D2O-exchangeable), 11.1 (s, 2H, SO2NH, D2O-exchangeable). 13C-NMR (DMSO-d6, δ, ppm): 26.8 (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 C16H17N3O5S: C, 55.37; H, 5.68; N, 14.35%; found: C, 55.62; H, 5.33; N, 14.16%.

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

Yield 79%, m.p. 188.9°C. IR (KBr, cm–1): 3391, 3362, 3212 (NH, NH2), 3072 (CH aril), 1681 (C=O), 1378, 1156 (SO2). 1H-NMR (DMSO-d6, δ, ppm): 1.9–2.0 (m, 2H, CH2CH2CH2, cyclopenyl), 2.6–2.8 (m, 4H, 2CH2 cyclopenyl), 3.9 (s, 2H, CH2CO), 5.9 (s, 1H, NHCH3, D2O-exchangeable), 6.4–7.8 (m, 9H, Ar-H + SO2NH2), 10.2 (s, 1H, NHCO, D2O-exchangeable). 13C-NMR (DMSO-d6, 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 C31H30N5O5S: C, 59.11; H, 5.22; N, 11.17%; 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, 3256 (NH, NH2), 3099 (CH aril), 2962, 2909 (CH aliph.), 1378, 1161 (SO2). 1H-NMR (DMSO-d6, δ, ppm): 3.0–3.7 (m, 8H, 4CH2 morpholin), 4.3 (d, 2H, CH2CO, J = 7.0 Hz), 6.8 (s, 1H, NHCH3, D2O-exchangeable), 7.0–7.9 (m, 10H, Ar-H + SO2NH2), 11.1 (s, 1H, NHCO, D2O-exchangeable). 13C-NMR (DMSO-d6, 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 C21H23N5O5S: C, 55.7; H, 5.68; N, 14.35%; found: C, 55.62; H, 5.33; N, 14.16%.

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

Yield 91%, m.p. 263.7°C. IR (KBr, cm–1): 3386, 3318, 3256 (NH, NH2), 3100 (CH aril), 2991, 2868 (CH aliph.), 1386, 1156 (SO2). 1H-NMR (DMSO-d6, δ, ppm): 3.9 (s, 2H, CH2CO), 4.1 (s, 2H, CH2NH), 6.0 (s, 2H, OCH2O), 6.9–7.9 (m, 9H, Ar-H + SO2NH2), 9.6 (s, 1H, NHCH3, D2O-exchangeable), 11.2 (s, 1H, NHCO, D2O-exchangeable). 13C-NMR (DMSO-d6, 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 C21H19N5O5S: C, 52.88; H, 4.72; N, 11.56%; found: C, 52.56; H, 4.48; N, 11.21%.

2-(6-Fluorobenzothiazol-2-ylamino)-N-(4-sulfamoylphenyl)acetamide (6)

Yield 68%, m.p. 207.6°C. IR (KBr, cm–1): 3410, 3368, 3271 (NH, NH2), 3081 (CH aril), 2936, 2836 (CH aliph.), 1688 (C=O), 1612 (C=NN), 1383, 1160 (SO2). 1H-NMR (DMSO-d6, δ, ppm): 4.2 (s, 2H, CH2CO), 7.0–8.0 (m, 9H, Ar-H + SO2NH2), 8.5 (s, 1H, NHCH3, D2O-exchangeable), 10.7 (s, 1H,
Cytotoxic activity of some novel sulfonamide derivatives 81

NHCO, D2O-exchangeable). 13C-NMR (DMSO-d6, 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 C15H13FN4O3S2 (341.41): C, 33.56; H, 3.09; N, 20.19%; found: C, 33.58; H, 3.03; N, 20.19%.

2-(6-Ethoxybenzo[d]thiazol-2-ylamino)-N-(4-sulfamoylphenyl)acetamide (8)

Yield 74%, m.p. 154.1°C. IR (KBr, cm−1): 3441, 3377, 3189 (NH, NH), 3086 (CH arom.), 2976, 2880 (CH aliph.), 1666 (C=O), 1627 (C=N), 1388, 1180 (SO2). 1H-NMR (DMSO-d6, δ, ppm): 1.2 (t, 3H, CH3), 2.3 (s, 1H, NHCO, D2O-exchangeable). 13C-NMR (DMSO-d6, δ, ppm): 14.3, 28.2, 55.6, 119.1 (2), 126.7 (2), 138.6, 140.1, 160.9, 160.1, 166.6, 169.9. Analysis: calcd. for C15H14N5O3S2 (373.47): C, 38.59; H, 4.05; N, 18.75%; found: C, 38.29; H, 4.27; N, 18.51%.

2-(5,6-Dimethylbenzo[d]thiazol-2-ylamino)-N-(4-sulfamoylphenyl)acetamide (7)

Yield 73%, m.p. 147.1°C. IR (KBr, cm−1): 3410, 3376, 3312 (NH, NH), 3092 (CH arom.), 2936, 2872 (CH aliph.), 1689 (C=O), 1618 (C=N), 1382, 1155 (SO2). 1H-NMR (DMSO-d6, δ, ppm): 2.3 (s, 6H, 2CH3), 4.1 (s, 2H, CH2), 5.4 (s, 1H, NH), 5.5 (s, 1H, NHCO, D2O-exchangeable), 10.6 (s, 1H, NHCO, D2O-exchangeable). 13C-NMR (DMSO-d6, δ, ppm): 19.2, 25.3, 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 C15H14N5O3S (390.46): C, 52.29; H, 4.65; N, 14.35%; found: C, 52.61; H, 4.39; N, 14.55%.

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

Yield 64%, m.p. 238.7°C. IR (KBr, cm−1): 3368, 3290, 3186 (NH, NH), 3075 (CH arom.), 2978, 2912 (CH aliph.), 1694 (C=O), 1599 (C=N), 1378, 1156 (SO2). 1H-NMR (DMSO-d6, δ, ppm): 1.3 (t, 3H, CH3), 3.9 (q, 2H, CH2), 4.0 (2H, CH2CO), 6.6–8.1 (m, 8H, Ar-H + 2 CH pyrazole + SO2NH), 10.5 (s, 1H, NH, D2O-exchangeable), 10.7 (s, 1H, NHCO, D2O-exchangeable). 13C-NMR (DMSO-d6, 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 C15H14N5O3S (332.37): 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), 3100 (CH arom.), 2984, 2836 (CH aliph.), 1678 (C=O), 1619 (C=N), 1377, 1161 (SO2). 1H-NMR (DMSO-d6, δ, ppm): 1.1 (t, 3H, CH3), 2.9 (2H, CH2, J = 6.9 Hz), 5.4 (s, 1H, NH, D2O-exchangeable), 7.0–7.9 (m, 6H, Ar-H + SO2NH), 10.7 (s, 1H, NHCO, D2O-exchangeable). 13C-NMR (DMSO-d6, 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 C15H14N5O3S2 (341.41): C, 42.22; H, 4.43; N, 20.51%; found: C, 42.46; H, 4.11; N, 20.19%.
130.8, 138.8 (2), 143.4, 155.2, 157.3, 169.0.
Analysis: calcd. for C_{17}H_{16}N_{4}O_{3}S (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, NH₂), 2981, 2848 (CH aliph.), 1687 (C=O), 1378, 1160 (SO₂), 1276 (C=S). ¹H-NMR (DMSO-d₆, δ, ppm): 2.2 (s, 3H, CH₃), 6.5 (s, 2H, NH₂, D₂O-exchangeable), 6.7–7.9 (m, 10H, Ar-H + SO₂NH₂), 10.6 (s, 1H, NH, D₂O-exchangeable). ¹³C-NMR (DMSO-d₆, 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_{4}O_{3}S₃ (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, NH₂), 3095 (CH arom.), 2961, 2861 (CH aliph.), 1681 (C=O), 1388, 1156 (SO₂), 1276 (C=S). ¹H-NMR (DMSO-d₆, δ, ppm): 3.8 (s, 3H, OCH₃), 6.6 (s, 2H, NH₂, D₂O-exchangeable), 6.7–8.0 (m, 10H, Ar-H + SO₂NH₂), 10.9 (s, 1H, NH, D₂O-exchangeable). ¹³C-NMR (DMSO-d₆, 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_{4}O_{4}S₃ (436.53): C, 46.77; H, 3.69; N, 12.83%; found: C, 46.48; H, 3.42; N, 13.62%.

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, NH₂), 3100 (CH arom.), 1672 (C=O), 1376, 1152 (SO₂), 1269 (C=S). ¹H-NMR (DMSO-d₆, δ, ppm): 6.4 (s, 2H, NH₂, D₂O-exchangeable), 7.0–8.1 (m, 10H, Ar-H + SO₂NH₂), 11.2 (s, 1H, NH, D₂O-exchangeable). ¹³C-NMR (DMSO-d₆, 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_{17}H_{16}FN_{4}O_{3}S (442.49): 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, 3184 (CH arom.), 1654 (C=O), 1508, 1307 (SO₂), 1203 (C=S). ¹H-NMR (DMSO-d₆, δ, ppm): 6.7 (s, 2H, NH₂, D₂O-exchangeable), 6.9–7.9 (m, 10H, Ar-H + SO₂NH₂), 10.9 (s, 1H, NH, D₂O-exchangeable). ¹³C-NMR (DMSO-d₆, δ, ppm): 77.4, 120.7 (2), 123.6 (2), 126.4 (2), 128.3 (2), 133.7, 141.4, 142.6, 145.0, 158.2, 162.7, 190.1. Analysis: calcd. for C_{17}H_{16}N_{4}O_{4}S (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 (CH arom.), 1676 (C=O), 1376, 1165 (SO₂), 1218 (C=S). ¹H-NMR (DMSO-d₆, δ, ppm): 6.2 (s, 2H, NH₂, D₂O-exchangeable), 7.2–8.0 (m, 10H, Ar-H + SO₂NH₂), 10.8 (s, 1H, NH, D₂O-exchangeable). ¹³C-NMR (DMSO-d₆, 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_{17}H_{16}BrN_{4}O_{3}S (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-methoxyphenyl)-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, NH₂), 3076 (CH arom.), 1684 (C=O), 1394, 1161 (SO₂), 1254 (C=S). ¹H-NMR (DMSO-d₆, δ, ppm): 6.5 (s, 2H, NH₂, D₂O-exchangeable), 7.0–8.1 (m, 10H, Ar-H + SO₂NH₂), 10.6 (s, 1H, NH, D₂O-exchangeable). ¹³C-NMR (DMSO-d₆, 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_{17}H_{16}IN_{4}O_{3}S (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, 3206 (NH, NH₂), 3066 (CH arom.), 2992, 2942 (CH aliph.), 2212 (C=N), 1652 (C=O), 1376, 1156 (SO₂). ¹H-NMR (DMSO-d₆, δ, ppm): 7.0-8.1 (m, 10H, Ar-H + SO₂NH₂), 8.3 (s, 1H, CH), 10.9 (s, 1H, NH, D₂O-exchangeable). ¹³C-NMR (DMSO-d₆, δ, ppm): 105.6, 114.3 (2), 114.9, 122.6 (2) 127.8 (2), 129.9, 130.8, 137.3, 152.6, 163.1, 164.9. Analysis: calcd. for C₁₆H₁₂BrN₃O₃S (406.25): C, 47.30; H, 2.98; N, 10.34%; found: C, 47.62; H, 2.66; N, 10.59%.

2-Cyano-3-(4-bromophenyl)-2-cyano-N-(4-sulfamoylphenyl)acrylamide (21)

Yield 86%; m.p. 167.2°C. IR (KBr, cm⁻¹): 3343, 3309, 3275 (NH, NH₂), 3076 (CH arom.), 1336, 1156 (SO₂). ¹H-NMR (DMSO-d₆, δ, ppm): 7.0-7.9 (m, 10H, Ar-H + SO₂NH₂), 8.9 (s, 1H, CH), 10.6 (s, 1H, NH, D₂O-exchangeable). ¹³C-NMR (DMSO-d₆, 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 C₁₆H₁₂FN₃O₃S (345.35): C, 55.65; H, 3.50; N, 12.51%; found: C, 60.64; H, 3.29; N, 7.33%.

2-Cyano-3-(3-bromophenyl)-2-cyano-N-(4-sulfamoylphenyl)acrylamide (22)

Yield 86%; m.p. 233.3°C. IR (KBr, cm⁻¹): 3337, 3310, 3206 (NH, NH₂), 3066 (CH arom.), 2980, 2942 (CH aliph.), 2212 (C=N), 1652 (C=O), 1376, 1156 (SO₂). ¹H-NMR (DMSO-d₆, δ, ppm): 7.0-8.0 (m, 12H, Ar-H + SO₂NH₂), 9.1 (s, 1H, CH), 10.7 (s, 1H, NH, D₂O-exchangeable). ¹³C-NMR (DMSO-d₆, 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 C₂₁H₁₇N₃O₄S (470.44): 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)pent-2,4-dienamide (24)

Yield 59%, m.p. 240.2°C. IR (KBr, cm⁻¹): 3360, 3315, 3272 (NH, NH₂), 3091 (CH arom.), 129.4, 130.2, 130.7, 131.0, 132.7, 133.7, 135.6, 138.7, 141.5, 149.7, 164.2. Analysis: calcd. for C₂₀H₂₀N₄O₃S (394.40): C, 60.91; H, 3.58; N, 7.10%; found: C, 60.92; H, 3.50; 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, NH₂), 3076 (CH arom.), 1700, 1673 (2C=O), 1374, 1184 (SO₂). ¹H-NMR (DMSO-d₆, δ, ppm): 7.4-8.1 (m, 12H, Ar-H + SO₂NH₂), 8.5 (s, 1H, CH), 10.3 (s, 1H, NH, D₂O-exchangeable). ¹³C-NMR (DMSO-d₆, 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 C₂₉H₂₆N₂O₄S (439.40): 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 IC₅₀ 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.
(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 × 10^4/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, NH2), (CH aromatic), (CH aliphatic), (C=O), (SO 2). 1H-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 aryliothiocyanate yielded

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>MDA-MB-231 IC₅₀ (µM)*</th>
<th>HT-29 IC₅₀ (µM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>NA</td>
<td>49.22 ± 0.02</td>
</tr>
<tr>
<td>2</td>
<td>NA</td>
<td>109.94 ± 0.01</td>
</tr>
<tr>
<td>3</td>
<td>147 ± 0.3</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
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<tr>
<td>6</td>
<td>NA</td>
<td>96.61 ± 0.085</td>
</tr>
<tr>
<td>7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>171.76 ± 0.7</td>
<td>45.62 ± 0.04</td>
</tr>
<tr>
<td>9</td>
<td>NA</td>
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</tr>
<tr>
<td>10</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>221.53 ± 0.08</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>271.67 ± 0.03</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>184.82 ± 0.08</td>
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<td>14</td>
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</tr>
<tr>
<td>15</td>
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</tr>
<tr>
<td>16</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>17</td>
<td>66.6 ± 0.04</td>
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</tr>
<tr>
<td>18</td>
<td>NA</td>
<td>77.96 ± 0.01</td>
</tr>
<tr>
<td>19</td>
<td>139.4 ± 0.2</td>
<td>74.46 ± 0.09</td>
</tr>
<tr>
<td>20</td>
<td>NA</td>
<td>60.84</td>
</tr>
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<td>21</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>22</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>23</td>
<td>236.78 ± 0.11</td>
<td>NA</td>
</tr>
<tr>
<td>24</td>
<td>85.31 ± 0.02</td>
<td>131.86 ± 0.018</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>77.28 ± 0.2</td>
<td>10.23 ± 0.09</td>
</tr>
</tbody>
</table>

* IC₅₀: 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. * Activity is above 150 µM.
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, 1H-NMR and 13C-NMR spectral data. IR spectra revealed the absence of C≡N band and the presence of the characteristic bands for NH, NH2, C=O, and C=S. 1H-NMR spectra showed a singlet at around 6.2–6.7 ppm assigned to (NH2) group. 13C-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 SO2 groups, while 1H-NMR spectra showed the

![Scheme 1. Synthesis of novel sulfonamide derivatives (2–13)](attachment://Scheme_1.png)
disappearance of CH\textsubscript{3} 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-naphthaldehyde 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. ¹H-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\textsubscript{50} of 66.6 µM compared with that of the positive control – 5-fluorouracil (IC\textsubscript{50} = 77.28 µM). Also, the sulfonamide 24 containing 2-cyano-5-(4-N,N-dimethyl-phenylamino)penta-2,4-dienamide was slightly less active than 5-fluorouracil as reference drug against MDA-MB-231 (IC\textsubscript{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\textsubscript{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\textsubscript{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

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REFERENCES


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