Scientific paper

Some Studies in Sulfadiazine Incorporating Pyridine, Pyrimidine, Oxadiazole, and Azo Moieties Endowed with Pharmaceutical Potency

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Abstract

A set of substituted sulfadiazine compounds was prepared as cytotoxic and antitumor agents by using 4-amino-*N*-(pyrimidin-2-yl)benzenesulfonamide (**1**) as the starting material. Compound **1** was reacted with different reagents to give the corresponding sulfadiazines **2**–**18** and hydrozaones **19a**–**h** which were evaluated for their *in vitro* cytotoxicity versus four cancer cell lines. Compounds **3**, **5**, **19d** and **19h** were active against the tested cancer cells.

Keywords: Anticancer; Sulfonamide; Oxadiazole; Pyridine; Thiazole

1. Introduction

Sulfonamides have numerous biological actions, such as antibacterial,[1] hypoglycemia,[2] diuretic,[3] anti-carbonic anhydrase[3,4] and antithyroid.[5] Recently, sulfonamides have been notified to exhibit fundamental antitumor action *in vitro* and/or *in vivo*.[6,7] In addition, pyridine, pyrimidine, oxadiazole, and azo compounds are recognized to have various biological actions containing anticancer activity.[8–15] So, the first goal in this realization is to synthesis several novel structures having anticancer action and the second goal is to exam the effect of the substitution of pyridine, pyrimidine, oxadiazole, and azo derivatives on the anticancer action and to research their structure action relationships.

2. Experimental

2. 1. Materials and Methods

2. 1. 1. Chemicals and Reagents

All the chemicals and solvents used in this study were obtained from Merck (Germany) and Sigma-Aldrich cheical company (Germany).

2. 1. 2. Instruments

All melting points are measured on Gallenkamp electric melting point apparatus and are uncorrected. The Infrared spectra ν cm^{-1} (KBr) was measured on (Perkin Elmer Infrared Spectrophotometer Model 157, Grating). The ^{13}C and ^{1}H NMR spectra were run on Varian Spectrophotometer at 400 MHz and 100 MHz using TMS as an internal reference and DMSO-d_6 as solvent. The MS (EI) were measured on 70 eV with Kratos MS equipment and/or a Varian MAT 311 A Spectrometer at Cairo University, Giza, Egypt, and were carried on a GC-MS QP-100 EX Shimadzu (Japan). Elemental analyses (C, H, and N) were determined at the Microanalytical Center of Cairo University, Giza, Egypt. The results were in good agreement with the calculated values.

2. 2. Synthesis

2. 2. 1. General Procedure for the Syntheses of (1,3-Dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide Derivatives 2–7

A mix of **1** (0.01 mmol) and anhydride derivatives namely; phthalic anhydride (0.01 mmol), 3-nitrophthalic anhydride (0.01 mmol), 4-nitrophthalic anhydride (0.01 mmol), 3,4,5,6-tetrabromophthalic anhy-

dride (0.01 mmol), 1,2,4-benzenetricarboxylic anhydride (trimellitic anhydride), and 1,2,4,5-benzenetetracarboxylic dianhydride (0.01 mmol) in *N*,*N*-dimethylformamide (15 mL) containing a few drops of triethylamine (3 drops) were boiled for 4 h. The reaction mixture was left to cool to room temperature, and then put into ice-cold water. The insoluble precipitated product was purified and dried to yield sulfonamides **2**–**7**, respectively.

4-(1,3-Dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (2)

Yield (83%), yellow powder, m.p. 288–290 °C; IR (KBr): ν/cm^{-1} 3335 (NH), 1632 (C=O, imidic), 1575 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.76 and 7.71 (dd, 4H, Ar-H AB system), 7.68–8.38 (m, 3H, Ar-H of pyrimidine ring), 9.13 (s, 1H, NH); MS *m/z* (%) 378 (M$^+$–2, 99.90), 347 (67.60), 189 (30.80), 151 (14.50); Anal. calcd. for $C_{18}H_{12}N_4O_4S$ (380.06): C, 56.84; H, 3.18; N, 14.73. Found: C, 56.79; H, 3.11; N, 14.72.

4-(4-Nitro-1,3-dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl) benzenesulfonamide (3)

Yield (89%), white powder, m.p. 297–301 °C; IR (KBr): ν/cm^{-1} 3214 (NH), 1631 (C=O, imidic), 1551, 1337 (NO_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 111.5, 122.3 (2C), 123.6, 127.8, 128.2 (2C), 134.1, 134.9, 135.7, 136.5, 138.3, 146.4, 156.4 (2C), 163.1 (2C), 167.6; MS *m/z* (%) 423 (M$^+$–2, 4.18), 373 (63.15), 244 (100), 73 (20.34), 64 (47.39), 53 (14.39); Anal. calcd. for $C_{18}H_{11}N_5O_6S$ (425.04): C, 50.82; H, 2.61; N, 16.46. Found: C, 50.93; H, 2.57; N, 16.41.

4-(5-Nitro-1,3-dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl) benzenesulfonamide (4)

Yield (86%), yellow powder, m.p. 226–228 C; IR (KBr): ν/cm^{-1} 3361 (NH), 1721 (C=O, imidic), 1540, 1380 (NO_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 111.5, 122.3 (2C), 123.3, 125.7, 128.2 (2C), 129.5, 133.6, 134.3, 136.5, 138.5, 152.1, 156.4 (2C), 163.1 (2C), 167.6; MS *m/z* (%) 423 (M$^+$–2, 67.35), 373 (82.65), 244 (100), 73 (100); Anal. calcd. for $C_{18}H_{11}N_5O_6S$ (425.04): C, 50.82; H, 2.61; N, 16.46. Found: C, 50.73; H, 2.60; N, 16.57.

N-(Pyrimidin-2-yl)-4-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)benzenesulfonamide (5)

Yield (80%), pale yellow powder, m.p. 257–260 °C; IR (KBr): ν/cm^{-1} 3360 (NH), 1632 (C=O, imidic),1330 (SO_2), 760 (C-Br); ^{13}C NMR (DMSO-d_6) δ (ppm): 111.5, 122.3 (2C), 126.1 (2C), 128.2 (2C), 129.4 (2C), 135.5, 136.5, 138.9 (2C), 156.4 (2C), 163.1 (2C), 167.6; MS *m/z* (%) 691 (M$^+$, 12.3), 361 (16.91), 360 (84.34), 330 (7.98), 314 (27.23), 221 (26.41), 185 (13.75), 164 (13.19), 138 (9.36), 103 (53.22), 95 (23.72), 79 (21.64), 75 (71.93), 64 (34.34), 53 (19.52); Anal. calcd. for $C_{18}H_8Br_4N_4O_4S$ (691.70): C, 31.06; H, 1.16; N, 8.05. Found: C, 31.02; H, 1.11; N, 8.17.

1,3-Dioxo-2-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl) isoindoline-5-carboxylic acid (6)

Yield (89%), white powder, m.p. 299–301 °C; IR (KBr): ν/cm^{-1} b. 3442 (OH of COOH), 3103 (NH), 1720 (C=O, imidic); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.51–8.35 (m, 7H, Ar-H), 9.01 (s, 1H, CH of phthalimide), 8.31 and 8.46 (2 s, 2H, 2CH), 9.13 (s, 1H, NH), 12.23 (s, 1H, COOH); MS *m/z* (%) 426 (M$^+$+2, 15.26), 425 (M$^+$+1, 9.17), 361 (39.24), 360 (93.28), 330 (29.17), 314 (37.79), 221 (61.99), 185 (38.54), 164 (41.46), 138 (15.48), 103 (51.84), 95 (28.52), 79 (20.39), 75 (75.23), 64 (23.62), 53 (17.63); Anal. calcd. for $C_{19}H_{12}N_4O_6S$ (424.05): C, 53.77; H, 2.85; N, 13.20. Found: C, 53.69; H, 2.91; N, 13.21.

Pyromellitimide Derivative 7

Yield (84%), white powder, m.p. 270–273 °C; IR (KBr): ν/cm^{-1} 3243 (NH), 1646 (C=O, imidic), 1588 (C=N), 1579 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.59–8.31 (m, 14H, Ar-H), 10.18 (s, 2H, 2CH), 9.15 (s, 2H, 2NH); MS *m/z* (%) 680 (M$^+$–2, 22.35), 425 (12.76), 361 (29.18), 360 (85.11), 330 (17.45), 314 (19.28), 221 (34.85), 185 (21.69), 164 (39.22), 138 (26.34), 103 (49.74), 95 (11.47), 79 (27.43), 75 (62.53), 64 (51.46), 53 (19.61); Anal. calcd. for $C_{30}H_{18}N_8O_8S_2$ (682.07): C, 52.78; H, 2.66; N, 16.41. Found: C, 52.73; H, 2.72; N, 17.39.

4-(2,4-Dioxo-1,2-dihydroquinazolin-3(4H)-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (8)

A mix of **1** (0.01 mmol) and isatoic anhydride (0.01 mmol) in *N*,*N*-dimethylformamide (15 mL) including a few drops of triethylamine (3 drops) were boiled for 4 h. The reaction mixture was left to cool to room temperature, and then put into ice. The insoluble precipitated product was purified and dried to offer sulfonamide **8**. Yield (79%), white powder, m.p. 296–299 °C; IR (KBr): ν/cm^{-1} 3367 (2NH), 1679 (CO, imidic); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.28 (s, 1H, NH), 7.61–8.31 (m, 11H, Ar-H), 9.13 (s, 1H, NH); MS *m/z* (%) 393 (M$^+$–2, 41.46), 170 (50.00), 84 (82.32), 56 (100); Anal. calcd. for $C_{18}H_{13}N_5O_4S$ (395.07): C, 54.68; H, 3.31; N, 17.71. Found: C, 57.93; H, 3.27; N, 17.71.

2. 2. 2. Syntheses of Diethyl 2-((4-(N-Pyrimidin-2-ylsulfamoyl)phenylamino)methylene) malonate (9)

To a solution of **1** (0.01 mmol), diethyl 2-(ethoxymethylene)malonate (0.01 mmol) was added in *N*,*N*-dimethylformamide (25 mL) including a few drops of trimethylamine. The mixture was boiled for 4 h and left to cool to room temperature, and then put into ice. The insoluble precipitated product was purified, dried to give compound **9**. Yield (82%), yellow powder, m.p. 181–183 °C; IR (KBr): ν/cm^{-1} 3373 (NH), 1689 and 1654 (2 C=O, ester); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.24, 1.28 (2 t, 6H, 2 CH_3), 4.14, 4.23 (2 q, 4H, 2 CH_2), 8.35 (s, 1H, CH), 7.13–7.77 (m,

7H, Ar-H), 9.07, 10.79 (2 s, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 26.5, 70.1, 110.5, 115.9 (2C), 117, 122.4, 129.7, 130.8 (2C), 132, 137.2, 142.6, 153.1, 155.4, 164.3, 177.2, 177.8; MS *m/z* (%) 422 (M^++2, 6.50), 232 (29.10), 189 (99.90), 134 (22.90); Anal. calcd. for $C_{18}H_{20}N_4O_6S$ (420.11): C, 51.42; H, 4.79; N, 13.33. Found: C, 53.71; H, 2.78; N, 13.21.

2. 2. 3. Syntheses of Ethyl 4-Oxo-6-(N-pyrimidin-2-ylsulfamoyl)-1,4-dihydroquinoline-3-carboxylate (10)

The cyclization reaction was performed by adding portions of **9** (0.01 mmol) to boiling diphenyl ether (15 mL). The reaction mix was boiled for 2 h, cooled to room temperature, then added petroleum ether (10 mL). The obtained insoluble precipitated product was purified, washed with diethyl ether and dehydrated to offer sulfonamide **10**. Yield (70%), gray powder, m.p. charring at 277 °C; IR (KBr): ν/cm^{-1} 3219 (NH), 1681 (C=O, ester), 1623 (*α,β*-unsaturated C=O), 1516 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.30 (t, 3H, CH_3), 4.31 (q, 2H, CH_2), 7.24 (s, 1H, C_2-H of quinoline), 7.69–7.85 (m, 6H, Ar-H), 8.94, 9.17 (2 s, 2 H, 2 NH); MS *m/z* (%) 375 (M^++1, 69.15), 310 (100), 270 (86.17), 205 (94.68); Anal. calcd. for $C_{16}H_{14}N_4O_5S$ (374.07): C, 51.33; H, 3.77; N, 14.97. Found: C, 51.39; H, 3.78; N, 14.81.

2. 2. 4. yntheses of 3-(Hydrazinecarbonyl)-4-oxo-N-(pyrimidin-2-yl)-1,4-dihydroquinoline-6-sulfonamide (11)

The cyclization reaction was performed by adding portions of **10** (0.01 mmol) to boiling diphenyl ether (15 mL). The mix was boiled for 1 h, cooled to room temperature, then added petroleum ether (10 mL). The obtained insoluble precipitated product was purified, washed with diethyl ether and dehydrated. The resulting insoluble precipitate recrystallized from ethanol to yield sulfonamide **11**. Yield (79%), white powder, m.p. 122–125 °C; IR (KBr): ν/cm^{-1} 3435 (NH_2), 3360 (NH), 1685 (C=O, amidic), 1624 (*α,β*-unsaturated C=O), 1566 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.44 (s, 2H, NH_2), 7.36–8.38 (m, 6H, Ar-H), 8.38 (s, 1H, C_2-H of quinoline), 9.05, 9.18, 9.74 (3 s, 3 H, 3 NH); MS *m/z* (%) 361 (M^++1, 1.20), 215 (25.50), 103 (31.60), 43 (99.90); Anal. calcd. for $C_{14}H_{12}N_6O_4S$ (360.06): C, 46.66; H, 3.36; N, 23.32. Found: C, 56.53; H, 3.27; N, 23.41.

2. 2. 5. Syntheses of 2-(4-Oxo-6-(N-pyrimidin-2-ylsulfamoyl)-1,4-dihydroquinoline-3-carbonyl)hydrazinecarbodithioic acid (12)

To a solution of **11** (10 mmol) in ethanol containing a few drops of glacial acetic acid (4 drops) or in pyridine (20 mL), carbon disulphide (10 mL) was added and the reaction mixture was boiled for 4 h. The solution was left to cool to room temperature and then put into ice. The insoluble precipitated was purified, dehydrated and recrystallized from ethanol to offer sulfonamide **12**. Yield (81%), white powder, m.p. 221–223 °C; IR (KBr): ν/cm^{-1} 3287 and 3214 (3NH), 1688 (C=O, amidic), 1625 (*α,β*-unsaturated C=O), 1332 (C=S); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.93 (s, 1H, SH), 7.61–8.24 (m, 6H, Ar-H), 9.02 (s, 1H, C_2-H of quinoline), 9.22 (s, 1H, NH), 10.65, 10.81 (2s, 2H, 2NH); MS *m/z* (%) 432 (M^+–4, 2.30), 378 (21.20), 283 (99.90), 165 (31.80); Anal. calcd. for $C_{15}H_{12}N_6O_4S_3$ (436.01): C, 41.27; H, 2.77; N, 19.25. Found: C, 41.23; H, 2.86; N, 19.31.

2. 2. 6. Syntheses of 3-(5-Mercapto-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-oxo-N-(pyrimidin-2-yl)-1,4-dihydroquinoline-6-sulfonamide (13)

A solution of compound **12** in ethanol (25 mL) including TEA (4 drops) was boiled for 4 h. The formed precipitate was purified while heating, dehydrated and washed by ethanol to yield oxadiazole derivative **13**. Yield (85%), white powder, m.p. 271–273 °C; IR (KBr): ν/cm^{-1} 3224 (NH), 2615 (SH), 1615 (*α,β*-unsaturated C=O), 1561 (C=N), 1332 (C=S); ^{13}C NMR (DMSO-d_6) δ (ppm): 111.5, 117.1, 118.2, 123.6, 131.1, 131.3, 133.7, 142.4, 151.6, 155.3, 156 (2C), 167.1, 167.6, 173.9; MS *m/z* (%) 402 (M^+, 45.10), 342 (76.80), 122 (99.90), 43 (87.00); Anal. calcd. for $C_{15}H_{10}N_6O_4S_2$ (402.02): C, 44.77; H, 2.50; N, 20.88. Found: C, 44.63; H, 2.66; N, 20.81.

2. 2. 7. Syntheses of 3-(5-(Methylthio)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-oxo-N-(pyrimidin-2-yl)-1,4-dihydroquinoline-6-sulfonamide (14)

A mix of oxadiazole **13** (10 mmol), sodium hydroxide solution (10 mmol), and methyl iodide (10 mmol) was stirred in water (15 mL) for 14 h. The forming thioether solution was removed by evaporation, and the residue collected by filteration, washed with water, dehydrated and recrystallized from ethanol to yield sulfonamide **14**. Yield (85%), gray powder, m.p. 172–175 °C; IR (KBr): ν/cm^{-1} b. 3253 (2NH), 1636 (*α,β*-unsaturated C=O), and 1581 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.96 (s, 3H, SCH_3), 2.52 (s, 2H, NH_2), 9.02 (s, 1H, C_2-H of quinoline), 7.60–8.24 (m, 3H, Ar-H), 10.66 (s, 1H, NH), 10.82 (s, 1H, NH); MS *m/z* (%) 413 (M^++3, 27.5), 258 (16.5), 248 (19.8), 233 (65.9), 209 (16.5), 207 (62.6), 143 (34.1), 115 (26.4), 77 (54.1), 76 (14.3), 69 (11.0), 65 (13.2), 51 (45.1), 50 (14.3); Anal. calcd. for $C_{16}H_{12}N_6O_4S_2$ (416.04): C, 46.15; H, 2.90; N, 20.18. Found: C, 46.33; H, 2.86; N, 20.01.

2. 2. 8. Syntheses of 4-Oxo-N-(pyrimidin-2-yl)-3-(5-thioxo-4-((para-tolylamino)methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1,4-dihydroquinoline-6-sulfonamide (15)

A mix of **13** (10 mmol) and *para*-touluidine (10 mmol) was boiled in ethanol (30 mL) with 30% formaldehyde (20 mmol) for 3 h. The resulting insoluble precipitate was recrystallized from ethanol to yield sulfonamide **15**. Yield (72%), brown powder, m.p. 193–195 °C; IR (KBr): ν/cm^{-1} 3325 (NH), 2969 (CH), 1635 (*α,β*-unsaturated C=O), 1610 (C=N), 1267 (C=S); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.16 (s, 3H, CH_3), 4.97 (s, 1H, N-CH_2-NH), 5.85 (s, 2H, N-CH_2-NH), 7.60–8.24 (m, 10H, Ar-H), 8.39 (s, 1H, C_2-H of quinoline), 9.15 (s, H, NH), 11.74 (s, H, NH); MS *m/z* (%) 521 (M$^+$, 17.87), 415 (45.76), 401 (43.51), 301 (21.22), 220 (76.16), 158 (68.25), 120 (28.15), 100 (50.12), 77 (84.41), 76 (19.35), 69 (12.46), 65 (27.35), 50 (28.30); Anal. calcd. for $C_{23}H_{19}N_7O_4S_2$ (521.09): C, 52.96; H, 3.67; N, 18.80. Found: C, 52.93; H, 3.65; N, 18.71.

2. 2. 9. Syntheses of 2-Cyano-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)acetamide (16)

A mix of **1** (0.01 mmol) and ethyl cyanoacetate (0.01 mmol) was boiled in *N,N*-dimethylformamide (25 mL) for 4 h. The reaction mixture was cooled to room temperature and then put into ice. The precipitated insoluble precipitated product was purified, dried and recrystallized from ethanol to yield sulfonamide **16**. Yield (89%), pale yellow powder, m.p. 237–239 °C; IR (KBr): ν/cm^{-1} 3357 (NH), 2155 (CN), 1647 (C=O, amidic); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.25 (s, 2H, CH_2), 7.62–8.26 (m, 3H, Ar-H and Ar-H of pyrimidine), 10.94, 11.19 (2s, 2H, 2NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 26.5, 112.7, 117, 122.4, 125.8 (2C), 129.7 (2C), 133.9, 141.2, 143.6, 153.1, 164.3; MS *m/z* (%) 317 (M$^+$, 68.74), 218 (86.32), 126 (88.42), 73 (100); Anal. calcd. for $C_{13}H_{11}N_5O_3S$ (317.06): C, 49.21; H, 3.49; N, 22.07. Found: C, 49.19; H, 3.52; N, 22.81.

2. 2. 10. Syntheses of 4-Amino-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide (17)

Compound **1** (0.01 mmol) was boiled in *N,N*-dimethylformamide (30 mL) including trimethylamine for 4 h. The reaction mixture was cooled to room temperature; then put into ice. The insoluble precipitated product was purified, dried and recrystallized from ethanol to offer sulfonamide **17**. Yield (90%), yellow crystals, m.p. 210–213 °C; IR (KBr): ν/cm^{-1} 3357 (NH), 1713 (C=O, amidic), 1651 (*α,β*-unsaturated C=O), and 1584 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.82 (s, 2H, NH_2), 8.33 (s, 1H, C_2-H of quinoline), 7.58–8.34 (m, 6H, Ar-H), 8.85 (s, H, NH), 10.15 (s, H, NH); MS *m/z* (%) 322 (M$^+$-5, 52.46), 320 (83.59), 231 (100), 135 (35.66); Anal. calcd. for $C_{13}H_{11}N_5O_3S$ (317.06): C, 49.21; H, 3.49; N, 22.07. Found: C, 49.25; H, 3.43; N, 22.01.

2. 2. 11. Syntheses of 3-Oxo-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)butanamide (18)

A mix of **1** (0.01 mmol) and ethyl acetoacetate (10 mmol) was boiled in *N,N*-dimethylformamide (25 mL) including a few drops of trimethylamine for 3 h. The reaction mixture was cooled to room temperature and then put into ice. The precipitated solid product was purified, dried and recrystallized from ethanol to offer sulfonamide **18**.

Yield (95%), white powder, m.p. 228–230 °C; IR (KBr): ν/cm^{-1} b. 3315 (2NH), 1725 (C=O, amidic), 1689 (C=O), 1567 (C=N), 1549 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.31 (s, 3H, CH_3), 3.33 (s, 2H, CH_2), 7.45-8.21 (m, 7H, Ar-H), 8.47 (s, 1H, NH), 10.16 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 25, 29.1, 38.6, 71.3, 110.2, 117, 122.4, 133.9, 137.2, 149.8, 152 (2C), 164.3, 177.8; MS *m/z* (%) 335 (M$^+$+1, 9.80), 180 (87.00), 150 (51.10), 91 (99.90); Anal. calcd. for $C_{14}H_{14}N_4O_4S$ (334.07): C, 50.29; H, 4.22; N, 16.76. Found: C, 50.25; H, 4.34; N, 16.78.

2. 2. 12. General Procedure for the Syntheses of Aryl Hydrazone Derivatives 19a–h

A well stirred solution of aromatic amines (20 mmol) in concentrated HCl (6 mL) and water (4 mL) was cooled in an ice bath and diazotized with a solution of sodium nitrite (1.39 g, 20 mL) in water (5 mL).

The above cooled diazonium salt solution was added drop wise to a well stirred cooled solution of **1** in pyridine (10 mL). The reaction mixture was stirred for 1–2 h until giving a complete coupling reaction. The crude insoluble precipitate was purified, dehydrated well and recrystallized from ethanol to offer compounds **19a–h**, respectively.

(E)-3-Oxo-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)-2-(2-(thiazol-2-yl)hydrazono)butanamide (19a)

Yield (80%), dark gray powder, m.p. charring at 271 °C; IR (KBr): ν/cm^{-1} b. 3250 (3NH), 1700 (C=O, amidic), 1663 (C=O), 1550 (N=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.23 (s, 3H, CH_3), 6.57 (d, 1H, CH of thiazole ring), 7.04 (d, 1H, CH of thiazole ring), 7.82 (d, 2H, Ar-H), 7.93 (d, 2H, Ar-H), 7.65–8.39 (m, 3H, Ar-H of pyrimidine), 8.82 (s, H, NH), 9.04 (s, H, NH), 10.16 (s, H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 26.5, 114.7, 117, 122.4, 124.1 (2C), 127.4 (2C), 131.5, 133.9, 141.6, 143.4, 145.6, 153.1, 164.3, 169, 177.8; MS *m/z* (%) 445 (M$^+$, 41.23), 366 (12.34), 287 (24.18), 158 (12.56), 98 (59.76), 84 (69.34), 79 (78.46), 76 (83.76); Anal. calcd. for $C_{17}H_{15}N_7O_4S_2$ (445.06): C, 45.83; H, 3.39; N, 22.01. Found: C, 45.91; H, 3.33; N, 22.01.

(E)-2-(2-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)hydrazono)-3-oxo-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)butanamide (19b)

Yield (82%), reddish brown powder, m.p. 213–215 °C; IR (KBr): ν/cm^{-1} b. 3320 (3NH), 1697 (C=O, amidic), 1662 (C=O), 1562 (N=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.77 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.47 (d, 2H Ar-H), 7.63 (d, 2H Ar-H), 6.87 and 7.20 (m, 3H, Ar-H), 8.80 (s, H, NH), 9.00 (s, H, NH), 10.19 (s, H, NH); MS *m/z* (%) 548 (M$^+$, 32.27), 469 (17.86), 391 (24.54), 314 (69.33), 202 (61.47), 98 (71.27), 79 (56.84), 76 (81.49); Anal. calcd. for $C_{25}H_{24}N_8O_5S$ (548.16): C, 54.74; H, 4.41; N, 20.43. Found: C, 54.71; H, 4.33; N, 20.41.

(E)-3-Oxo-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)-2-(2-(4-sulfamoylphenyl)hydrazono)butanamide (19c)

Yield (82%), yellow powder, m.p. 162–165 °C; IR (KBr): ν/cm^{-1} 3453 (NH_2), b. 3250 (3NH), 1703 (C=O, amidic), 1667 (C=O), 1551 (N=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.23 (s, 3H, CH_3), 3.95 (s, 2H, NH_2), 7.62 and 7.59 (dd, 4H, Ar-H), 7.82 (d, 2H Ar-H), 7.93 (d, 2H, Ar-H), 7.65–8.39 (m, 3H, Ar-H of pyrimidine), 8.82 (s, H, NH), 9.04 (s, H, NH), 10.16 (s, H, NH); MS *m/z* (%) 517 (M$^+$, 47.37), 438 (26.41), 359 (62.64), 171 (74.91), 158 (69.23), 99 (84.16), 79 (69.65), 77 (85.22); Anal. calcd. for $C_{20}H_{19}N_7O_6S_2$ (517.08): C, 46.41; H, 3.70; N, 18.94. Found: C, 46.53; H, 3.73; N, 18.89.

(E)-3-Oxo-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)-2-(2-(4-(N-thiazol-2-ylsulfamoyl)phenyl)hydrazono)butanamide (19d)

Yield (84%), dark brown powder, m.p. charring at 300 °C; IR (KBr): ν/cm^{-1} b. 3261 (4NH), 1723 (C=O, amidic), 1663 (C=O), 1580 (N=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.23 (s, 3H, CH_3), 6.51 (s, H, CH of thiazole ring), 7.14 (s, H, CH of thiazole ring), 6.81 and 7.34 (dd, 4H, Ar-H), 7.82 (d,2H Ar-H), 7.93 (d,2H Ar-H), 7.65–8.39 (m, 3H, Ar-H of pyrimidine), 8.82 (s, H, NH), 9.04 (s, H, NH), 10.16 (s, H, NH), 10.35 (s, H, NH); MS *m/z* (%) 600 (M$^+$, 74.42), 442 (25.33), 254 (12.03), 171 (16.74), 158 (62.48), 156 (43.64), 85 (82.09), 78 (68.96); Anal. calcd. for $C_{23}H_{20}N_8O_6S_3$ (600.07): C, 45.99; H, 3.36; N, 18.66. Found: C, 45.93; H, 3.33; N, 18.69.

(E)-2-(2-(Benzo[d]thiazol-2-yl)hydrazono)-3-oxo-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)butanamide (19e)

Yield (74%), brown powder, m.p. charring at 200 °C; IR (KBr): ν/cm^{-1} b. 3341 (3NH), 1714 (C=O, amidic), 1669 (C=O), 1571 (N=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.23 (s, 3H, CH_3), 7.82 (d, 2H, Ar-H), 7.93 (d, 2H, Ar-H), 7.65–8.39 (m, 7H, Ar-H of pyrimidine and benzene rings), 8.82 (s, H, NH), 9.04 (s, H, NH), 10.16 (s, H, NH); MS *m/z* (%) 495 (M$^+$, 42.74), 337 (36.75), 261 (26.82), 249 (29.35), 149 (15.77), 135 (46.44), 99 (75.24), 79 (62.96), 77 (88.57); Anal. calcd. for $C_{21}H_{17}N_7O_4S_2$ (495.08): C, 50.90; H, 3.46; N, 19.79. Found: C, 50.93; H, 3.33; N, 19.69.

(E)-2-(2-(1H-Imidazol-2-yl)hydrazono)-3-oxo-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)butanamide(19f)

Yield (85%), brown powder, m.p. charring at 232 °C; IR (KBr): ν/cm^{-1} b. 3441 (4NH), 1706 (C=O, amidic), 1664 (C=O), 1563 (N=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.23 (s, 3H, CH_3), 7.03 and 7.05 (d, 2H, 2CH), 7.82 (d, 2H, Ar-H), 7.93 (d, 2H, Ar-H), 7.65–8.39 (m, 3H, Ar-H of pyrimidine), 8.82 (s, H, NH), 9.04 (s, H, NH), 10.16 (s, H, NH), 12.81 (s, H, NH of imidazole ring); MS *m/z* (%) 433 (M$^+$+5, 36.00), 231 (41.10), 202 (99.90), 186 (39.10); Anal. calcd. for $C_{17}H_{16}N_8O_4S$ (428.10): C, 47.66; H, 3.76; N, 26.15. Found: C, 47.63; H, 3.83; N, 26.39.

(E)-2-(2-(1H-Benzo[d]imidazol-2-yl)hydrazono)-3-oxo-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)butanamide (19g)

Yield (78%), pale brown powder, m.p. charring at 251 °C; IR (KBr): ν/cm^{-1} b. 3267 (4NH), 1700 (C=O, amidic), 1668 (C=O), 1573 (N=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.23 (s, 3H, CH_3), 7.82 and 7.93 (dd, 4H, Ar-H), 7.65–8.39 (m, 7H, Ar-H of pyrimidine and benzene rings), 8.82 (s, H, NH), 9.04 (s, H, NH), 10.16 (s, H, NH), 10.81 (s, H, NH); MS *m/z* (%) 483 (M$^+$+5, 1.20), 283 (87.60), 267 (99.90), 171 (82.40); Anal. calcd. for $C_{21}H_{18}N_8O_4S$ (478.1): C, 52.71; H, 3.79; N, 23.42. Found: C, 52.64; H, 3.83; N, 23.35.

(E)-3-Oxo-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)-2-(2-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)hydrazono) butanamide (19h)

Yield (83%), black powder, m.p. charring at 251 °C; IR (KBr): ν/cm^{-1} b. 3339 (4NH), 1731 (C=O, amidic), 1665 (C=O), 1571 (N=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.23 (s, 3H, CH_3), 7.79–7.96 (dd, 8H, Ar-H), 7.65–8.39 (m, 6H, Ar-H of pyrimidine), 8.82 (s, 2H, 2NH), 9.04 (s, H, NH), 10.16 (s, H, NH); MS *m/z* (%) 595 (M$^+$, 28.63), 249 (59.26), 157 (74.59), 101 (48.42), 98 (64.88), 98 (49.04), 93 (59.69); Anal. calcd. for $C_{24}H_{21}N_9O_6S_2$ (595.11): C, 48.40; H, 3.55; N, 21.16. Found: C, 48.51; H, 3.43; N, 21.33.

2. 3. Cytotoxicity Activity

RPMI-1640 medium (Sigma Co., St. Louis, USA), Foetal Bovine serum (GIBCO, UK), and the cell lines from ATCC were used.

The cytotoxic activities of the prepared sulfonamides were examined versus HepG2, WI-38, MCF-7, and VERO, carried out according to the previously reported procedure.[16]

3. Results and Discussion

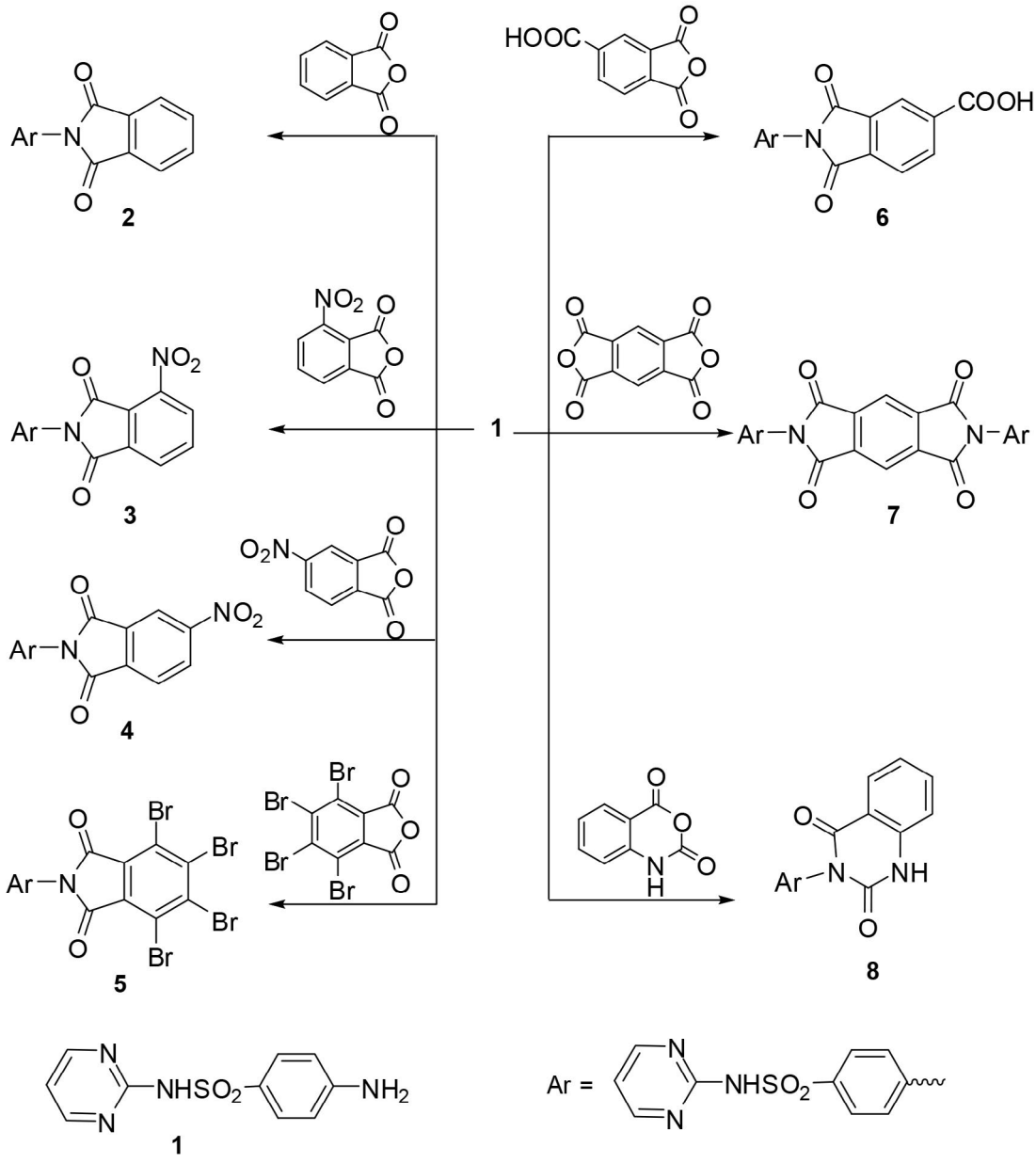
3. 1. Chemistry

From the above reports in sulfonamide chemistry, we prepared some new heterocyclic compounds containing sulfonamide moiety to evaluate their biological activi-

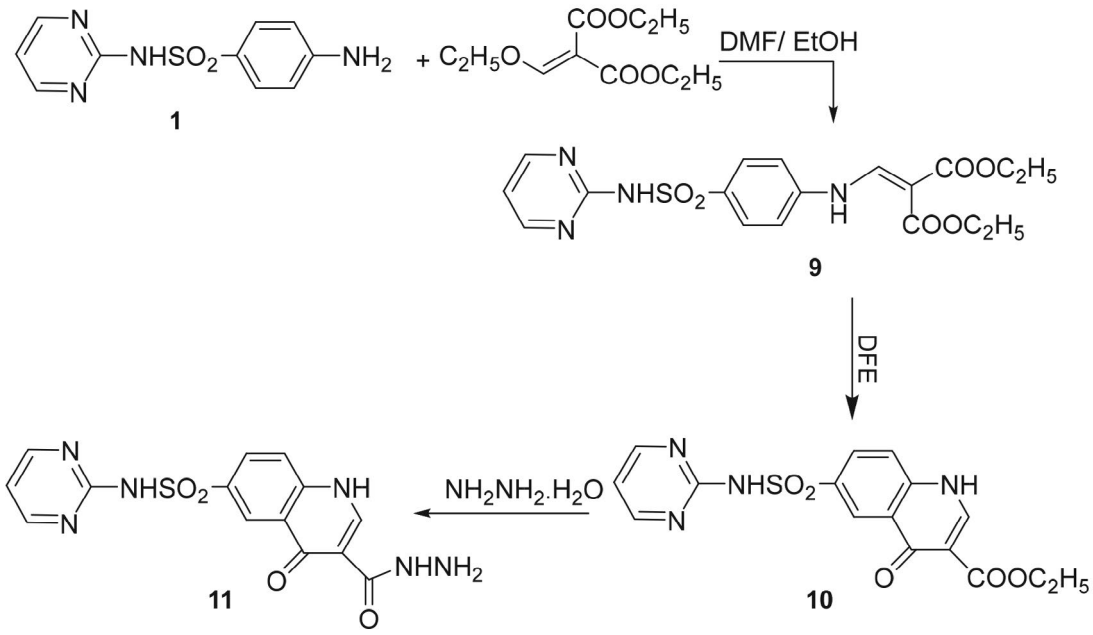
ties. Condensation of compound **1** with acid anhydrides, namely phthalic anhydride, 3-nitrophthalic anhydride, and 4-nitrophthalic anhydride in refluxing *N*,*N*-dimethylformamide containing a few drops of triethylamine yielded sulfonamides **2**–**4**. The infrared spectra of sulfonamides **2**–**4**, in general, displayed no absorption of NH_2 at 3426 cm^{-1} of sulfonamide **1**, and instead, appeared new bands within the region 1631–1721 cm^{-1} due to carboximide groups. The MS spectra of sulfonamides **2**–**4** offered the molecular weight at *m/z* 378 (M^+–2) and at *m/z* 423 (M^+–2) corresponding to molecular formulae $C_{18}H_{12}N_4O_4S$ and/or $C_{18}H_{11}N_5O_6S$, respectively.

Similarly, condensation of compound **1** with 3,4,5,6-tetrabromophthalic anhydride, and 1,2,4-benzenetricarboxylic anhydride (trimellitic anhydride) in boiling *N*,*N*-dimethylformamide including a few small drops of triethylamine gave sulfonamides **5** and **6**, respectively. Structures **5** and **6** were elucidated by different analyses. The infrared spectra of compounds **5** and **6** exhibited bands at 1720, 1632, and 1330 cm^{-1} due to CO groups and SO_2 functional groups. The MS spectra of **5** and **6** offered molecular weight at *m/z* 691 (M^+) and 426 (M^++2), respectively

On the other hand, heating of sulfonamide **1** with pyromellitic anhydride in ethanol with a few drops of triethylamine in a molar ratio 1:2 gave pyromellitimide **7**. The infrared spectrum of compound **7** showed a similar picture to that of **5** and **6**. The MS spectrum of **7** gave molecular



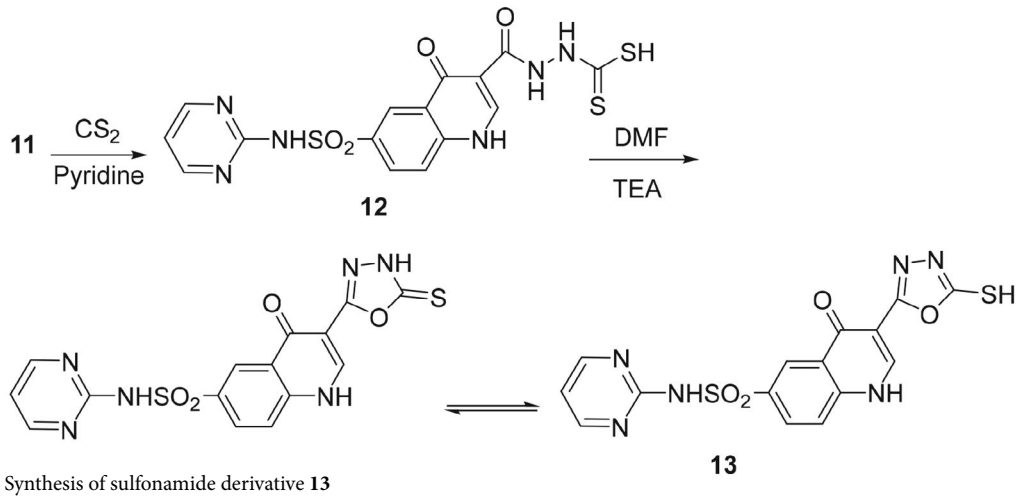
Scheme 1. Synthesis of sulfonamide derivatives **2**–**8**



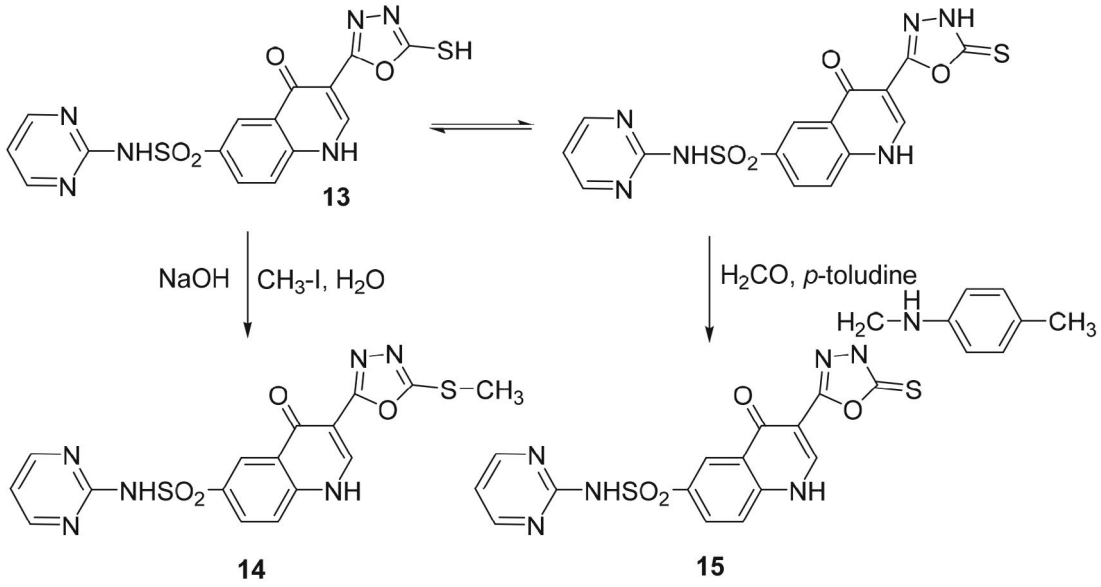
Scheme 2. Synthesis of acid hydrazide **11**

weight at *m/z* 680 (M^+–2). In addition, stirring of sulfonamide **1** with isatoic anhydride in ethanol including a few small drops of triethylamine at room temperature yielded compound **8**. The infrared spectrum of sulfonamide derivative **8** displayed band at **ν** 1679 cm^{-1} corresponding to carboximide functional group. The MS spectrum gave additional confirmation for the correct structure of sulfonamide **8** as it gave a molecular ion peak at *m/z* 393 (M^+–2).

The starting material **1** was refluxed with diethyl 2-(ethoxymethylene)malonate in a mixture of *N*,*N*-dimethylformamide and ethanol (1:1 ratio) to give compound **9** in high yield. The infrared spectrum of **9** displayed a band at 1689 cm^{-1} for ester carbonyl functional group, and an absorption frequency at 3373 cm^{-1} corresponding to NH group. The MS spectum of **9** offered molecular weight at *m/z* 422 (M^++2) confirming the formula $C_{18}H_{20}N_4O_6S$. Cyclization reaction of compound **9** was performed by boiling in diphenyl ether to give ethyl 4-oxo-6-(*N*-pyrimidin-2-ylsulfamoyl)-1,4-dihydroquinoline-3-carboxylate (**10**) in acceptable yield. The infrared spectrum of **10** displayed the distinctive bands at ν 3219, 1681, 1623, and 1516 cm^{-1} due to NH, C=O of ester, *α*,*β*-unsaturated C=O and C=C groups. Its ^{1}H NMR spectrum revealed a triplet signal at *δ* 1.30 ppm (CH_3), a quartet signal at *δ* 4.31 ppm (CH_2), a D_2O exchangeable two NH at *δ* 8.94 and 9.17 ppm as singlet signals, and a singlet signal for C_2-H of quinoline ring at *δ* 7.24 ppm besides the aromatic hydrogens of quinoline and pyrimidine rings at *δ* 7.69–7.85 ppm. In addition, the MS offered another confirmation for compound **10** as it gave its molecular weight at *m/z* 375 (M^++1) corresponding to the formula $C_{16}H_{14}N_4O_5S$.



Scheme 3. Synthesis of sulfonamide derivative **13**



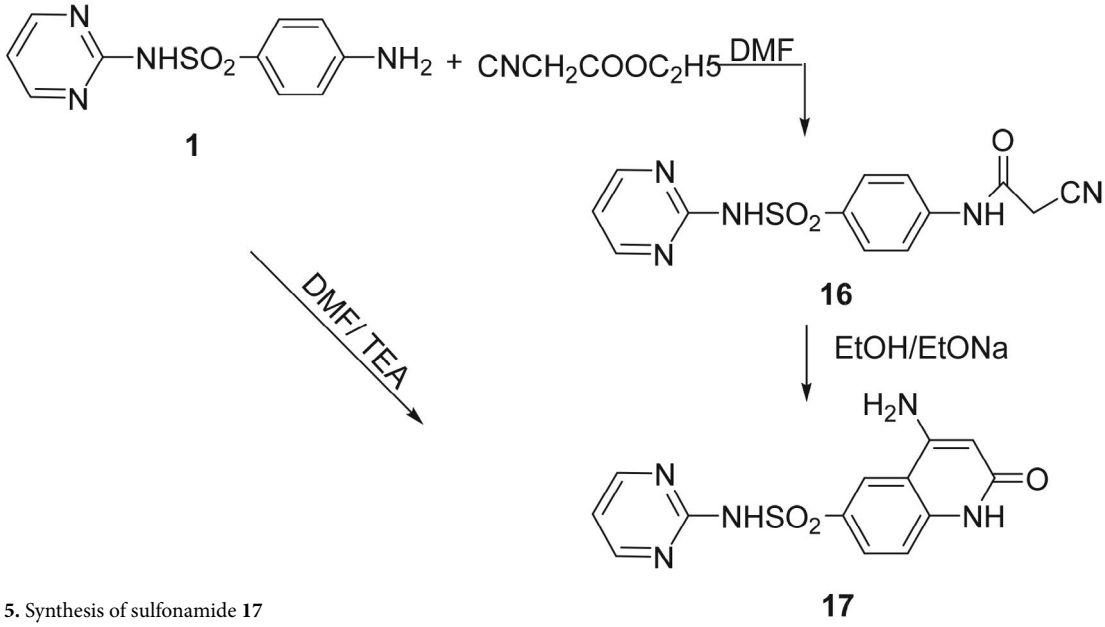
Scheme 4. Synthesis of sulfonamide derivative **14** and **15**

Boiling **10** with hydrazine hydrate in ethanol/DMF solution (1:1 ratio) afforded the corresponding acid hydrazide **11**. The infrared spectrum of **10** displayed bands at ν 3435 and 3360 cm^{-1} due to $NHNH_2$ group, besides the presence of amide carbonyl group at **ν** 1685 cm^{-1}

Reaction of hydrazide **11** with carbon disulphide in refluxing pyridine afforded the thioic acid **12**. The infrared spectrum displayed absorption bands at **ν** 3287, 3214, 1688, 1625, and 1332 cm^{-1} due to stretching vibration of NH, amide CO, *α,β*-unsaturated ketone, and C=S groups. The MS spectrum of compound **12** offered a molecular weight at *m/z* 432 (M^+–4).

When thioic acid derivative **12** was heated under reflux in *N*,*N*-dimethylformamide containing a few drops of triethylamine, sulfonamide derivative **13** was afforded. The infrared spectrum of **13** showed a strong band at **ν** 1332 cm^{-1} due to C=S functional group, and a weak band at **ν** 2615 cm^{-1} due to SH vibration in a tautomeric mixture as well. The MS spectrum displayed its molecular weight at *m/z* 402 (M^+).

It has been found that compound **13**, when subjected to react with methyl iodide in sodium hydroxide solution, afforded the SCH_3 derivative **14** (Scheme 4), while when **13** reacted with formaldehyde and *para*-toluidine it afforded the Mannich base **15** (Scheme 4); such reactions were carried out to indicate the thiol-thione tautomerism.



Scheme 5. Synthesis of sulfonamide **17**

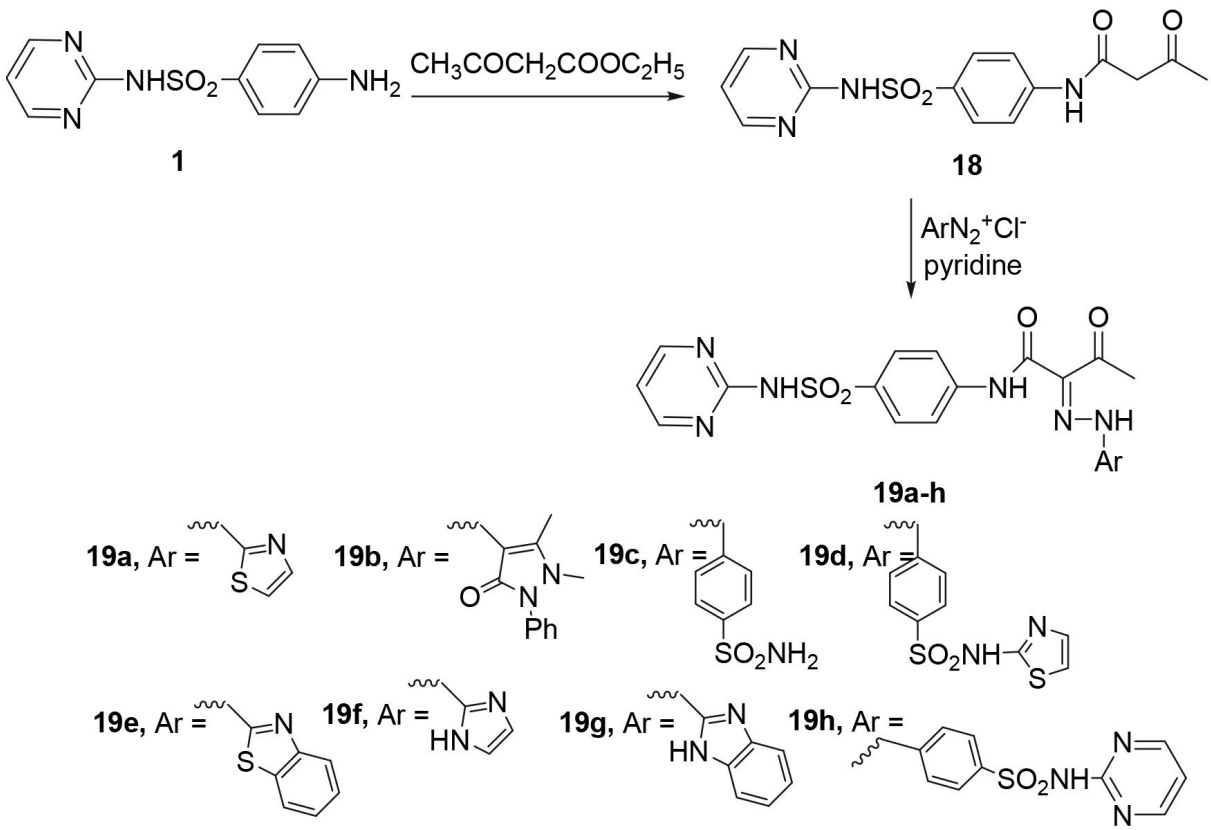
We have observed that thiol-thione tautomerism exists in compounds **14** and **15**. ^{1}H NMR of compound **14** showed signal at 1.96 ppm referred to SCH_3 protons, while the infrared spectrum of **15** offered a band at ν 1267 cm^{-1} due to C=S.

Moreover, it was found that ethyl acetoacetate reacted with compound **1** in refluxing *N*,*N*-dimethylformamide including a few small drops of trimethylamine to give the acetamide derivative **16**.

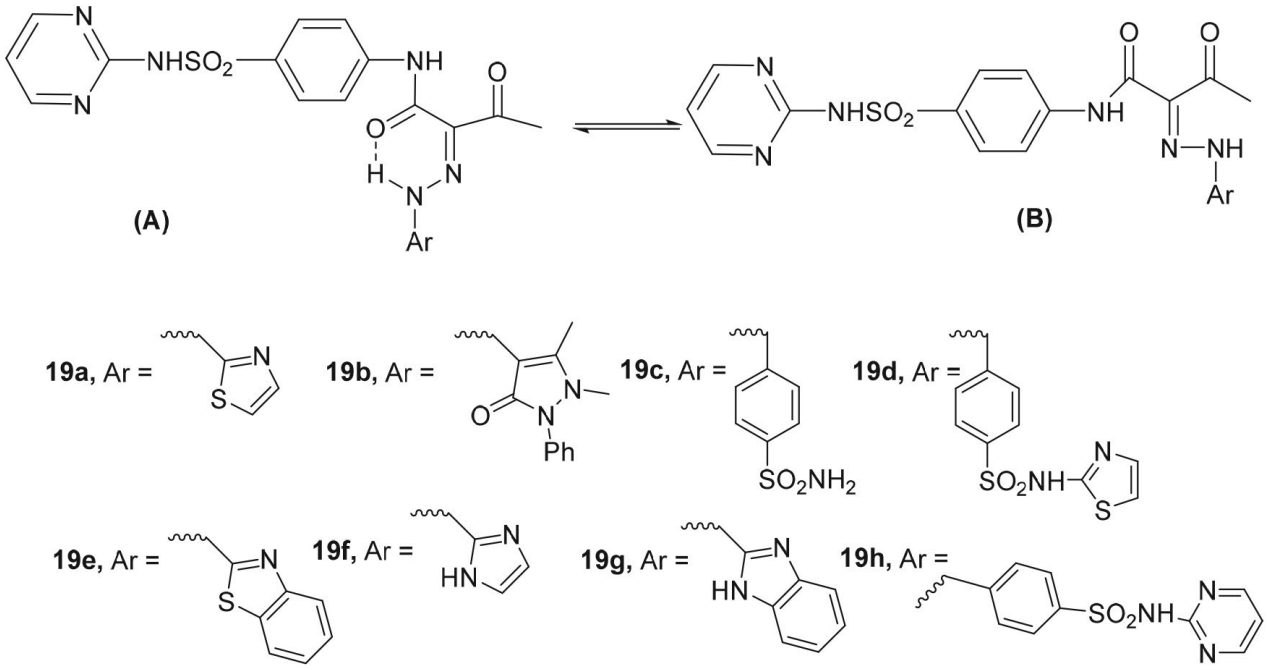
The infrared spectrum of sulfonamide **16** gave 3 lines at 16**47**, **2155**, and 3357 cm^{-1} characteristic to amide CO, CN, and N-H groups. Its ^{1}H NMR spectrum showed signals at δ 4.25 ppm corresponding to CH_2 protons and 11.19 ppm corresponding to amide NH group. The MS spectrum showed additional confirmation to validate the compound as it showed the molecular weight at *m/z* 317 (M^+). When compound **16** was heated in ethanol containing sodium ethoxide, a cyclization occured forming the corresponding 4-amino-2-oxo-*N*-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide (**17**). Structure **17** was established based on its correct spectral and elemental analyses. The infrared spectrum displayed lines at 3357, 1713, 1651, and 1584 cm^{-1} corresponding to NH, amidic carbonyl, *α*,*β*-unsaturated ketone, and C=C groups. ^{1}H NMR also revealed a very characteristic signal at δ 4.82 ppm due to NH_2 functional group. The MS spectrum offered a molecular weight at *m/z* 312 (M^+–5). Structure **17** was confirmed also chemically by an alternative preparation. Thus, heating of sulfonamide **1** in the presence of *N*,*N*-dimethylformamid and triethylamine afforded compound conforming in all its properties (m.p., TLC, and infrared spectrum) to the sulfonamide derivative **17**.

When sulfonamide **1** reacted with ethyl acetoacetate in dry boiling xylene, it gave the acyclic intermediate 3-oxo-*N*-(4-(*N*-pyrimidin-2-ylsulfamoyl)phenyl)butanamide (**18**). The infrared spectrum of compound **18** offered new absorption bands at 1689 and 1725 cm^{-1} corresponding to carbonyl of COOR and amide C=O functional groups, while the ^{1}H NMR spectrum of sulfonamide **18** displayed a characteristic signal at *δ* 2.31 ppm as a singlet for CH_3 protons, *δ* 3.33 ppm signal for CH_2 protons besides the aromatic protons of pyrimidine ring and benzene ring at *δ* 7.45–8.21 ppm. The mass spectrometry measurement gave *m/z* 335 (M^+–1) conforming to the molecular weight of compound **18**.

Coupling of sulfonamide **18** with aromatic amine diazonium salts (namely 2-aminothiazole diazonium salt, 4-aminoantipyrine diazonium salt, sulfanilamide diazonium salt and sulfathiazole diazonium salt, 2-aminobenzthiazole diazonium salt, 2-aminoimidazole diazonium salt, 2-aminobenzimidazole diazonium salt, and sulfadiazine diazonium salt) in pyridine at 0–5 °C gave the corresponding hydrazono compounds **19a**–**h**. The spectral and elemental analyses are in harmony with the suggested compound structures. Thus, ^{1}H NMR spectrum of compound **19a** displayed the disappearance of protons at *δ* 3.33 ppm



Scheme 6. Synthesis of hydrazono structures **19a**–**h**



Scheme 7. Intramolecular hydrogen bonding is in support of the hydrazone moieties in sulfonamides **19a**–**h**

due to CH_2 and the appearance of two doublet signals at δ 6.57 and 7.04 ppm due to two CH of thiazole ring. Similarly, the ^{1}H NMR of compound **19b** showed two singlet signals appeared at δ 1.77 and 2.68 ppm for CH_3 protons. The infrared spectrum of sulfonamides **19a**–**h** in general exhibited a band in the area 3200–3450 cm^{-1} due to NH vibration of the hydrazone moiety and a band at 1550–1580 cm^{-1} due to the azo form in its tautomeric equilibrium as well. Such shift of NH band was notified by Ramirez and Kerby[17] for these hydrazone derivatives, this being due to the intra-molecular hydrogen bonding as depicted in structure **A** (Scheme 7). These facts indicate that sulfonamide derivatives **19a**–**h** offer confirmation for intramolecular hydrogen bonding which supports the hydrazone compounds. Infrared spectra of sulfonamides **19a**–**h** displayed bands at 1662–1731 cm^{-1} corresponding to vibration of C=O functions.

Among the structural factors that make minimizing of the vibration of carbonyl functional group are conjugation and hydrogen bonding. Albeit, even when allowance is exhibited for conjugation, the carbonyl frequencies of the sulfonamides calculated are still much smaller than those in α,β-unsaturated ketones. This marked variance suggests that the carbonyl function of these sulfonamides should participate in hydrogen bonding in the solid state, as demonstrated by the suggested compound **A**. The ultraviolet spectra of the diazonium coupling products gave an extra confirmation that sulfonamides are in the tautomeric equilibrium with monohydrazones. Maximum of the dyes displayed 4 absorption bands at 196–438 nm. The comparatively low variance in λ_{max} may correspond to the polarity variation of the band due to solvent actions corresponding to the common solvent effect.[18] It has been seen that the ultraviolet spectra of monophenylazo structures differ from those of monophenylhydrazones. The azo structures commonly display two bands at 400–410 and 290–300 nm due to n–π^* and π–π^* transitions, respectively.[19]

Moreover, monophenylhydrazones display tree bands at 220–230, 250–280 and 330–390 nm regions. The ultraviolet spectra of sulfonamides **19a**–**h** can be explained in terms of the tautomeric mixture. These dyes show four bands, of these, the medium and high wavelength bands appear to be dependent on the type of the polar substituents in the arylazo function, while the low wavelength bands is not affected. The UV spectral data show that both electron withdrawing groups and electron donating groups shift the absorption maxima to longer wavelengths. Moreover, it showed that the presence of this has not caused any observed higher or lower values of λ_{max} in the apparent region and log ε has stayed nearly constant. This does point to the presence also of hydrazine structure where the resonance actions with the functions in the diazo structure are lower due to steric effects. In addition, the structure of sulfonamides **19a**–**h** was elucidated by mass spectra which displayed the correct molecular weight.

3. 2. Pharmacology

3. 2. 1. Cytotoxicity

The use of heterocyclic structures has a significant role in the treatment of cancer and in its removal plans.[20] Heterocycles are generally used as scaffolds on which

pharmacophores are coordinated to give effective and electic drugs. This is especially correct for five membered-ring heterocyclic compounds,[21] which serve as the core components of a huge number of compounds that have a broad motivating range of biological action.[22–24] The goal of this study was to prepare new drugs for anticancer elucidation as a trial to give novel antitumor agents of a maximum action and minimize side effects. In this paper, the chosen sulfonamides regarding to pyridine, pyrimidine, oxadiazole, and azo compounds were elucidated and screened *in vitro* for prevention of the growth of HepG2 (human hepatocellular liver carcinoma cell lines), WI 38 (human lung fibroblasts), VERO (cell line was initiated from the kidney of a normal adult African green monkey), and MCF-7 (breast cancer cell lines) were compared with the known anticancer drug 5-fluorouracil (5-Fu) and as a trial to get more potent agents with lower toxicity. The collected data are presented as the concentration of sulfonamides that made 50% inhibition of cells growth (IC_{50}).

The *in vitro* elucidation showed that some of the examined sulfonamides displayed (and also that all the modern prepared structures revealed) a certain action against tumor cell lines examined, although the action was commonly maximal towards HepG2 cancer line than the breast cancer one. Compounds **3** and **5** showed an effective antitumor action versus the four tumor cell lines examined (IC_{50} = 11 and 12.4 against HepG2 and IC_{50} = 7.3 and 9.32 against VERO, respectively) in contrast to the effective anticancer drug 5-fluorouracil used as the reference standard. So, we found that all examined sulfonamides including electron withdrawing groups (Br or NO_2) in the benzene ring of phthaliamide moiety displayed a higher to moderate action, so the real effects depend on the existence of thiazole or pyrimidine ring attached to sulfonamide group. It is obvious that compound **19d** showed strong action against two various cell lines and compound **19h** showed strong action versus four various cell lines corresponding to a long π-conjugated system joined to thiazole and pyrimidine rings, besides azo functional group and benzene ring. These outcomes demonstrate that variable molecular structure and orientation could enhance commonly observed antitumor action against the four examined cancer cells.

Table 1: Cytotoxicity (IC_{50}) of examined sulfonamides on various cell lines[a]

Compound No.	IC_{50} (μg/mL)[a]			
	HepG2	WI-38	VERO	MCF-7
5-Fu	8.6	3.2	6.5	2.3
2	88	74	90	85.5
3	**11**	**17.1**	**7.3**	**10.5**
4	23.2	33.7	30.3	26.1
5	**12.4**	**20**	**9.32**	**12.5**
6	26	40.3	38.1	45
7	102	120	100	200
8	29.5	27.6	36.5	29.9
19a	42	46.1	43.1	42.2
19b	65.2	70.3	86	71.6
19c	26	40.3	38.1	45.5
19d	**15.5**	**16.6**	**26.5**	**27.9**
19e	33.1	39.8	42.6	45.6
19f	88.2	74	90	85.5
19g	92	99.3	75.2	94.3
19h	**10.4**	**15.1**	**9.3**	**11.5**

[a] IC_{50} (μg/mL): 1–10 (very strong), 11–25 (strong), 26–50 (moderate), 51–100 (weak), 100–200 (very weak), above 200 (non cytotoxic). 5-FLU = 5-Fluorouracil

4. Conclusion

In the current research, fifteen sulfonamides were examined and most of them showed an antitumor action on four cancer cell lines. The most effective compounds **3**, **5**, **19d** and **19h** showed eclectic effect on HepG2 cancer cell line. The gained data exhibit the necessity or further developments to facilitate the future research based on the antitumor potential of the examined sulfonamides.

5. References

1. A. A. Fadda, A. M. Khalil, M. M. El-Habbal, *Pharmazie* **1991**, *46*, 743–744.
2. A. E. Boyd, *Diabetes* **1988**, *37*, 847–850. **DOI:**10.2337/diabetes.37.7.847
3. C. T. Supuran, A. Scozzafava, *Exp. Opin. Ther. Patents* **2000**, *10*, 575–600. **DOI:**10.1517/13543776.10.5.575
4. C. T. Supuran, A. Scozzafava, *Curr. Med. Chem. Immunol. Endocr. Metabol. Agents* **2001**, *1*, 61–97. **DOI:**10.2174/1568013013359131
5. C. W. Thornber, *Chem. Soc. Rev.* **1979**, *8*, 563–580. **DOI:**10.1039/cs9790800563
6. S. A. Rostom, *Bioorg. Med. Chem.* **2006**, *14*, 6475–6485. **DOI:**10.1016/j.bmc.2006.06.020
7. M. S. Al-Said, M. M. Ghorab, M. S. Al-Dosari, M. M. Hamed, *Eur. J. Med. Chem.* **2011**, *46*, 201–207. **DOI:**10.1016/j.ejmech.2010.11.002
8. A. A. Fadda, E. M. Afsah, R S. Awad, *Eur. J. Med. Chem.* **2013**, *60*, 421–430. **DOI:**10.1016/j.ejmech.2012.11.017
9. A. A. Fadda, K. Elattar, *Med. J. Chem.* **2013**, *2013*, 10. **DOI:**10.1155/2013/928106
10. A. A. Fadda, H. A. Etman, A. A. Sarhan, Sherihan A. El-Hadidy, *Phosphorus, Sulfur, Silicon Relat. Elem.* **2010**, *185*, 526–536. **DOI:**10.1080/10426500902839863
11. A. A. Fadda, M. A. Berghot, F. A. Amer, D. S. Badawy, Nesma M. Bayoumy, *Arch. Pharm. Chem., Life Sci (Archiv der Pharmazie)* **2012**, *345*, 378–355. **DOI:**10.1002/ardp.201100335
12. Hanaa Abuo-Melha, A. A. Fadda, *Spectrochimica Acta Part A:*

Molecular and Biomolecular Spectroscopy **2012**, *89*, 123–128. **DOI:**10.1016/j.saa.2011.12.054
13. A. A. Fadda, A. A.-H. Abdel-Rahman, W. A. El-Sayed, T. A. Zidan, F. A. Badria, *Chem. Heterocyc. Compd.* **2011**, *47*, 856–864. **DOI:**10.1007/s10593-011-0847-4
14. A. A. Fadda, E. Abdel-Latif, R. E. El-Mekawy, *Pharmacol. Pharm.* **2012**, *3*, 148–157. **DOI:**10.4236/pp.2012.32022
15. A. El-Shafei, A. A. Fadda, A. M. Khalil, T. A. E. Ameen, F. A. Badria, *Bioorg. Med. Chem.* **2009**, *17*, 5096–5105. **DOI:**10.1016/j.bmc.2009.05.053
16. A. A. Fadda, A. M. El Defrawy; Sherihan A. El-Hadidy, *Am. J. Org. Chem*. **2012**, *2(4)*, 87–96. **DOI:**10.5923/j.ajoc.20120204.03
17. F. Ramirez, A. F. Kirby, *J. Am. Chem. Soc.* **1954**, *76*, 1037. **DOI:**10.1021/ja01633a034
18. A. E. Gilman, E. S. Stern, *An introduction to electronic absorption spectroscopy in organic chemistry*, 2nd ed., Edward Arnold Publisher Ltd, London **1957**, pp. 302.
19. A. E. Gilman, E. S. Stern, *Electronic absorption spectroscopy*, Edward Arnold Publisher Ltd, London **1960**, pp. 271.
20. S. Abu-Melha, *Acta Chim. Slov*. **2017**, *64*, 910–930.
21. T. Foud, C. Nielsen, L. Brunn, E. B. Pederson, *Sc. J. Az. Med. Fac. (Girls)* **1998**, *19*, 1173–1187.
22. E. H. Tawfik, K. S. Mohamed, H. M. Dardeer, A. A. Fadda, *Acta Chim. Slov*. **2018**, *65*, 787–794. **DOI:**10.17344/acsi.2018.4294
23. E. H. EL-Sayed,A. A. Fadda, *Acta Chim. Slov*. **2018**, *65*, 853–864. **DOI:**10.17344/acsi.2018.4506
24. S. Botros, O. M. Khalil, M. M. Kamal, Y. S. El-Dash, *Acta Chim. Slov.* **2017**, *64*, 102–116. **DOI:**10.17344/acsi.2016.2901
25. R. M. Mohareb, N. Y. M. Abo, F. O. Al-Farouk, *Acta Chim. Slov.* **2017**, *64*, 117–128. **DOI:**10.17344/acsi.2016.2920

Povzetek

Na osnovi izhodne spojine 4-amino-*N*-(pirimidin-2-il)benzensulfonamida (**1**) smo pripravili serijo substituiranih sulfadiazinskih spojin in preučili njihovo citotoksično in antitumorsko delovanje. Spojino **1** smo reagirali z različnimi reagenti in tako pripravili sulfadiazine **2**–**18** ter hidrazone **19a**–**h** in preučili njihovo *in vitro* citotoksičnost na štiri rakave celične linije. Ugotovili smo, da so spojine **3**, **5**, **19d** in **19h** aktivne proti preiskovanim rakavim celicam.