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Synthesis and Cytotoxic Activity of Some New Sulfa Drugs Containing Thiadiazole

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ABSTRACT Treatment of the appropriate sulfonamide diazonium chlorides **2a-f** with phenacyl thiocyanate **3** in methanol containing pyridine afforded the 2-imino-1,3,4-thiadiazols **5 a-f** through the intermediates **4a-f.** The cytotoxic activity of the synthesized compounds against a liver (**HepG2**)**,** colon (**HCT-116**)**,** breast (**MCF-7**)**,** and prostate (**PC3**) human cancer cell lines was evaluated. The results revealed that the tested compounds displayed moderate to weak cytotoxic activity.

KEYWORDS Sulfa drugs, Thiazole, Thiadiazole, Diazonium chloride, Cytotoxic activity.

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INTRODUCTION

Sulfonamide derivatives are crucial objectives in the synthetic organic chemistry due to their pharmacological activities.[1-3] Furthermore, some derivatives act as antibacterial,[4] anti-cancer,[5] and anti-inflammatory.[6] Recently, Gouda *et al*. synthesized a series of sulfadimidine containing thiophene nucleus and curcumin derivative bearing sulfonamide as antioxidant.[7,8] Furthermore, 1,3,4-thiadiazoles were reported to exhibit a wide range of biological activities such as anti-cancer,[9,10] antifungal,[11] antidepressant,[12] anti-leishmanial,[13] anti-inflammatory,[14] and anticonvulsant.[15,16] Moreover, thiazole derivatives displayed a wide range of pharmaceutical activities such as anticancer,[17] antitubercular,[18] anti-inflammatory,[19] and antifungal[20]. In view of the above mentioned and in continuation of our research program on the chemistry of thiazole[21-23] and thiadiazole,[24-26] the present work describes the synthesis and cytotoxic evaluation of some new substituted-1,3,4-thiadiazole derivatives containing sulfonamide moiety.

RESULTS AND DISCUSSION

Chemistry

Scheme 1 displays the preparation of the desired molecules. Treatment of the appropriate sulfonamide diazonium chlorides **2a-f** with phenacyl thiocyanate **3** in methanol containing pyridine afforded the 2-imino-1,3,4-thiadiazols **5 a-f** through the intermediates **4a-f**.[27,28] The structure of thiadiazols **5a-f** was elucidated through the spectroscopic and analytical data. For example, compound **5b** showed absorption bands at ν=(1039,1157), 1641 (br), and 3114, 3237, 3313 cm^{-1} due to SO_2, (C=O, C=NH), and (NH_2, NH) groups, respectively. Furthermore, its ^{1}H-NMR spectrum showed two broad singlet signals at δ 7.60 and 9.70 ppm due to the NH_2 and NH protons, respectively, in addition to multiple signals at 7.62–8.21 due to nine aromatic protons. Moreover, its ^{13}C-NMR spectrum showed signals at δ (122.2-142.2), (148.7, 158.5), and 183.1 ppm due to Ar carbons, (C_5 and C_2 of thiadiazole moiety), and C=O, respectively. Furthermore, its mass spectrum revealed

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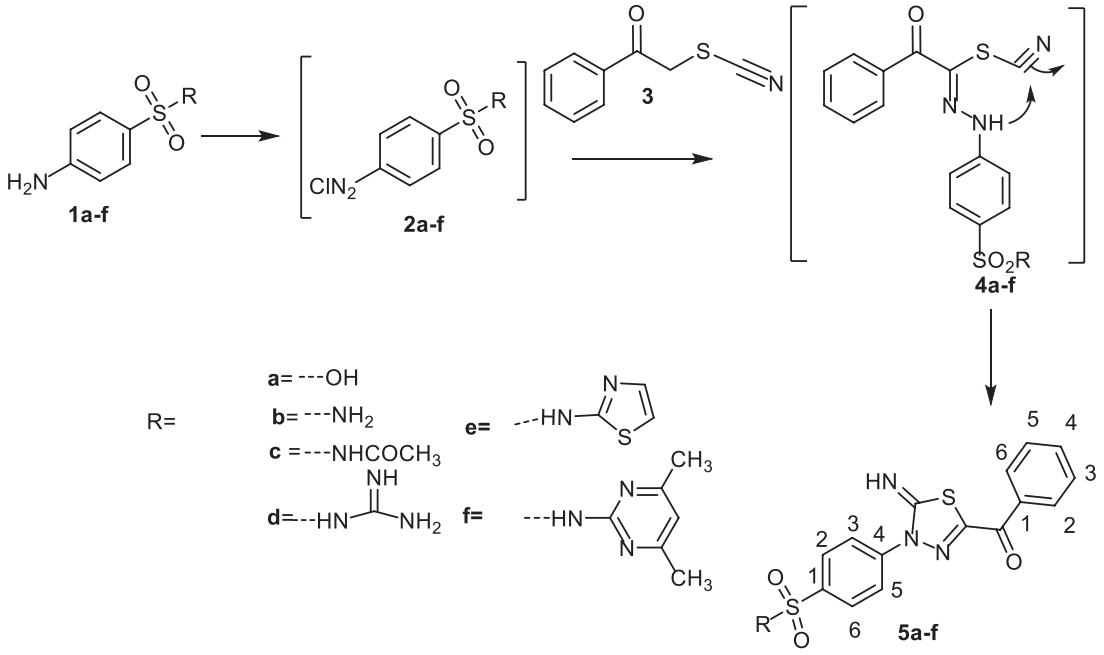

Scheme 1: Synthesis of thiadiazoles 5a-f

the molecular ion peak and the base at *m/z* 360.8 and 170, which agree with its molecular formula $C_{15}H1_2N4O_3S_2$ and 4-aminobenzenesulfinamide-H2.

BIOLOGICAL ACTIVITY

The thiadiazoles **5a-f** were evaluated for their *in vitro* cytotoxic activities against a liver (**HepG2**), colon (**HCT-116**), breast (**MCF-7**), and prostate (**PC3**) human cancer cell lines **[Table 1]**. Doxorubicin was used as standard drug. The results revealed that the tested compound displayed moderate to weak cytotoxic activity. Compound **5d** was found to be the most active one activity, probably due to the presence of gundine nucleus.

Table 1: Cytotoxic activity of the sulfa drugs 5a-f

Compound No.	*In vitro* cytotoxicity IC50 (µg/mL)*			
	HePG2	HCT-116	MCF-7	PC3
Doxorubicin	4.50±0.2	5.23±0.3	4.17±0.2	8.87±0.6
5a	41.48±3.1	52.65±3.4	57.26±3.5	63.56±3.7
5b	67.47±4.3	89.88±5.0	93.18±4.8	>100
5c	64.20±4.2	79.83±4.5	81.57±4.6	>100
5d	28.30±2.2	48.17±3.3	36.62±2.7	68.20±3.9
5e	49.02±3.5	71.60±4.2	62.74±3.9	>100
5f	82.44±4.6	>100	>100	>100

*IC50 (µg/mL): 1–10 (very strong). 11–20 (strong). 21–50 (moderate). 51–100 (weak) and above 100 (non-cytotoxic)

MATERIALS AND METHODS

General

All melting points were recorded on Gallen Kamp electronic melting point apparatus. IR spectra (KBr) were decided on a Mattson 5000 FT-IR spectrometer (cm^{-1}). ^1H- and ^{13}C-NMR spectra were evaluated on a JEOL FT-NMR spectrometer (400 and 100 MHz for ^1H and ^{13}C, respectively) using DMSO-d6 as the solvent. Mass spectra were recorded on a Varian TQ 320 GC/MS/MS mass spectrometer. Elemental analyses (C, H, and N) were performed on Microanalytical Center of Cairo University, Giza, Egypt. The biological activities had been carried in Pharmacognosy Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

General procedure for the synthesis of thiadiazoles 5a-f

The corresponding sulfa drug [(4-aminobenzenesulfonamide, *N*-((4-aminophenyl) sulfonyl)acetamide, 4-amino-*N*-carbamimidoylbenzenesulfonamide, 4-amino-*N*-(thiazol-2-yl)benzenesulfonamide, and 4-amino-*N*-(4,6-dimethylpyrimidin-2-yl) benzenesulfonamide**1b-f]** (10 mmol) was dissolved in a mixture of concentrated HCl, AcOH, and water (10 mL, 1:1; 2) and the obtained solution was stirred and cooled in an ice bath to 0–5°C. Then, a solution of $NaNO_2$ 0.88 gm, 13 mmol in 4 mL H_2O) was added dropwise to the previously prepared solution to give the corresponding diazonium salts **2b-f.** In case of the diazonium salt of 4-aminobenzenesulfonic acid **2a**, sulfanilic acid (1.73 g, 10 mmol) was dissolved in a solution of sodium carbonate (0.5 g in 7 ml H_2O) and then a solution of $NaNO_2$ 00.88 gm, 13 mmol in 4 mL H_2O) was added. The obtained solution was stirred and cooled in an ice bath to 0–5°C and 4 ml of concentrated HCl was added dropwise over 10 min and the resulting reaction mixture was stirred for further 30 min to give the diazonium salt **2a**. The formed diazonium chlorides **2a-f** were added dropwise respectively to a cold stirring solution of 1-phenyl-2-thiocyanatoethan-1-one **3 (**1.77 gm, 10 mmol) in 30 mL methanol: pyridine (20 ml 1:1V). The reaction mixture was stirred for 3 h at

0–5°C, then stand overnight at RT. The reaction mixture was diluted with cooled water and formed precipitate was filtered, washed with methanol 50%, and recrystallized from ethanol/benzene to give the corresponding thiadiazols **5a-f.**

4-(5-Benzoyl-2-imino-1,3,4-thiadiazol-3(2H)-yl) benzenesulfonic acid (*5a*)

Yield (55%), mp = 160–162°C. FT-IR (cm^{-1}): 3239 (OH), 3063(NH),3013(C-H-Ar), 1659 (CO), 1153, 1029 (SO_2); ^{1}H-NMR (400 MHz; DMSO-d6): δ:6.91–7.82 (m, 9H, Ar-H), 11.30 (br, 1H, C=NH),14.03 (br, 1H, OH).MS (70 ev, %) m/z361.48, M^+, 80.4), 339 (49.9), 294 (29.3), 267 (84.3), 239 (86.1), 218 (83.8), 190 (47.6), 181 (55.3), 162 (37.7), 125 (51.5), 121 (100), 56 (70.2), 48 (62.6). Analysis calculated for $C_{15}H_{11}N_3O_4S_2$ (361.39): C, 49.85; H, 3.07; N, 11.63%. Found: C, 49.72; H, 3.16; N, 11.70%.

4-(5-Benzoyl-2-imino-1,3,4-thiadiazol-3(2H)-yl) benzenesulfonamide (*5b*)

Yield (75%), mp = 210–212°C. FT-IR (cm^{-1}):3313, 3237, 3114 (NH,NH_2),1641, (br, C=O, C=N), 1157, 1039, (SO_2);^{1}H-NMR (400 MHz; DMSO-d6): δ:7.60 (br, 2H, NH_2),7.62-8.21 (m, 9H, Ar-H), 9.70 (br, 1H, =NH);^{13}C-NMR (100 MHz; DMSO-d6): δ: 183.1 (CO), 158.5 (C=N), 148.7($C_{5\text{-thiadiazole}}$),142.2 (C_4), 134.7, ($C_{4'}$),134.4, ($C_{1'}$),130.6 (2C, $C_{2,6}$),129.2 (2C, $C_{3',5'}$),127.0 (2C, $C_{2',6'}$),126.9 (2C, $C_{2',6}$'), 122.2 (2C, $C_{3,5}$).MS (70 ev, %) m/z360.8, M^+, 58.9), 337 (60.6), 318 (62.1), 287 (85.7), 215 (58.7), 198 (85.6), 191 (70.1), 175 (69.9), 170 (100), 148 (59.8), 127 (37.1), 104 (61.6), 80 (33.2), 68 (48.4), 56 (79.1), 50 (46.0). Analysis calculated for $C_{15}H1_2N4O_3S_2$ (360.41): C, 49.99; H, 3.36; N, 15.55%. Found: C, 49.91; H, 3.29; N, 15.50%.

N-((4-(5-Benzoyl-2-imino-1,3,4-thiadiazol-3(2H)-yl)phenyl)sulfonyl)acetamide (*5c*)

Yield (84%), mp =190–192°C. FT-IR (cm^{-1}): 3313, 3254, 3113(2NH), 1723,1643, (2C=O, C=N), 1162, 1037(SO_2);^{1}H-NMR (400 MHz; DMSO-d6): δ:1.99 (s, 3H, CH_3), 7.61–8.26 (m, 9H, Ar-H), 9.82 (br, 1H, C=NH), 12.22 (br, 1H, NHCO);^{13}C-NMR (100 MHz; DMSO-d6): δ: 183.1 (CO),169.4 (CH_3CONH), 158.5 (C=N), 149.2($C_{5\text{ thiadiazole}}$), 143.1 (C_4), 136.8 ($C_{4'}$), 134.6, (C_1), 134.5, ($C_{1'}$), 130.7 (2C, $C_{2,6}$),129.2 (2C, $C_{3',5'}$), 129.1 (2C, $C_{2',6}$'), 122.6 (2C, $C_{3,5}$), 23.7 (CH_3). MS (70 ev, %) m/z402.0, M^+, 14.5), 398 (45.5), 371 (45.4), 364 (43.2), 334 (45.7), 325 (36.4), 309 (29.0), 289 (43.7), 205 (33.8), 162 (27.5), 115 (52.0), 95 (73.9), 84 (100), 63 (49.4), 42 (65.6). Analysis calculated for $C_{17}H_{14}N_4O_4S_2$ (402.44): C, 50.74; H, 3.51; N, 13.92%. Found: C, 50.83; H, 3.45; N, 14.02%.

4-(5-Benzoyl-2-imino-1,3,4-thiadiazol-3(2H)-yl)-N-carbamimidoylbenzenesulfon-amide (*5d*)

Yield (78%), mp = 230–232°C. FT-IR (cm^{-1}):3438, 3335, 3299, 3197(NH_2, 3NH),1630 (br, C=O, C=N),1162,1063 (SO_2);^{1}H-NMR (400 MHz; DMSO-d6): δ:6.78 (br, 3H, NH_2, NH), 7.28–8.23 (m, 10H, Ar-H, $NHSO_2$), 9.79 (br, 1H, C=NH);^{13}C-NMR (100 MHz; DMSO-d6): δ:183.0 (CO), 158.6 (C=NH),149.0 (NH=C-NH_2), 143.0 ($C_{5,\text{thiadiazole}}$), 140.8 (C_4), 134.6 (C_1'),134.5 ($C_{4'}$),131.1(C_1),130.1 (2C, $C_{2,6}$),129.3 (2C, $C_{3',5'}$), 126.9 (2C, $C_{2',6}$), 123.1 (2C, $C_{3,5}$). MS (70 ev, %) m/z402.41, M^+, 22.8), 361 (16.2), 336 (12.3), 306 (4.6), 281 (14.1), 244 (15.4), 226 (16.3), 215 (50.6), 169 (16.2), 147 (23.3), 118 (54.9), 104 (33.4), 96 (90.2), 91 78.6), 82 (19.9),70 (70), 69 (100), 65 (72). Analysis calculated for $C_{16}H_{14}N_6O_3S_2$ (402.45): C, 47.75; H, 3.51; N, 20.88%. Found: C, 47.67; H, 3.59; N, 20.75%.

4-(5-Benzoyl-2-imino-1,3,4-thiadiazol-3(2H)-yl)-N-(thiazol-2-yl)benzenesulfon- amide (5e)

Yield (57%), mp = 200–202°C. FT-IR (cm^{-1}): 3250, 3101 (2NH), 1686, 1647 (C=O, 2C=N), 1146, 1089 (SO_2);^{1}H-NMR (400 MHz; DMSO-d6): δ:6.90 (d, 1H, C5-H, j=8.8 hz), 7.31 (d, 1H, C4-H, j=8.8 hz),7.59-8.25 (m, 10H, Ar-H, =NH), 12.93 (br, 1H, $NHSO_2$). MS (70 ev, %) m/z443.51, M^+, 86.7), 421 (75.7), 410 (59.1), 363 (63.4), 345 (85.3), 263 (59.8), 258 (59.8), 231 (100), 201 (11.2), 197 (51.5), 166 (64.0), 150 (43.3), 108 (51.9), 93 (20.0). Analysis calculated for $C_{18}H_{13}N_5O_3S_3$ (443.51): C, 48.75; H, 2.95; N, 15.79; %. Found: C, 48.83; H, 3.02; N, 15.70; %.

(4-(5-Benzoyl-2-imino-1,3,4-thiadiazol-3(2H)-yl)-N-(4,6-dimethylpyrimidin-2-yl) benzenesulfonamide (*5f*)

Yield (70%), mp = 165–167°C. FT-IR (cm^{-1}):3317, 3121 (2NH), 1670 (C=O),1627 (C=N), 1162,1085(SO_2); ^{1}H-NMR (400 MHz; DMSO-d6): δ:2.27 (s, 3H, 2 Me), 6.77(s, 1H, C-5H, pyrimidine), 6.90 (d, 1H, C5-H, j=8.8 hz), 7.59-8.20 (m, 9H, Ar-H), 9.73(br, 1H, NH=), 12.03 (br, 1H, NH- SO2). MS (70 ev, %) m/z443.51, M^+, 86.7), 421 (75.7), 410 (59.1), 363 (63.4), 345 (85.3), 263 (59.8), 258 (59.8), 231 (100), 201 (11.2), 197 (51.5), 166 (64.0), 150 (43.3), 108 (51.9), 93 (20.0).Analysis calculated for $C_{21}H_{18}N_6O_3S_2$ (466.53): C, 54.06; H, 3.89; N, 18.01; %. Found: C, 54.13; H, 3.81; N, 18.08%.

BIOLOGICAL ACTIVITY

The reagents RPMI-1640 medium (Sigma Co., St. Louis, USA) Fetal Bovine serum (GIBCO, UK) and the human cell lines HepG2, HCT-116, MCF-7, and PC3 were obtained from ATCC. The cell lines mentioned above had been used to determine the inhibitory results of compounds on cell growth using the MTT assay. More details about the MTT assay, cytotoxicity activity, and IC_{50} for each compound are presented in literature.[29-31]

CONCLUSION

A series of 2-imino-1,3,4-thiadiazols **5a-f** was prepared through coupling of the appropriate sulfonamide diazonium chlorides **2a-f** with phenacyl thiocyanate **3** in pyridine, the structure of synthesized compounds has been elucidated through spectral data. The cytotoxic of these compounds revealed that the tested compound displays moderate to weak cytotoxic activity. Compound **5d** displayed maximum activity probably due to the presence of guanidine nucleus.

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