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Design, Synthesis, and Anticancer Evaluation of New Coumarin and Pyrazole Derivatives Bearing Benzenesulfonamide Moiety

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ABSTRACT The search for new anticancer agents is considered a dynamic field of medicinal chemistry. In recent years, the synthesis of compounds with potential anticancer has increased and a large number of structurally varied compounds displaying potent anticancer activities have been published. Some new sulfonamides bearing either pyrazole or coumarin moieties were prepared and screened for their antitumor activity against breast cancer cell line (MCF-7). The results of this investigation revealed that compounds **5**, 7, **8**, and **10** had significant anticancer activity against the MCF-7 cancer cell line with IC_{50} values 28.0, 17.9, 13.9, and 20.2 µM, respectively, in relation to the standard drug, doxorubicin.

KEYWORDS Coumarins, Pyrazoles, Antitumor, Sulfonamides.

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INTRODUCTION

Cancer still is one of the most dreadful diseases in the world despite immense advances in the field of basic and clinical research, which have resulted in higher cure rates for several malignancies. Although chemotherapy is the mainstay of cancer therapy, the use of available chemotherapeutics is often limited mainly due to the undesirable many side effects and it underscores the need of developing novel efficient anticancer agents for more effective cancer treatments.[1,2] Among the wide range of compounds tested as potential anticancer agents, sulfonamide derivatives are an important class of promising compounds with diverse biological activities including anti-cancer[3-7] and serve as the major carbonic anhydrase inhibitors (CAIs) which block the function of CAs by directly coordinating the catalytic zinc ion present within the of the hCAs active sites and establishes two additional hydrogen bonds with a residue nearby (Thr199).[8-10] Sulfonamides have been marketed for cancer therapy, such as Belinostat, Venetoclax (ABT-199), and Amsacrine.

Recently, some fused 1,2,4-triazoles and 4-functionalized pyrazoles bearing benzene sulfonamide have been reported as selective inhibitors of CA IX and XII.[11-13] Further, 1,2,3-triazole ring-containing compounds are gaining interest in diverse therapeutic fields such as antiproliferative,[14] antitubercular, antimicrobial,[15] antifungal, antibacterial,[16] anticancer,[17,18] anti-inflammatory,[19] anti-HIV,[20] antiviral,[21] antiobesity,[22] as well as in several DNA-alkylating, crosslinking agents,[23] and β-lactamase inhibitors.[24] Some 1,2,3-triazole ring containing selective CAIs have also been reported (**Figure 1**).[23,25]

In addition, it is well known that coumarin derivatives are an important class of natural plant metabolites that offer a variety of biological activities. Coumarin derivatives are not only effective as anticancer agents, but also possess minimum side effects, and can readily interact with diverse enzymes and receptors in cancer cells through weak bond interactions; hence, coumarin is a highly privileged pharmacophore for the development of new anticancer agents.[26,27] Coumarin and its derivatives have been reported as drugs, as the anticoagulants warfarin, acenocoumarin, and phenprocoumon, all acting as vitamin K antagonists, the choleretics armillarisin A and hymecromone (umbelliferone), and the antibiotic novobiocin (**Figure 2**).[28]

Moreover, pyrazoles present an interest group of compounds, many of which possess widespread

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2 (3.61 g, 10 mmol) was added slowly to this mixture and stirred for 5 h. The crude reaction was then quenched into water (1 L) and stirred for an additional 1 h the solid formed was separated, washed with water, dried, and crystallized from methanol to afford **8** as pale yellow crystals (3.50 g, 75% yield), m.p. = 239–240°C. FT-IR (KBr, *v*, cm^{-1}): *v* = 2187 (CN), 1689, 1635 (2CO), 1620 (C=N), 1352, 1149 (SO_2); ^{1}H-NMR (500 MHz, *δ*, ppm, DMSO-d_6): *δ* = 9.70 (s, 1H, CHO), 8.28 (s, 1H, pyrazole H-5), 8.00 (d, 2H, *J* = 8.5 Hz, Ar–H), 7.81 (d,2H, *J* = 8.5 Hz, Ar–H),7.79 (s, 1H, CH=N),4.11 (s, 2H, CH_2), 3.19 (s, 3H, NCH_3), 3.14 (s, 3H, NCH_3), 2.60 (s, 3H, CH_3); ^{13}C-NMR (125 MHz, DMSO-d_6) *δ*c 10.49 (CH_3), 18.59 (CH_2), 48.64 ($2NCH_3$), 119.44, 125.77, 126.60 (2C, Ar-), 127.47 (2C, Ar-), 128.25, 130.35, 133.02 (triazole C4), 137.98(triazole C5), 142.68, 144.00, 156.84, 160.17 (CO) 181.10 (CO). MS: *m/z* = 454 [M+] (82 %).Calcd for $C_{19}H_{18}N_8O_4S$ (454.47): C, 50.21; H, 3.99; N, 24.66. Found C, 50.30; H, 3.90; N, 24.50.

(E)-4-[4-(1-(2-(2-Cyano-3, 3-bis (methylthio) acryloyl) hydrazineylidene) ethyl)-5-methyl-1H-1, 2, 3-triazol-1-yl] benzenesulfonamide (9)

To a stirred suspension of finely powdered potassium hydroxide (0.26 g, 5 mmole) in absolute ethanol (50 ml), compound **2 (**3.61 g, 10 mmol) was added, the resulting mixture was cooled at 10°C in an ice bath, then carbon disulfide was added slowly over 15 min. After addition was completed stirring of the reaction, mixture was continued for an additional 2 h. Then, dimethyl sulfate (5 mmole) was added to the mixture while cooling and stirring for 1 h. The temperature reached r.t. and the stirring continued for another 1 h. The mixture was then poured into crushed ice and the resulting precipitate was filtered off, washed several times with water, dried, and crystallized from ethanol to give **9** pale yellow crystals (3.70 g, 79.6% yield), m.p. = 210–211°C. FT-IR (KBr, *v*, cm^{-1}): *v* =3441, 3278 (NH_2), 3188 (NH), 2237 (CN), 1689 (CO), 1625 (C=N), 1595 (C=C), 1357, 1170 (SO_2); ^{1}H-NMR (500 MHz, *δ*, ppm, DMSO-d_6): *δ* = 11.20 (s, 1H, NH), 8.06 (d, 2H, *J* = 8.5 Hz, Ar–H), 7.88 (d,2H, *J* = 8.5 Hz, Ar–H),7.0 (s, 2H, NH_2), 2.64 (s, 3H, SCH_3), 2.55 (s, 3H, SCH_3), 2.48 (s, 3H, CH_3), 2.46 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) *δ*c9.76 (CH_3), 13.89 (CH_3), 61.36 ($2SCH_3$), 125.99 (2C, Ar-), 127.21 (2C, Ar-), 128.67,131.69 (triazole C4), 137.36 (triazole C5), 138.01, 143.02, 145.05, 145.33, 166.95(CO), 193.38(C=S). MS: *m/z* = 465 [M+] (65 %). Calcd for $C_{17}H_{19}N_7O_3S_3$ (465.57): C, 43.86; H, 4.11; N, 21.06. Found C, 43.70; H, 4.20; N, 21.10.

(E)-4-[4-(1-(2-(3-Amino-5-(methylthio) -1H-pyrazole-4-carbonyl) hydrazineylidene) ethyl)-5-methyl-1H-1, 2, 3-triazol-1-yl] benzenesulfonamide (10)

To a solution of compound **9 (**2.32 g, 5 mmol) in ethanol (50 mL), hydrazine hydrate was added. The reaction mixture was heated under reflux for 4 h. and then left to cool. The resulting precipitate was filtered off, dried, and crystallized from ethanol to give **10** a colorless crystals (1.80 g, 80% yield), m.p. = 228–230°C. FT-IR (KBr, *v*, cm^{-1}): *v* =3366 - 3227 ($2NH_2$), 3217 (NH), 1615 (C=N), 1347, 1160 (SO_2); ^{1}H-NMR (500 MHz, *δ*, ppm, DMSO-d_6): *δ* 12. 98 (s, 1H, NH), 11.35 (s, 1H, NH), 8.02(d, 2H, *J* = 8.5 Hz, Ar–H), 7.83 (d,2H, *J* = 8.5 Hz, Ar–H), 7.44 (s, 2H, NH_2), 6.20 (s, 2H, NH_2), 2.64 (s, 3H, SCH_3), 2.45(s, 3H, CH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) *δ*c 9.72 (CH_3), 13.21 (CH_3), 27.33 (SMe), 125.99 (2C, Ar-), 127.21 (2C, Ar-), 128.67, 131.77 (triazole C4), 137.60 (triazole C5), 138.01, 143.02, 145.45 (pyrazole C5), 151.25 (pyrazole C4), 154.33 (pyrazole C3), 166.95(CO), MS: *m/z* = 449 [M+]. Calcd for $C_{16}H_{19}N_9O_3S_2$ (449.51): C, 42.75; H, 4.26; N, 28.04. Found C, 42.60; H, 4.30; N, 28.10.

CONCLUSION

The reactivity of **(***E***)**-4-[4-(1-(2-(2-cyanoacetyl) hydrazineylidene) ethyl)-5-methyl-1*H*-1,2,3-triazol-1-yl] benzenesulfonamide (**2**) was investigated as a versatile and readily accessible building block for the synthesis of new pyrazoles and coumarins incorporating a sulfonamide moiety of biological and pharmaceutical importance. The antitumor evaluation assay indicates that designating a sulfonamide bearing pyrazole or coumarin moieties in one frame may enhance antitumor activity against MCF-7.

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