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Synthesis, anticancer and radiosensitizing evaluation of some novel sulfonamide derivatives

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ABSTRACT

In this study, novel series of sulfonamide derivatives were synthesized starting from 2-cyanoacetyl) hydrazono)ethyl)phenyl)benzenesulfonamide **4a** and 2-cyanoacetyl)hydrazono)ethyl)phenyl)-4-methylbenzenesulfonamide **4b.** Different biologically active moieties as pyrazol, thiophene, pyridine and pyrimidines were introduced in order to investigate their *in-vitro* anticancer activity, in addition to a novel series of sulfonamide chalcones were synthesized from the reported 4-acetyl-N-(P-tolyl) benzenesulfonamide **3b**. The newly synthesized sulfonamide derivatives were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analyses and were tested for their *in-vitro* anticancer activity against human tumor liver cell line (HEPG-2). The most potent compounds in this study were compounds **4a**, **4b**, **5a**, **6a**, **6b, 8, 9, 11, 13, 18** and **19** which showed higher activity than doxorubicin with IC_{50} ranging from 11.0 to 31.8 μM. Additionally, eight compounds among the most potent were evaluated for their ability to enhance the cell killing effect of γ-radiation.

1. Introduction

The hepatocellular carcinoma (HCC) is the most frequent histological type of primary liver carcinoma and is one of the cancer types of highest incidence worldwide [1]. The majority of patients diagnosed with HCC have low recovery rates, and conventional and modified therapies currently available are rarely beneficial [2]. The human liver cancer cell line HepG2, established in 1979, is the best characterized and most frequently used cell line to predict overall hepatotoxicity [3]. On the other hand, sulfonamides possess many types of biological activities [4,5]. Also, from the Literature survey it was found that aryl/heteroaryl sulfonamides may act as antitumor agents through several mechanisms [6]. Previously we studied about synthesis and biological activity of some sulfonamide containing different biologically active moieties and we observed many compounds have promising anticancer activity [7–20]. In addition, many hetrocyclic compounds incorporating pyridine, thiophene or benzothiophene moieties showed potential anticancer activities [21–25]. Furthermore, particular interest has been focused on the anticancer activity of chalcones which represent an important group of the polyphenolic family [26]. This family possesses an interesting spectrum of biological activities, including antimicriobial [27,28], anti-inflammatory [29], immunosuppressive [30] and anticancer activity [31,32]. Compounds of this family have been shown to interfere with each step of carcinogenesis, including initiation, promotion and progression [33]. Moreover, numerous chalcones appear to show activity against cancer cells, suggesting that these molecules or their derivatives may be considered as potential anticancer drugs [34]. In the design of new drugs, the development of hybrid molecules through the combination of different pharmacophores may lead to compounds with interesting biological profiles. In recent years, combination chemotherapy with agents possessing different mechanisms of action is one of the methods, which are, being adopted to treat cancer [35,36]. Following this approach and as a part of an ongoing effort to find alternate chemotherapeutic agents for hepatocellular carcinoma [11,12,37,38], we herein, report the design and synthesis of novel sulfonamide derivatives bearing a biologically active pyridine, thiophene, benzothiophene and chalcone moieties for evaluation as anticancer on liver human tumor cell lines (HEPG2) and as

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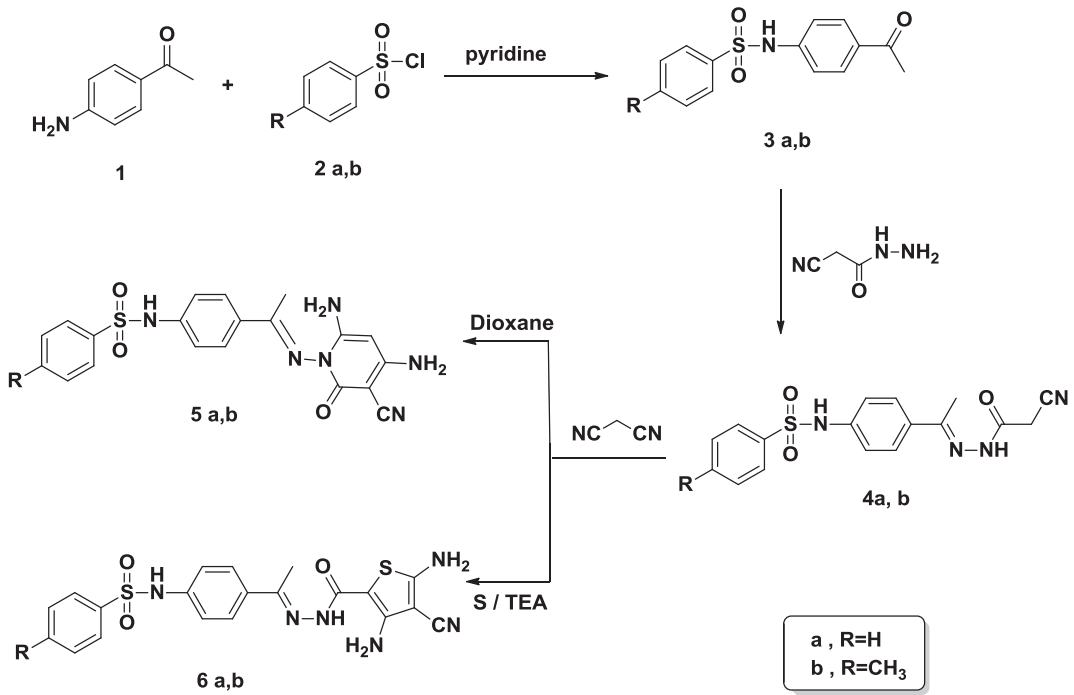
radiosensitizing agents.

2. Results and discussion

2.1. Chemistry

The synthetic strategies utilized for the synthesis of the target compounds are outlined in (Schemes 1–3) which could assemble entirely the desired sulfonamide derivatives (**4**a,b-**26**) from the strategic starting materials N-(4-acetyl-N-(P-substituted) phenyl benzenesulfonamide (**3a,b**) [39,40]. Hence, to develop a more widely applicable approach for the synthesis of the target compounds we chose to evaluate two synthetic strategies based on substitution of the acetyl group, the first pathway is the reaction of the nitrogen nucleophile 2-cyanoacetohydrazide with compounds **3a,b** to yield (E)-N-(4-(1-(2-(2-cyanoacetyl) hydrazono) ethyl)-N-(P- substituted) phenyl benzenesulfonamide **4a,b** in good yield (Scheme 1). The structural assignments to synthesized compounds were based on their physico-chemical characteristics and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data) investigations. IR spectrum of compound **4a** revealed characteristic strong intensity bands at 3340, 3219 and 2259 cm^{-1} for the introduced (2NH and C≡N), respectively confirming the formation of cyanoacetyl hydrazono derivative. ^{1}H NMR spectrum displayed up-field singlet at 3.3 ppm for the introduced CH_2 group and downfield shifted singlet appearing at 10.9 ppm due to addition of NH group. ^{13}C NMR exhibited new up-field signal at 27.3 ppm for CH_2 and new signal at 125.7 ppm assigned to C≡N. IR spectrum of compound **4b** revealed characteristic strong intensity bands at 3438, 3245 and 2259 cm^{-1} for the introduced (2NH and C≡N), respectively confirming the formation cyanoacetyl hydrazono derivative. ^{1}H NMR spectrum displayed up-field singlet at 3.6 ppm for the introduced CH_2 group and downfield shifted singlet appearing at 10.9 ppm, due to addition of NH group. ^{13}C NMR exhibited new up-field signal at 38.6 ppm for CH_2 and new signal at 126.6 ppm ascribed to C≡N. A subsequent ring-closure approach effort for the synthesis of the target compounds **5**–**13** involves reaction of **4a, b** with malononitrile in dioxane to give (Z)-4-(1-((4,6-diamino-3-cyano-2-oxopyridin-1(2H)-yl)imino)ethyl)-N-p-substituted-phenyl-benzenesulfonamide (**5a,b**) (Scheme 1). IR spectrum of compound **5a** revealed characteristic strong intensity bands at 3338 and 3210 cm^{-1} for the introduced two NH_2 groups. ^{1}H NMR spectrum displayed up-field singlet at 4.5 ppm assigned for the CH group and downfield shifted singlet appearing at 8.5 ppm, due to addition of NH_2 group. ^{13}C NMR exhibited new up-field signal at 83.1 ppm for CH pyridine, 148.4 ppm for (N—C—NH_2) and 177.9 ppm for (C—NH_2). IR spectrum of compound **5b** revealed characteristic strong bands at 3389 and 3315 cm^{-1} for the two of NH_2 groups. ^{1}H NMR spectrum displayed up-field singlet at 4.1 ppm for the CH group and downfield shifted singlet appearing at 10.7 ppm, due to addition of NH_2 group. ^{13}C NMR exhibited new up-field signal at 83.1 ppm for CH pyridine, 143.6 ppm for (N—C—NH_2) and 177.9 ppm for (C—NH_2). Alternatively, malononitrile was reacted with compounds **4a, b** in the presence of elemental sulfur and in absolute ethanol containing 3 drops of triethyl amine to yield the corresponding thiophene derivatives **6a, b** (Scheme 1) this reaction goes in parallel to the reported Gewald's thiophene synthesis [41] and their spectroscopic data were consistent to their chemical structures. The corresponding N-(4-((Z)-1-(2-((E)-2-cyano-3-(dimethylamino) acryloyl) hydrazono) ethyl) phenyl)-4-methylbenzenesulfonamide **7** was obtained through the addition of DMF-DMA on **4b** in xylene (Scheme 2). IR spectrum revealed bands at 2929, 2830 cm^{-1} for CH_aliphatic. ^{1}H NMR spectrum displayed up-field singlet at 3.3 ppm for the addition of two group of CH_3 and downfield shifted singlet appearing at 7.5 ppm due to introduced CH group. ^{13}C NMR exhibited new up-field signal at 40.3 ppm for introduced two methyl group, 98.8 ppm for C—CN and down-field signal at 156 ppm for addition of CH group. Compound (Z)-2-cyano-3-(2-(1-(4-(4-methylphenylsulfonamido) phenyl) ethylidene) hydrazinyl)-3-oxopropanedithioic acid **8** was obtained via the reaction of CS_2 with **4b** in DMF containing KOH (Scheme 2), its IR spectrum revealed band at 1300 cm^{-1} for C=S group. ^{1}H NMR spectrum



Scheme 1. Synthetic pathways for compounds **3a,b**-**6a,b**.