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Design, synthesis and anticancer activity of novel hybrid compounds between benzofuran and *N*-aryl piperazine

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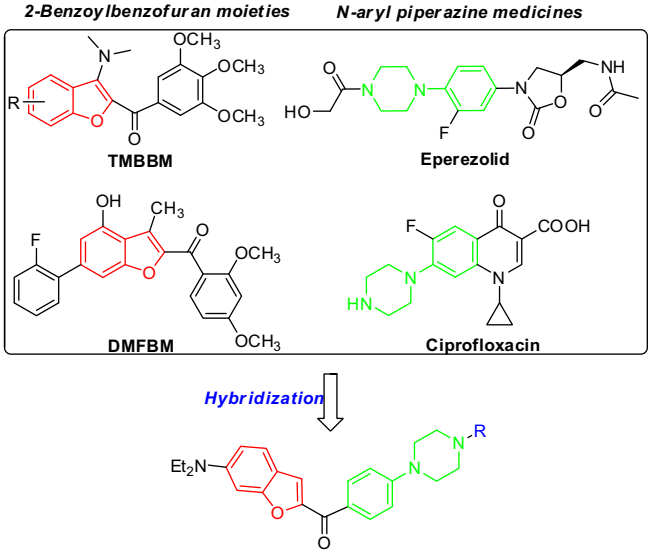
ABSTRACT

A series of novel hybrid compounds between benzofuran and *N*-aryl piperazine have been designed and prepared. These derivatives were evaluated for their in vitro anti-tumor activity against a panel of human tumor cell lines by MTT assay. The results demonstrated that amide derivatives were more bioactive than sulfonamide compounds in general, and that chloro or trifluoromethyl substituent was vital for modulating cytotoxic activity. In particular, compound **13** was found to be the most potent compound against 4 strains human tumor cell lines, and exhibited cytotoxic activity selectively against Hela (0.03 μM).

Cancer is a large family of diseases resulting from uncontrolled cell growth, which remains one of the most potentially life threatening diseases worldwide.[1] Despite the presence of a variety of anticancer medicines, no currently available agents can eradicate cancer cells without harming normal tissues. Therefore, the development of new anticancer agents and more selective treatment strategies for cancer has received more and more attention for medicinal chemists.

Benzofuran derivatives are a class of most important heterocyclic moieties, which have drawn considerable attention over past years. Natural and synthetic compounds containing benzofuran fragment displaying a broad range of biological activities, such as antioxidant, anti-inflammatory, antibacterial, anticancer and so on.[2–5] In addition, 2-benzoylbenzofuran derivatives have been identified to possess cytotoxic activity, as exemplified in Scheme 1, 2-benzoyl-phenylbenzofuran derivative (TMBBM)[6] and 2-(2,4-dimethoxybenzoyl)-phenyl benzofuran derivative (DMFBM)[7] showed potent antitumor activities.

Similarly, *N*-aryl piperazine moieties represent a series of important organic compounds that make up the core structures in medicines. Recently, *N*-aryl piperazine derivatives have attracted considerable interests for their versatile properties in chemistry and pharmacology, and these moieties have been widely developed to medicinal chemistry.[8–10]



Scheme 1. Design of novel hybrid compounds.

Molecular hybridization as one of the successful strategies for development of chemotherapeutic agents involves the combination of two distinct bioactive units. The combination of the benzofuran

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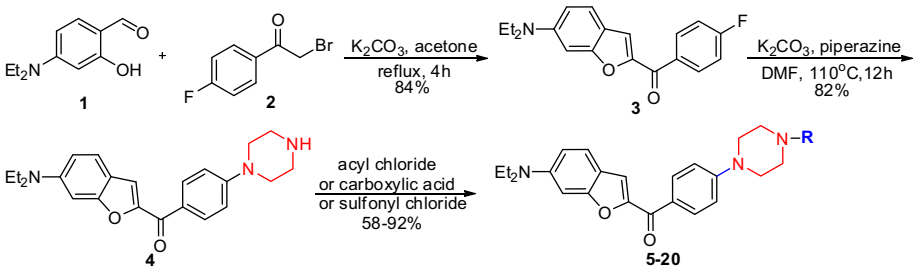


Scheme 2. Synthetic routes of hybrid derivatives.

Table 1
Structures and yields of compounds **5**–**20**

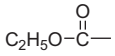
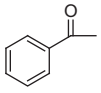
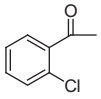
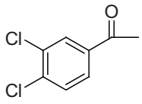
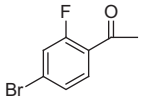
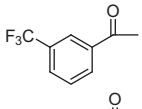
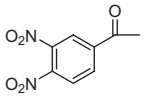
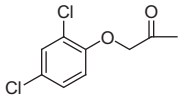
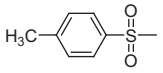
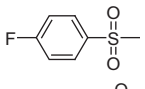
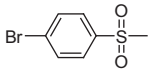
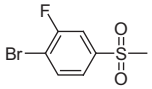
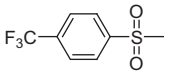
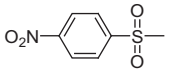
Compound	R	Molecular formula	Mp (°C)	Yields[a] (%)
5		$C_{25}H_{29}N_3O_3$	184–186	90
6		$C_{26}H_{31}N_3O_4$	179–180	92
7		$C_{30}H_{31}N_3O_3$	186–188	85
8		$C_{30}H_{30}ClN_3O_3$	190–192	86
9		$C_{30}H_{29}Cl_2N_3O_3$	193–195	84
10		$C_{30}H_{29}BrFN_3O_3$	188–190	79
11		$C_{31}H_{30}F_3N_3O_3$	193–194	83
12		$C_{30}H_{29}N_5O_7$	214–216	58
13		$C_{31}H_{31}Cl_2N_3O_4$	208–210	84
14		$C_{24}H_{29}N_3O_4S$	179–181	89
15		$C_{30}H_{33}N_3O_4S$	192–194	86
16		$C_{29}H_{30}FN_3O_4S$	197–198	77
17		$C_{29}H_{30}BrN_3O_4S$	194–196	86
18		$C_{29}H_{29}BrFN_3O_4S$	197–199	77

Table 1 (*continued*)

Compound	R	Molecular formula	Mp (°C)	Yields[a] (%)
19		$C_{30}H_{30}F_3N_3O_4S$	200–202	81
20		$C_{29}H_{30}N_4O_6S$	211–213	63

[a] Yields represent isolated yields.

and imidazole in one frame, has been reported with potential anticancer activity.[11] Moreover, in previous research, we have designed hybrid compounds between chalcone and *N*-aryl piperazine with excellent cytotoxic activities.[12] On the basis of these results, we were interested in designing and synthesizing a number of novel hybrid compounds bearing 2-phenzoyl benzofuran and *N*-aryl piperazine moieties (Scheme 1).

In the present research, we reported the synthesis of a series of novel hybrid compounds between benzofuran and *N*-aryl piperazine. These derivatives were evaluated for their in vitro antitumor activity against a panel of human tumor cell lines by MTT assay, with the aim of developing new potent anticancer agents.

The concise synthetic route used to synthesize title compounds is outlined in Scheme 2. Treatment of commercially available 5-diethylaminosalicylaldehyde (**1**) with 2-bromo-4′-fluoroacetophenone (**2**) gave the 2-phenzoylbenzofuran compound (**3**)[13] in the presence of K_2CO_3 in refluxing acetone. The corresponding benzofuran-*N*-aryl piperazine derivative (**4**)[14] was prepared from compound (**3**) by substitution with piperazine in the presence of Cs_2CO_3 at 110 °C in DMF in 82% yield. Based on our previous synthesis, the desired compounds (**5**–**20**) were prepared with excellent yields by reaction of intermediate (**4**) with acyl chloride, carboxylic acid or sulfonyl chloride. Comparative data for novel hybrid compounds with respective to structures and yield are provided in Table 1. All of the synthesized compounds were characterized by ^1H NMR and ^{13}C NMR, and some representative and biological compounds were characterized by HRMS analysis.[15]

Cytotoxic activity of novel synthesized hybrid derivatives were evaluated against human lung cancer cell lines according to procedures described in the literature by MTT assay,[16] using cisplatin (DDP) as the reference drug. The panel consisted of lung carcinoma (A549), cervical carcinoma (Hela), breast carcinoma (MCF-7) and gastric carcinoma (SGC7901). The biological results of hybrid compounds are summarized in Table 2 (IC_{50} values, defined as the concentration of compound that inhibit 50% of the cell growth).

As shown in Table 2, the structures of the hybrid compounds have an obvious influence on anticancer activities. To explore the