European Journal of Medicinal Chemistry 62 (2013) 111–121

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design, synthesis and biological evaluation of novel hybrid compounds of imidazole scaffold-based 2-benzylbenzofuran as potent anticancer agents

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ARTICLE INFO

Article history:
Received 7 October 2012
Received in revised form
20 November 2012
Accepted 23 December 2012
Available online 3 January 2013

Keywords:
Hybrid compound
2-Benzylbenzofuran
Imidazole
Cytotoxic activities
Structure–activity relationships

ABSTRACT

A series of novel hybrid compounds between 2-benzylbenzofuran and imidazole has been prepared and evaluated in vitro against a panel of human tumor cell lines. The results suggest that the existence of benzimidazole ring and substitution of the imidazolyl-3-position with a naphthylacyl or 4-methoxyphenacyl group were vital for modulating cytotoxic activity. In particular, hybrid compounds **46** and **47** were found to be the most potent derivatives against 5 strains human tumor cell lines and more active than cisplatin (DDP), and exhibited cytotoxic activities selectively against breast carcinoma (MCF-7) and myeloid liver carcinoma (SMMC-7721), respectively.

1. Introduction

Design and synthesis of new types of pharmacologically interesting hybrid compounds for drug discovery have received much attention during the past two decades [1–3]. Substituted-benzofurans are an important class of biologically active oxygen-containing heterocycles. Natural and synthetic products possessing the 2-benzylbenzofuran moiety exhibit a broad range of biological and pharmacological activities [4–7]. Recently, 2-benzylbenzofuran derivatives have been identified to possess antitumor activity [8,9]. As exemplified in Scheme 1, (2,4-dimethoxyphenyl)-[6-(3-fluorophenyl)-4-hydroxy-3-methylbenzofuran-2-yl]methanone (DMFBM) [9] was 2-benzy lbenzofuran derived compound exhibiting potent cytotoxic activities against human lung carcinoma cells.

Imidazole and its derivatives have attracted considerable interests in recent years for their versatile properties in chemistry and pharmacology. Biological activities of imidazolium salts have been reported [10–13], especially antitumor activity [14,15]. For example, two new imidazolium halides (Scheme 1), Lepidiline A and Lepidiline B, isolated from the roots of *Lepidium meyenii*, showed potent cytotoxic activity against the human cancer cell lines [16]. Recently, we have reported the synthesis of a series of novel hybrid compounds of benzofurans and imidazols moieties and their potential antitumor activities [17–21]. Studies on molecular mechanisms demonstrated that the imidazolium salt hybrids can induce the G1 phase cell cycle arrest and apoptosis in tumor cells [20].

Considering the anticancer activities of natural and synthetic 2-benzylbenzofuran derivatives, as well as the potent cytotoxic activities of imidazole derivatives, we were interested in synthesizing a number of new hybrid compounds bearing 2-benzylbenzofuran (as shown pink shadows in Scheme 1) and substituted imidazole (as shown green shadows in Scheme 1).

Although dihydrobenzofuran-triazole hybrid compounds were synthesized and found to possess antitubercular activity by Tripathi [22], and some benzofuran-based hybrid compounds were synthesized and found to exhibit cholinesterase inhibitory activity by Rampa [23], to the best of our knowledge, no reports concerning antitumor activity for 2-benzylbenzofuran-based imidazolium salt hybrids have been reported.

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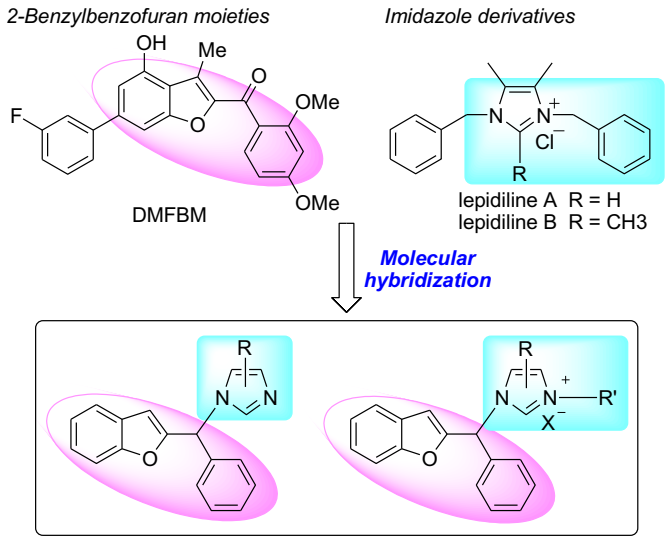
http://dx.doi.org/10.1016/j.ejmech.2012.12.040



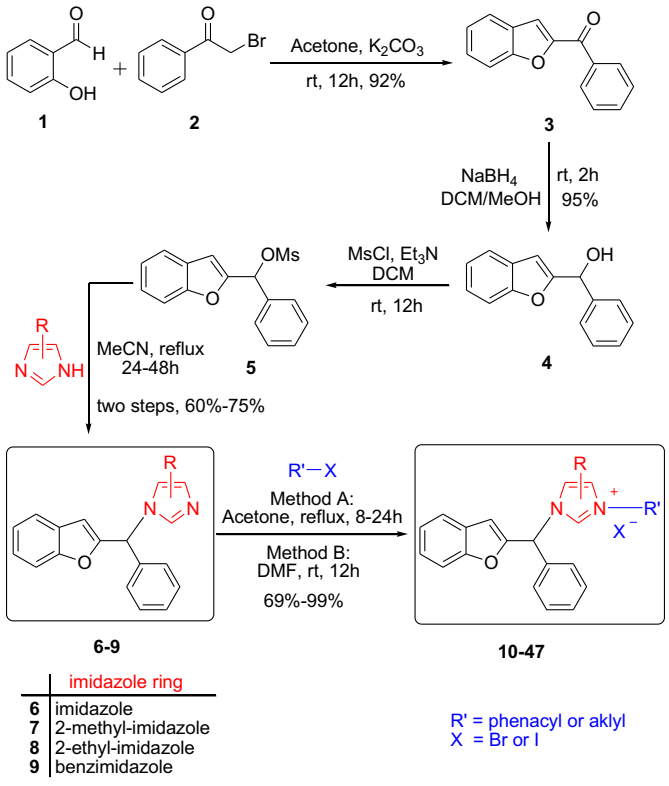
Scheme 1. Design of novel hybrid compounds.

In the present research, we designed and synthesized a series of novel hybrid compounds of imidazole scaffold-based 2-benzylb enzofurans. The purpose of this study was to investigate the anti-tumor activity of 2-benzylbenzofuran-imidazole hybrids, with the ultimate aim of developing novel potent antitumor agents.

2. Results and discussion

2.1. Chemistry

As shown in Scheme 2, commercially available salicylaldehyde **1** was chosen as the starting material for the preparation of a series of 2-benzylbenzofuran-imidazole hybrids **7**–**47**. Thus, the key step in the formation of the phenylbenzofuran backbone was readily achieved by reacting salicylaldehydes **1** with phenacyl bromide **2** to produce (benzofuran-2-yl)(phenyl)methanone (**3**, 92% yield) in base-mediated reaction for 12 h. Then, the (benzofuran-2-yl)(phenyl)methanone **3** were reduced with $NaBH_4$ to the respective (benzofuran-2-yl)(phenyl)methanol compound (**4**, 95% yields). Subsequently, the (benzofuran-2-yl)(phenyl)methanol **4** was transformed via the mesylate to the respective four 2-benzylbenzofuran–imidazole hybrids **6**–**9** with various substituted imidazole (imidazole, 2-methyl-imidazole, 2-ethyl-imidazole or benzimidazole) by refluxing under acetonitrile with 60–75% yields (two steps). Finally, thirty-eight novel 2-benzylbenzofuran-based imidazolium salts **10**–**47** were prepared with excellent yields by reaction of 2-benzylbenzofuran–imidazole hybrids **7**–**10** with the corresponding alkyl and phenacyl halides in refluxing acetone (69–99% yields). The structures and yields of hybrid compounds are shown in Table 1.



Scheme 2. Synthesis of hybrid compounds **6**–**47**.

2.2. Biological evaluation and structure–activity relationship analysis

The cytotoxic potential of all newly synthesized hybrid compounds was evaluated in vitro against a panel of human tumor cell lines according to procedures described in the literature [24,25]. The panel consisted of leukemia (HL-60), lung carcinoma (A549), colon carcinoma (SW480), breast carcinoma (MCF-7) and myeloid liver carcinoma (SMMC-7721). Cisplatin (DDP) was used as the reference drug. The results are summarized in Table 2 (IC_{50} value, defined as the concentrations corresponding to 50% growth inhibition).

As shown in Table 2, the structures of the hybrid compounds have an obvious influence on the cytotoxic activities. 2-Benzylbenzofuran–imidazole hybrids **7**–**10** lacked activities against all tumor cell lines investigated at the concentration of 40 μM. However, their imidazolium salts **10**–**47** exhibited some degree of cytotoxic activities or higher cytotoxic activities. This difference in cytotoxicity between neutral compounds and imidazolium salts may be due to the changes of molecular structure, charge distribution and water solubility [26].

In terms of the imidazole ring (imidazole, 2-methyl-imidazole, or 2-ethyl-imidazole, and benzimidazole), imidazolium salt hybrids **10**–**19** with imidazole ring displayed weak cytotoxic activities. Only compounds **15** and **18** showed medium cytotoxic activities with IC_{50} values of 2.64–8.47 μM against HL-60 and SMMC-7721 cell lines, and compound **19** with a naphthylacyl substituent at position-3 of the imidazole ring displayed higher cytotoxic activity in vitro compared with DDP (except SW480). Meanwhile, imidazolium salt hybrids **20**–**28** with 2-methyl-imidazole ring and **29**–**37** with 2-ethyl-imidazole ring exhibited medium cytotoxic activities. Among them, compounds **27**, **28**, **36** and **37**, bearing a 4-methoxyphenacyl or naphthylacyl substituent at position-3 of the 2-substituted imidazole, showed similar or higher cytotoxic activities in vitro compared with DDP. However, imidazolium salt hybrids **38**–**47** with benzimidazole ring exhibited powerful cytotoxic activities. Most of this kind of derivatives was found to be much more active than DDP, such as compounds **40**, **43**, **44**, **46** and **47**. Among them, compounds **46** and **47**, also bearing a 4-methoxyphenacyl or naphthylacyl substituent at position-3 of the benzimidazole, showed potent cytotoxic activities with IC_{50} values of 1.02–3.57 μM against five human tumor cell lines investigated.

In terms of the substituent at position-3 of imidazole ring, imidazolium salt hybrids **10**–**13**, **20**–**22**, **29**, **30**, and **38** with butyl, allyl or benzyl substituent, as well as hybrids **17**, **26**, **35** and **45** with 4-hydroxyphenacyl substituent at position-3 of imidazole ring showed lacked activities against five tumor cell lines.