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Synthesis and cytotoxic activities of novel hybrid 2-phenyl-3-alkylbenzofuran and imidazole/triazole compounds

Wen Chen [a,†], Xiao-Yan Deng [a,†], Yan Li [b], Li-Juan Yang [c], Wei-Chao Wan [a], Xue-Quan Wang [a], Hong-Bin Zhang [a], Xiao-Dong Yang [a,*]

[a] Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, PR China
[b] State Key Laboratory for Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Science, Kunming 650204, PR China
[c] Key Laboratory of Ethnic Medicine Resource Chemistry, State Ethnic Affairs Commission & Ministry of Education, Yunnan University of Nationalities, Kunming 650031, PR China

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ABSTRACT

A series of novel hybrid compounds of 2-phenyl-3-alkylbenzofuran and imidazole or triazole were prepared and evaluated in vitro against a panel of human tumor cell lines. The results suggest that the 2-ethyl-imidazole ring, and substitution of the imidazolyl-3-position with a 2-bromobenzyl or naphthylacyl group, were vital for modulating inhibitory activity. In particular, hybrid compound **31** was found to be the most potent derivative with IC_{50} values of 0.08–0.55 μM against five strains human tumor cell lines and was found to be more selective against breast carcinoma (MCF-7) and colon carcinoma (SW480) (IC_{50} values 40.8-fold and 40.1-fold lower than cisplatin (DDP)).

Cancer remains one of the most difficult diseases worldwide to treat and is one of the leading causes of human mortality.[1] Developing new anticancer drugs and more effective treatment strategies for cancer is of great importance.[2] Natural products represent a significant source of inspiration for the design of structural analogues with improved pharmacological profiles.[3] Naturally occurring substituted-benzofurans are an important class of biologically active oxygen-containing heterocycles. Natural products possessing the 2-phenyl-3-alkylbenzofuran moiety exhibit a broad range of biological and pharmacological activities.[4] Recently, natural occurring benzofurans have been identified to possess antitumor activity. As exemplified in Figure 1, Moracins O[5] and Ebenfuran III[6] are 2-phenyl-3-alkylbenzofuran derived compounds exhibiting potent cytotoxic activities against human hepatocellular cancer cells and breast cancer cells.[5,6]

Imidazole and triazole and their derivatives have attracted considerable interests for their broad range of biological and pharmacological activity,[7] especially antitumor activity.[8] For example, two new imidazolium halides (Fig. 1), Lepidiline A and Lepidiline B, isolated from the roots of *Lepidium meyenii*, showed potent cytotoxic activity against human cancer cell lines.[9] We have previously reported the synthesis of a series of novel imidazolium salts, such as MNIB (Fig. 1), and their potential antitumor activity.[10] Studies on molecular mechanisms demonstrated that the imidazolium salt hybrids can induce the G1 phase cell cycle arrest and apoptosis in tumor cells.[10a]

Molecular hybridization as a drug discovery strategy, involves the rational design of new chemical entities by the fusion of two drugs. The active compounds and/or pharmacophoric units are identified and derived from known bioactive molecules, as shown in the development of new anticancer, anti-Alzheimer, and antimalarial agents.[11] Considering the anticancer activities of naturally occurring 2-phenyl-3-alkylbenzofurans, as well as the potent cytotoxic activities of natural and synthetic imidazole or triazole derivatives, we were interested in synthesizing a number of new hybrid compounds bearing 2-phenyl-3-alkylbenzofuran (as shown pink shadows in Fig. 1) and *N*-benzyl or phenacyl substituted imidazole and triazole moieties (as shown green shadows in Fig. 1).

Although 2-benzylbenzofuran-triazole hybrid molecules were synthesized and found to exhibit CYP26A1 inhibitory activity,[12] to the best of our knowledge, no reports concerning antitumor activity of 2,3-disubstituted benzofuran-imidazole or triazole hybrid compounds have been reported.

In the present research, we designed and synthesized a series of novel hybrid compounds of 2-phenyl-3-alkylbenzofurans with imidazole or triazole. The purpose of this study was to investigate

* Corresponding author. Tel.: +86 871 65031119; fax: +86 871 65035538.
E-mail addresses: xdyang120@gmail.com, xdyang@ynu.edu.cn (X.-D. Yang).
† These authors contributed equally to this Letter.

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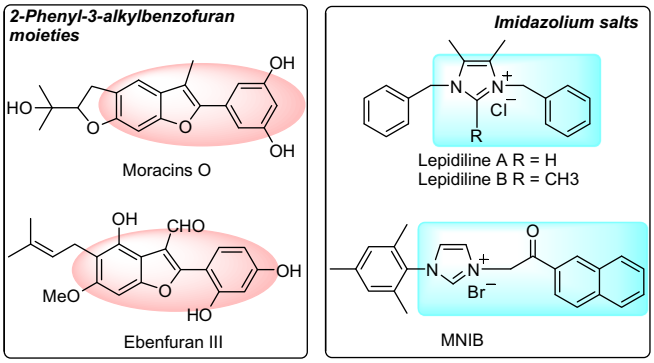
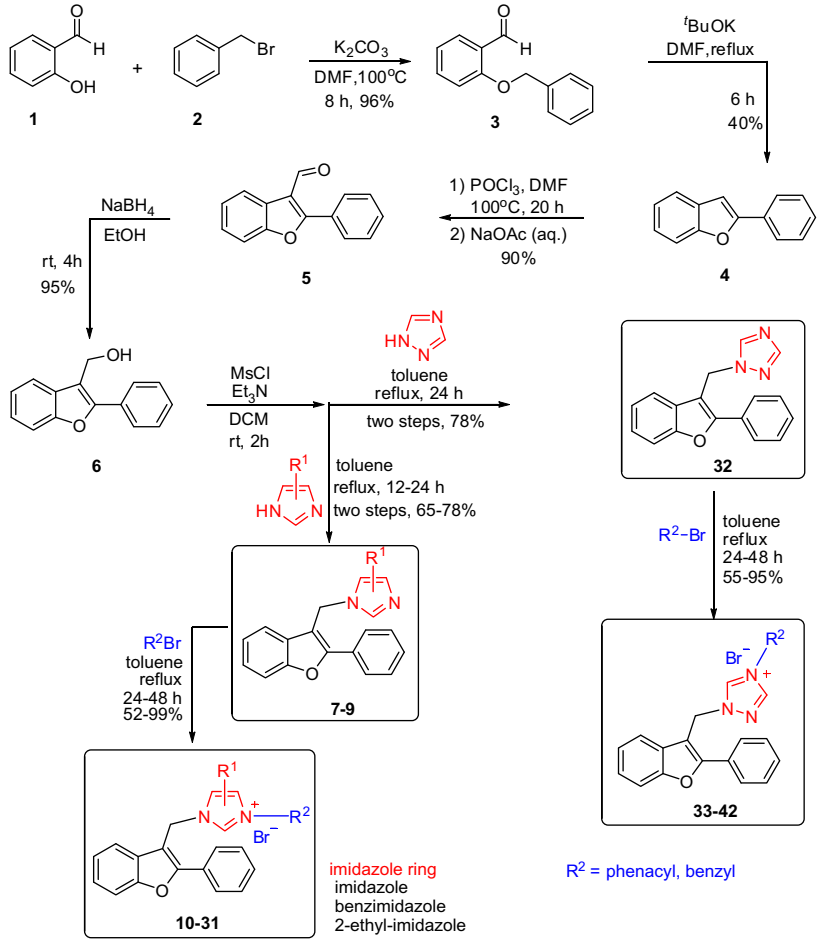


Figure 1. Representative structures of natural 2-phenyl-3-alkylbenzofurans and imidazolium salts.

the antitumor activity of 2-phenyl-3-alkylbenzofuran- imidazole/triazole hybrids, with the ultimate aim of developing novel potent antitumor agents.

To synthesize the 2-phenyl-3-alkylbenzofuran-imidazole hybrids, we used commercially available imidazole and triazole derivatives that were alkylated with 2-phenylbenzofuran 3-methanol, which was synthesized over four steps from readily available starting materials as shown in scheme 1. Salicylaldehyde **1** was chosen as the starting material for the preparation of a series of 2-phenyl-3-alkylbenzofuran-imidazole/triazole hybrids (**7**–**42**). Salicylaldehyde **1** was reacted with benzyl bromide **2** in DMF at 100 °C to give ether the ether **3** in 96% yields. The key step in the formation of the 2-phenylbenzofuran backbone was achieved by heating benzyl salicylaldehyde ether **3** in a base-mediated condensation to produce the intermediate 2-phenylbenzofuran (**4**, 40% yield). The formylation of 2-phenylbenzofuran **4** under Vilsmeier–Haack conditions followed by hydrolysis produced the known compound 2-phenylbenzofuran-3-carbaldehyde **5** in 90% yield. The 2-phenylbenzofuran-3-carbaldehyde **5** was reduced via $NaBH_4$ to the respective 2-phenylbenzofuran 3-methanol compound (**6**, 95% yields). Subsequently, the 2-phenylbenzofuran 3-methanol compound **6** was transformed via the mesylate to give the respective 2-phenyl-3-alkylbenzofuran–imidazole hybrids (**7**–**9**) and 2-phenyl-3-alkylbenzofuran–triazole hybrid **32** by refluxing under toluene with 65–78% yields (two steps).[13] Finally, thirty 2-phenyl-3-alkylbenzofuran-based imidazolium salts (**9**–**31**) and 2-phenyl-3-alkyl-benzofuranbased triazolium salts (**33**–**42**) were prepared with excellent yields by reaction of 2-phenyl-3-alkylbenzofuran–imidazole/triazole hybrids with the corresponding phenacyl and alkyl halides in refluxing toluene (52–99% yields).[14] The structures and yields of hybrid compounds are shown in Table 1.

The potential cytotoxicity of all newly synthesized hybrid compounds were evaluated in vitro against a panel of human tumor cell lines, according to procedures described in the literature.[15] The panel consisted of leukemia (HL-60), myeloid liver carcinoma (SMMC-7721), lung carcinoma (A549), breast carcinoma (MCF-7), and colon carcinoma (SW480). 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).



Scheme 1. Synthesis of hybrid compounds **7**–**42**.