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Synthesis and cytotoxic activity of novel tetrahydrobenzodifuran–imidazolium salt derivatives

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ABSTRACT

The synthesis of a series of novel 4-substituted 2,3,6,7-tetrahydrobenzo [1,2-*b*;4,5-*b*′]difuran–1*H*-imidazolium salts is presented. The biological properties of the compounds were evaluated *in vitro* against a panel of human tumor cell lines. Results suggest that the 5,6-dimethyl-benzimidazole or 2-methyl-benzimidazole ring, and substitution of the imidazolyl-3-position with a 2-naphthylmethyl substituent or 2-naphthylacyl substituent, were important to the cytotoxic activity. Notably, 3-(2-Naphthylmethyl)-1-((2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]difuran-4-yl)methyl)-1*H*-5,6-dimethyl-benzimidazol-3-ium bromide (**42**) was found to be the most potent derivative against five human tumor cell lines with IC_{50} values of 1.06–4.34 μM and more selective towards SMMC-7721, A549 and SW480 cell lines. 3-(2-Naphthylacyl)-1-((2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]difuran-4-yl)methyl)-1*H*-2-methyl-benzimidazol-3-ium bromide (**37**) showed higher selectivity to SMMC-7721 and MCF-7 cell lines with IC_{50} values 2.7-fold and 8.4-fold lower than DDP. Study regarding to the antitumor mechanism of action showed that compound **37** could induce cell cycle G1 phase arrest and apoptosis in SMMC-7721 cells.

Tetrahydrobenzodifurans and dihydrobenzofurans represent as important classes of biologically active oxygen-containing heterocycles. Naturally occurring compounds and biologically active agents with dihydrobenzofuran and tetrahydrobenzodifuran moieties exhibit a wide range of remarkable biological activities, especially antitumor activity.[1] As exemplified in Fig. 1, Megapodiol with dihydrobenzofuran moiety is an anti-leukaemic agent,[2] while Mesocyperusphenol A with tetrahydrobenzodifuran moiety showed powerful cytotoxic activity against human *T*-cell leukemia cells.[3] Further study showed that Mesocyperusphenol A was a potent 5-lipoxygenase inhibitor.[4] On the other hand, imidazole and their derivatives have attracted wide attention due to their pharmaceutical potential resulting from their significant biological activities,[5] especially antitumor activity.[6] For instance, natural imidazolium chlorides Lepidiline A and B (Fig. 1) showed potent cytotoxic activity against four human cancer cell lines.[7] However, to the best of our knowledge, no scientific study on the exactly molecular targets of Lepidilines was reported. Considering the value of imidazolium salts, we have previously reported the synthesis of a series of novel imidazolium salts, such as NMIB (Fig. 1), and their potential antitumor activity.[8] Further study of molecular mechanisms showed that the imidazolium salt hybrids can induce the cell cycle arrest and apoptosis in tumor cells.[8c,g] Studies on molecular targets demonstrated that the imidazolium salt hybrids may be the inhibitors of mTOR (mammalian target of rapamycin) signaling.[8i] And the docking calculations also supported this conclusion.[8f,i]

Molecular hybridization is a useful strategy in new drug design and development during the past two decades.[9] Considering the anticancer activities of tetrahydrobenzodifuran, as well as the potent cytotoxic activities of imidazole derivatives, we are interested in the preparation of the hybridizing compounds of 4-substituted 2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]difuran with imidazole moieties. During the past several years, some anticancer agents based on imidazolium salts were reported.[8,10] To the best of our knowledge, no reports concerning antitumor activity of 4-substituted 2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]difuran–imidazole hybrids could be found in the literature.

Herein, a series of novel 4-substituted 2,3,6,7-tetrahydrobenzo [1,2-*b*;4,5-*b*′] difuran imidazolium salts were synthesized to

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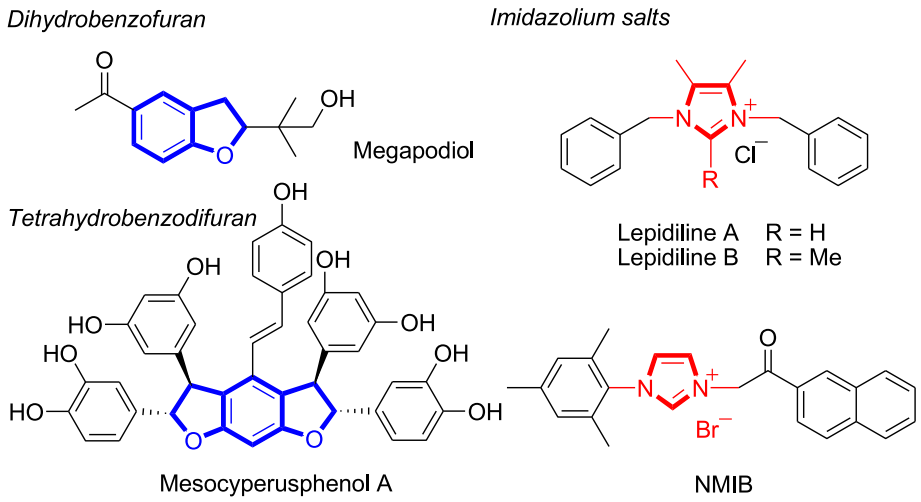
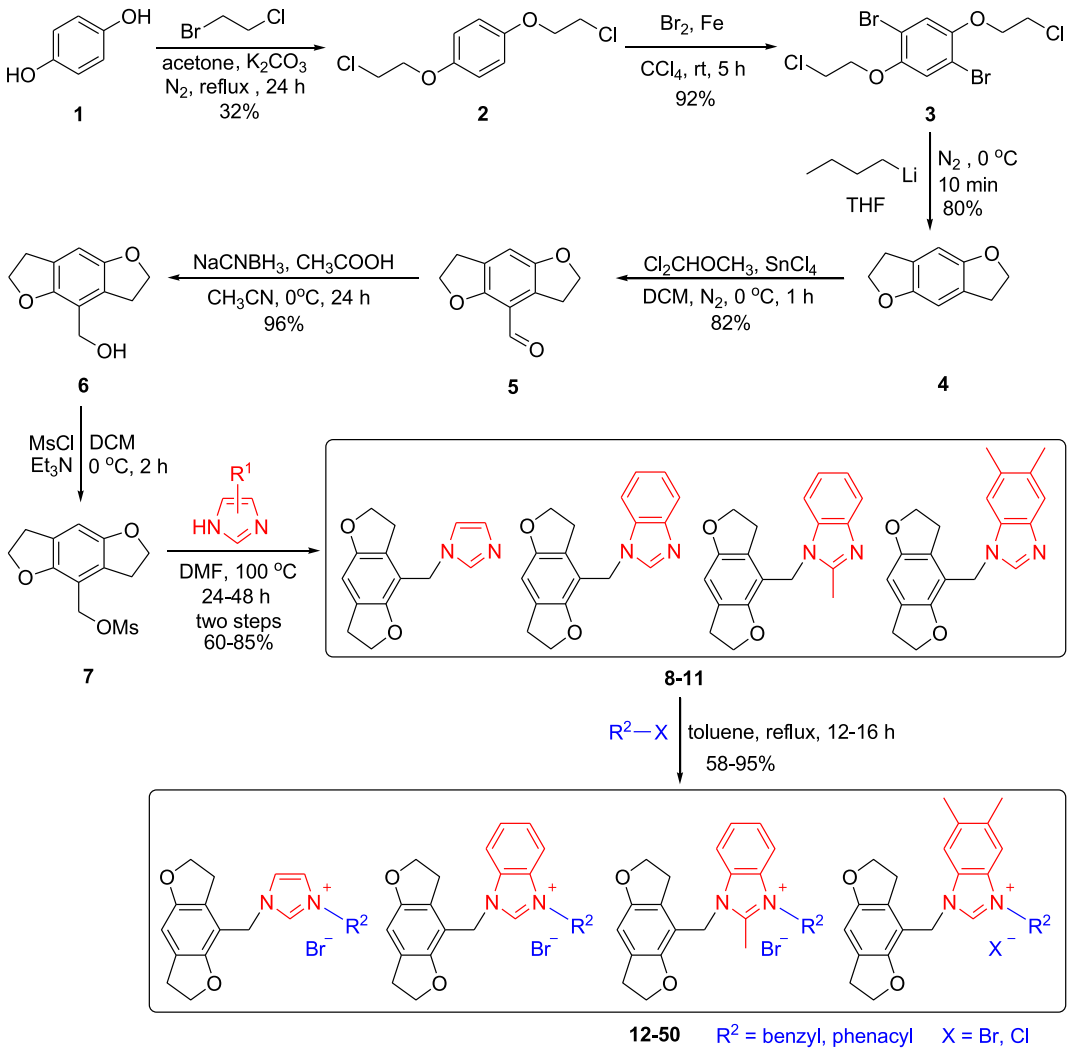


Fig. 1. Representative structures of dihydrobenzofuran, tetrahydrobenzodifuran and imidazolium salts.



Scheme 1. Synthesis of tetrahydrobenzodifuran–1*H*-imidazolium salts **12**–**46**.