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Synthesis, molecular docking and butyrylcholinesterase inhibitory activity of novel hydroxylated 2-benzylbenzofuran derivatives

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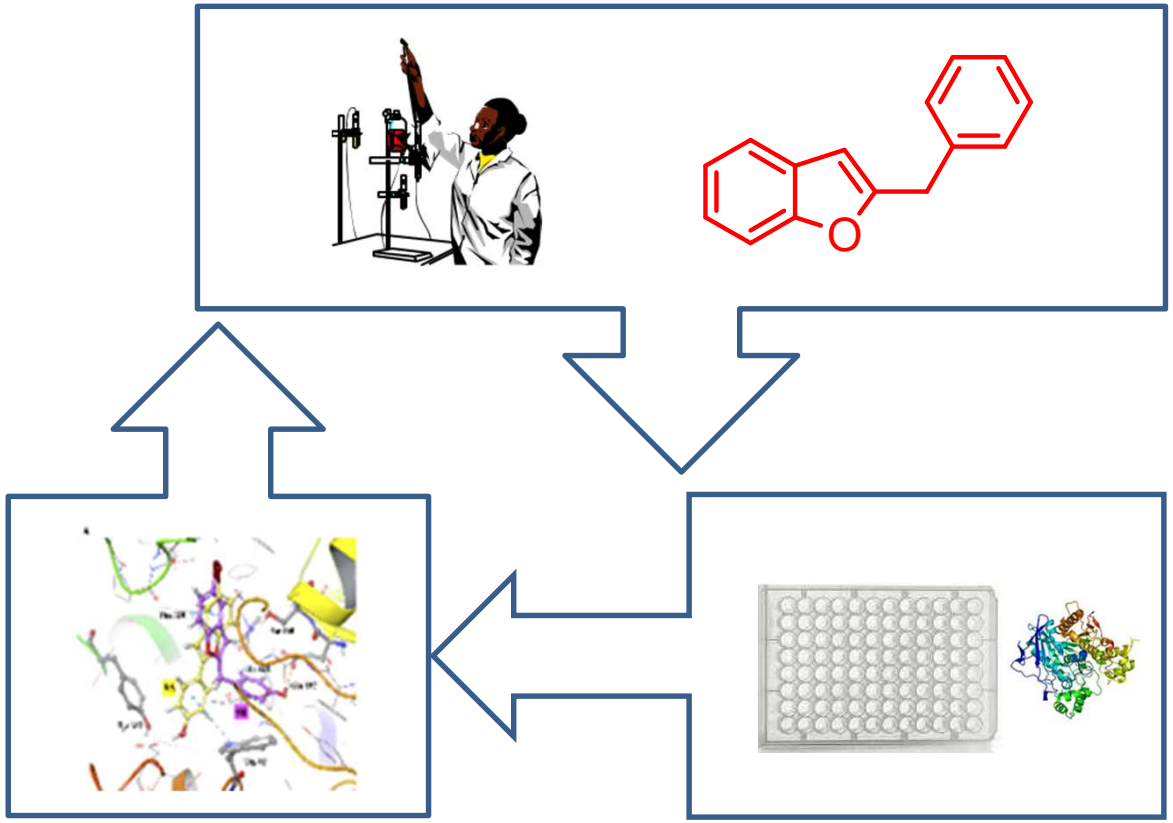
Synthesis, molecular docking and butyrylcholinesterase inhibitory activity of novel hydroxylated 2-benzylbenzofuran derivatives



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Abstract:

A benzofuran ring as a core of heterocyclic compounds is an essential structural unit of various biologically active natural medicines and synthetic chemical raw materials. Numerous studies have shown that 2-phenylbenzofurans have strong biological activities such as anti-cancer, anti-bacterial, anti-viral, anti-oxidative, anti-fungal and anti-microbial. Recent studies have demonstrated enzymatic inhibition properties of 2-phenylbenzofuran derivatives against butyrylcholinesterase and monoamine oxidase.

In our efforts to contribute to the development of novel compounds that may be useful in the treatment of neurodegenerative disorders such as Parkinson's disease or Alzheimer's disease, we are focusing on benzofuran substituted at the position 2 from a benzyl ring.

A preliminary study gives some insights into the synthesis and biological activity of these molecules against this important target. The position of hydroxyl group on the 2-benzyl ring and the position of halogen atom in the benzofuran nucleus, have an important influence on the inhibitory activity. The observed structure-activity relationship for these compounds was explain by molecular docking.

Further studies are still needed to optimize the structure and interaction with the enzyme, with the aim of increasing the potential of these molecules as inhibitors.

Keywords: benzofuran ring; butyrylcholinesterase inhibitors; molecular docking.

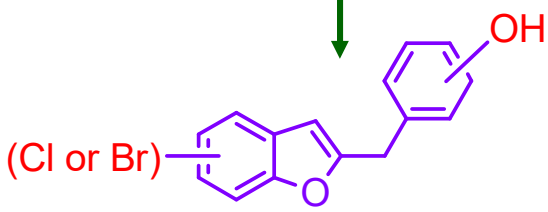
Introduction

Alzheimer's disease (AD)

- presence of amyloid-β deposits;
- τ-protein aggregation;
- oxidative stress;
- metal ions imbalance;
- deficit of acetylcholine (ACh).

One strategy

Restore the levels of ACh by inhibiting acetylcholinesterase (AChE, EC 3.1.1.7) and butyrylcholinesterase (BChE, EC 3.1.1.8), which are mainly responsible for ACh hydrolysis.

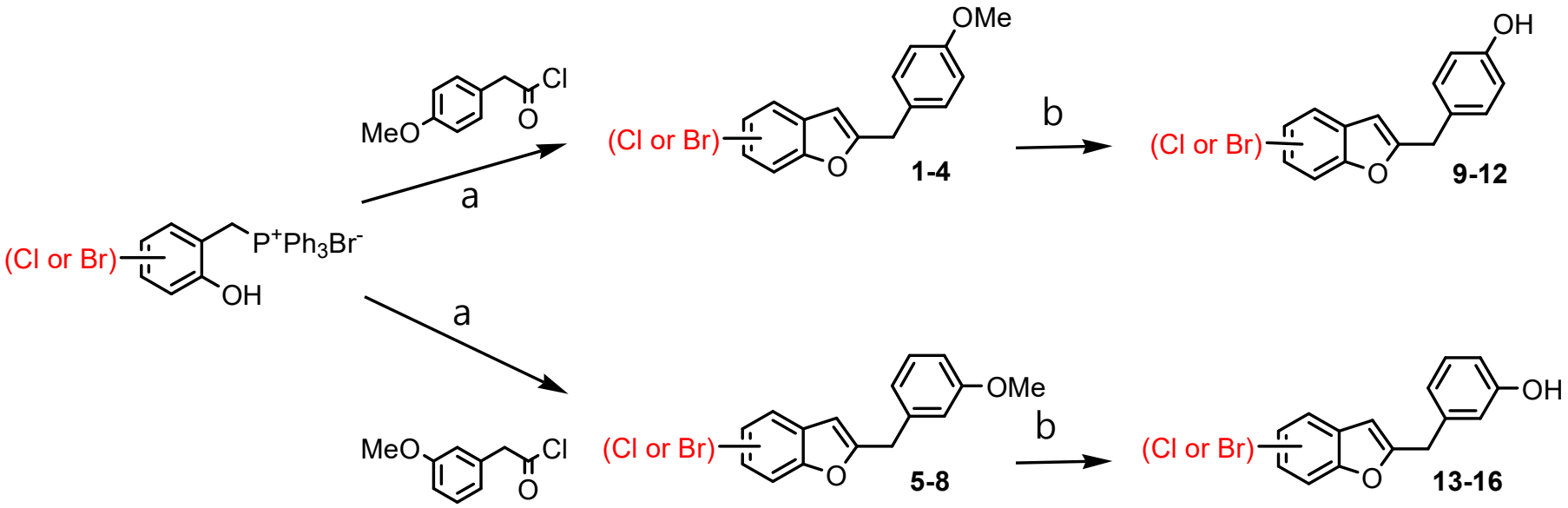


benzofuran derivatives

BChE inhibitors

Results and Discussion

2-Benzylbenzofurans **1**-**8** were efficiently prepared by an intramolecular Wittig reaction. Following the hydrolysis of the methoxy group of compounds **1-8**, the corresponding hydroxy derivatives **9-16** were obtained.

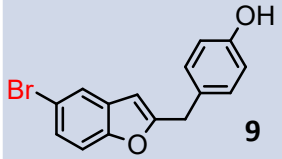
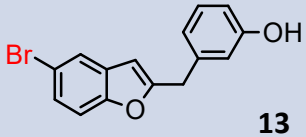
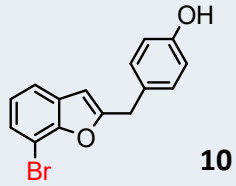
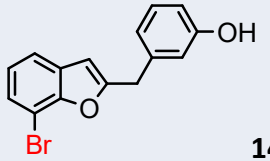
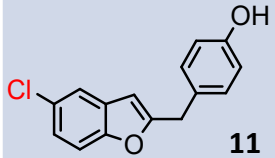
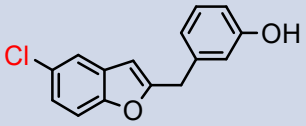
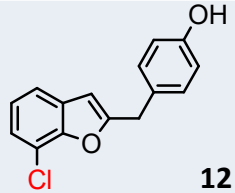
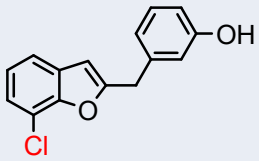


Reagents and conditions: a) toluene, Et_3N, 110 °C, 2 h; b) HI/AcOH/Ac_2O, 0 °C to reflux, 4h.

Results and Discussion

The inhibitory activity of compounds **9-16** was tested at the concentration of 50 µM and for each compound, the inhibition percentage was calculated, and the results are presented in Table 1. The standard inhibitor at about 28 µM determines a % inhibition equal to 50.

Table 1. Inhibitory activity of 2-benzylbenzofurans against BChE at 50 µM.

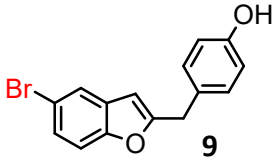
Compounds	Inhibition%± SD		Compounds	Inhibition%± SD
 **9**	98.2±1.8		 **13**	59.3±2.6
 **10**	58.9±3.5		 **14**	56.8±0.5
 **11**	44.5±6.1		 **15**	64.9±4.4
 **12**	53.7±2.6		 **16**	45.6±2.2

Results and Discussion

Among derivatives *para*-hydroxy substituted **9**-**12** the most active compound is the 5-bromo-2-(4-hydroxybenzyl) benzofuran (**9**), which totally inhibits the enzymatic activity at the concentration tested. Benzylbenzofuran isomer **10**, with the bromine atom in position 7 in the benzofuran ring, is less active than the previous one. Benzylbenzofurans **11** and **12** with the chlorine atom, in positions 5 and 7 respectively, are the least active of this series.

In the series of 2-benzylbenzofurans *meta*-hydroxy substituted **13**-**16** the most active compound is 5-chloro-2-(3-hydroxybenzyl)benzofuran (**15**).

Preliminary molecular docking was performed for compound **9** against hBChE protein and the result displayed the good docking energy value. Compound **9** can readily interact with residues crucial for hBChE inhibition.



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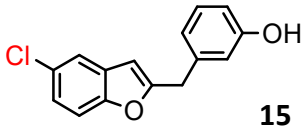

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Conclusions

The most active molecule (compound **9**) is a 2-benzylbenzofuran bearing a bromine group at position 5 of the in the benzofuran ring and a hydroxy one in *para* position of the 2-benzyl ring .

Docking simulations assisted in explaining the structure-activity relationships of this type of compounds.

Our results highlighted a relationship between the scaffold, the nature of the substituents and their position within the scaffold with BChE inhibitory activity.

Acknowledgments

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