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Design, synthesis and biological evaluation of benzofuran appended benzothiazepine derivatives as inhibitors of butyrylcholinesterase and antimicrobial agents

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This article is dedicated to Prof. Dr. Abbas Shafiee who recently passed away.

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ABSTRACT

A series of bezofuran appended 1,5-benzothiazepine compounds **7a–v** was designed, synthesized and evaluated as cholinesterase inhibitors. The biological assay experiments showed that most of the compounds displayed a clearly selective inhibition for butyrylcholinesterase (BChE), while a weak or no effect towards acetylcholinesterase (AChE) was detected. All analogs exhibited varied BChE inhibitory activity with IC_{50} value ranging between 1.0 ± 0.01 and 72 ± 2.8 μM when compared with the standard donepezil (IC_{50}, 2.63 ± 0.28 μM). Among the synthesized derivatives, compounds **7l**, **7m** and **7k** exhibited the highest BChE inhibition with IC_{50} values of 1.0, 1.0 and 1.8 μM, respectively. The results from a Lineweaver-Burk plot indicated a mixed-type inhibition for compound **7l** with BChE. In addition, docking studies confirmed the results obtained through *in vitro* experiments and showed that most potent compounds bind to both the catalytic anionic site (CAS) and peripheral anionic site (PAS) of BChE active site. The synthesized compounds were also evaluated for their *in vitro* antibacterial and antifungal activities. The results indicated that the compounds possessed a broad spectrum of activity against the tested microorganisms and showed high activity against both gram positive and gram negative bacteria and fungi.

1. Introduction

Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are two important types of cholinesterase species. They are mainly responsible for the hydrolysis of acetylcholine (ACh) into choline and acetic acid which is an essential process allowing for the control of the cholinergic transmission.[1] Low levels of ACh is a key pathological hallmark of Alzheimer's disease (AD).[2] AD is the leading cause of dementia and is characterized by a progressive decline in cognitive function, which typically begins with deterioration in memory.[3,4] In a healthy brain, ACh is predominantly (80%) hydrolyzed by AChE, whereas BChE plays a supplementary role. However, with progression of AD, the AChE activity decreases, whereas the activity of BChE gradually increases.[5,6] This phenomenon enhances the significance of BChE as an additional therapeutic target for reducing the cholinergic deficiency inherent in AD.[7,8] Currently, AD therapy is mainly founded on cholinesterase inhibitors, which are able to increase ACh levels in cholinergic synapses.[9] Recent studies have demonstrated that BChE inhibition results in improved cognitive potential with elevated levels of ACh in brain and hence, it may act as an effective therapeutic strategy for AD.[10–13]

1,5-Benzothiazeoines are considered privileged scaffolds in drug discovery for cardiovascular and neurodegenerative diseases. 1,5-Benzothiazepine derivatives have a broad spectrum of therapeutic applications as coronary vasodilator,[14] Ca^{+2} channel antagonists,[15] antidepressant,[16,14] acetylcholinesterase inhibitors,[17] butyrylcholinesterase inhibitors,[18] and antimicrobial agents.[19–21] Benzofurans, a groups of naturally occurring substances in many plants, exhibit a wide range of biological activities.[22,23] Benzofuran scaffold has emerged as an important pharmacophore for designing antiviral[24,25] and antimicrobial agents[26,27] and inhibitors of cyclin-dependent kinases (CDKs)[28] and cholinesterase.[29,30] Combination of 1,5-benzothiazepine and benzofuran moiety exhibited synergistic effect thereby, enhancing their potency.

In the light of above-mentioned findings, and as a continuation of our endeavor to identify new candidates that might be advantageous in designing new, potent, selective, and less toxic cholinesterase inhibitors,[31–34] we have reported the synthesis of 1,5-benzothiazepine derivatives containing benzofuran fragments at C-4 position. All synthesized compounds were screened for their ability to inhibit the enzyme activities of BChE and their *in vitro* antimicrobial activity. To better understand the enzyme inhibition

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mechanisms, in relation to the substituents and their positions in the presented compounds, molecular modeling studies were also performed.

2. Results and discussion

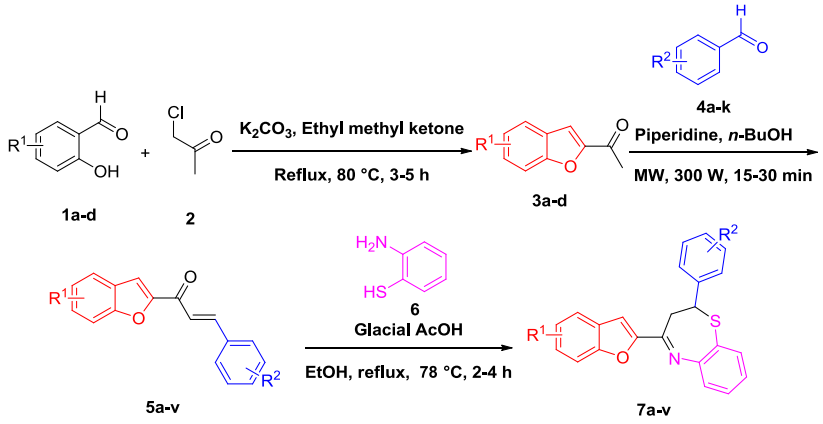
2.1. Chemistry

The synthesis of 1,5-benzothiazepine derivatives **7a–v** was outlined in Scheme 1. First, 2-acetylbenzofuranes **3a–d** were prepared from the ring closure reaction of salicylaldehyde derivatives **1a–d** and chloroacetone **2** (Table 1). Then, condensation of 2-acetylbenzofuranes **3a–d** with various benzaldehydes **4a–k** under microwave irradiation in the presence of catalytic amount of piperidine gave α, β-unsaturated carbonyl compounds **5a–v** (Table 2). Finally, the thia Michael addition and further cyclocondensation reaction of compounds **5a–v** with 2-aminothiophenol **6** was accomplished in refluxing ethanol in the presence of catalytic amount of glacial acetic acid to afford designed compounds **7a–v** in good to excellent yields (70–90%). The generality of this sequence was examined by using different salicylaldehyde derivatives in the first step and (het)aryl aldehydes in the second step. It was found that substrates containing various functional groups yielded the corresponding products **7a–v** in good to excellent yields.

As an initial attempt for optimization of the reaction conditions, the effect of various protic and aprotic solvents such as acetonitrile, toluene, dichloromethane, methanol, and ethanol for the cyclocondensation reaction of compound **5i** with 2-aminothiophenol **6** was evaluated (Table 3). The results clearly showed that among the different tested solvents, the best result was obtained using absolute ethanol under reflux condition which led to the formation of the corresponding product **7i** in high yield (80%).

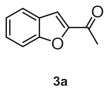
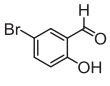
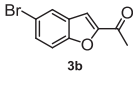
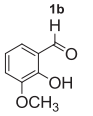
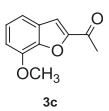
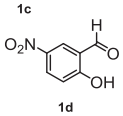
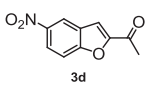
Then, evaluation of various catalytic systems for the formation of target compound **7i** was carried out. It was observed that in the absence of any catalyst, the reaction did not entirely proceed. Several catalysts such as conc. HCl, trifluoroacetic acid (TFA), *p*-toluene sulfonic acid (*p*-TSA), ammonium chloride (NH_4Cl) and piperidine were applied in this reaction but the reaction time and product yields were not appropriate (Table 4, entries 1–5). The most encouraging result was obtained in the presence of 0.1 equivalent of glacial acetic acid as catalyst for the preparation of the model compound **7i**. Increasing the amount of glacial acetic acid accompanied by the temperature did not lead to an increase in product yields (Table 4, entries 6–8).

Then, in regard to library construction, we extended our study with 22 different substituted chalcones under optimized reaction condition. All the reactions underwent smoothly and provided corresponding 1,5-benzothiazepines **7a–v** in high yield (Table 5).



Scheme 1. General scheme for the synthesis of 2,3-dihydro-1,5-benzothiazepine derivatives **7a–v**.

Table 1
Synthesis of 2-acetylbenzofuranes **3a–d** from chloroacetone and salicylaldehydes.

Entry	Salicylaldehyde	Product	Time (h)	Yield (%)	M.P. (°C)	M.P. [Lit.] (°C)
1	 1a	 3a	4	72	74–76	76[35]
2	 1b	 3b	3	75	109–111	110[35]
3	 1c	 3c	4	78	91–93	91[35]
4	 1d	 3d	5	65	174–176	175[35]