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# Novel biphenyl *bis*-sulfonamides as acetyl and butyrylcholinesterase inhibitors: Synthesis, biological evaluation and molecular modeling studies

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ABSTRACT

A series of new biphenyl *bis*-sulfonamide derivatives **2a**–**3p** were synthesized in good to excellent yield (76–98%). The inhibitory potential of the synthesized compounds on acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) was investigated. Most of the screened compounds showed modest *in vitro* inhibition for both AChE and BChE. Compared to the reference compound eserine ($IC_{50}$ 0.04 ± 0.0001 μM for AChE) and ($IC_{50}$ 0.85 ± 0.0001 μM for BChE), the $IC_{50}$ values of these compounds were ranged from 2.27 ± 0.01 to 123.11 ± 0.04 μM for AChE and 7.74 ± 0.07 to <400 μM for BuChE. Among the tested compounds, **3p** was found to be the most potent against AChE ($IC_{50}$ 2.27 ± 0.01 μM), whereas **3g** exhibited the highest inhibition for BChE ($IC_{50}$ 7.74 ± 0.07 μM). Structure–activity relationship (SAR) of these compounds was developed and elaborated with the help of molecular docking studies.


## 1. Introduction

Alzheimer's disease (AD), a progressive neurodegenerative disease, associated with selective loss of cholinergic neurons and reduced level of acetylcholine neurotransmitter. The disorder is characterized by multiple cognitive impairments including gradual loss of memory, judgment and learning ability [1,2]. Reports have revealed that an estimated 35.6 million people worldwide suffer from this ailment [3]. The amyloid β-peptide (Aβ) plaques, intracellular neurofibrillary tangles, loss of central cholinergic function are the typical pathological hallmarks of AD [4,5]. The cholinergic hypothesis manifests that AChE plays a major role in functioning of cholinergic system and is associated with AD through involvement in the acetylcholine metabolism [6]. In addition, cholinergic neurotransmission is co-regulated by BChE, whose activity is increased in AD. The current therapeutic approach implies inhibition of AChE and BChE [7–9] to enhance central cholinergic function [10] which in turn increase acetylcholine level in the brain. Therefore the existing remedies that are used to alleviate the symptoms of AD such as donepezil, [11] rivastigmine, [12] and more recently galantamine [13] belong to the class of cholinesterase inhibitors (Fig. 1).

Unfortunately, the potential effectiveness of these inhibitors is often limited as they suffer from central and peripheral side effects. Clinical studies have indicated that tacrine has hepatotoxic liability [14,15] and due to adverse events, it was discontinued [16]. Studies have revealed that inhibition of AChE-induced Aβ aggregation [17] by cholinesterase inhibitors employ additional benefits for AD treatment [18,19]. In recent years, a significant number of studies have shown advancement in the development of dual cholinesterase inhibitors [20,21].

Sulfonamides, an important class of pharmacophores, constitute nearly 200 drugs currently in the market. Numerous sulfonamide-based medicines have been developed as diuretics, anti-migraine agents, cyclooxygenase-II (COX-2)-specific anti-inflammatory drugs recently as AChE [22,23]. In addition, aromatic/heterocyclic sulfonamides possessing free amino function have shown effective inhibition of three carbonic anhydrase isozymes [24]. Since biphenyl based sulfonamides are considered great pharmacophores in medicinal chemistry, and recently we

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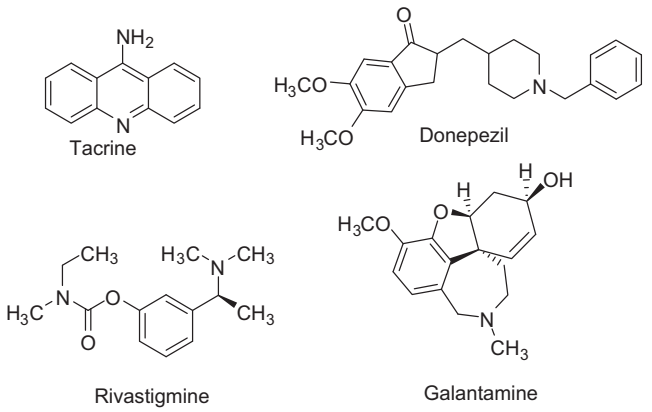



**Fig. 1.** Chemical structures of potent AChE inhibitors.

reported their LOX inhibition activity [25] and as part of our extensive efforts in the search of potent cholinesterase inhibitors [26]. Herein we report synthesis of a series of new biphenyl bis-sulfonamides analogues (**2a–3p**) (Scheme 1) and their AChE and BChE inhibition activities along with molecular modeling investigations.

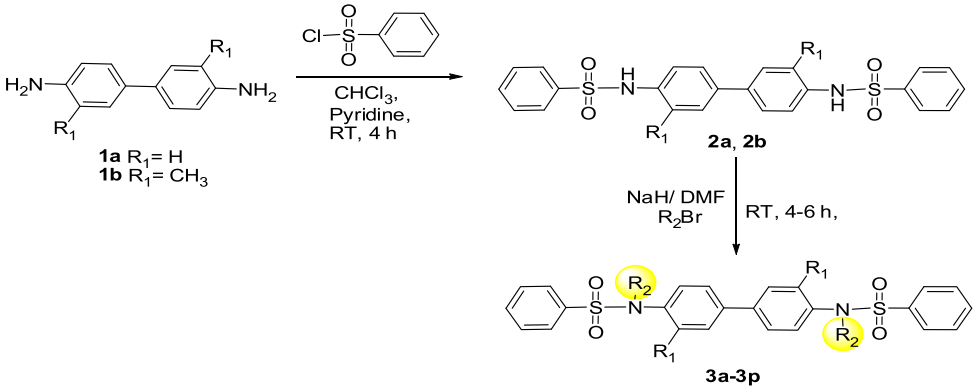
## 2. Results and discussion

### 2.1. Chemistry

A series of structurally related sulfonamides derivatives (**2a–3p**) were synthesized as outlined in Scheme 1. Condensation of appropriate benzidines (**1a** or **1b**) with benzenesulfonyl chloride yielded the corresponding sulfonamides **2a** and **2b**. N-alkylation or acylation of the intermediates **2a** and **2b** with appropriate alkyl or acyl halides in DMF at room temperature, using pyridine as a base, afforded the desired biphenyl bis(benzenesulfonamides) **3a–3p** in good to excellent yield (Scheme 1).

### 2.2. AChE and BChE inhibition

All synthesized compound (**2a–3p**) were screened for their *in vitro* inhibition against AChE and BChE using commercially




| Entry | Comp | $R_1$ | $R_2$ | Yield (%) | Entry | Comp | $R_1$ | $R_2$ | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 2a | H | H | 98% | **10** | 3h | H | $CH_2(C_6H_5)$ | 90% |
| **2** | 2b | $CH_3$ | H | 98% | **11** | 3i | $CH_3$ | $COCH_3$ | 82% |
| **3** | 3a | H | $COCH_3$ | 90% | **12** | 3j | $CH_3$ | $CH(CH_3)_2$ | 76% |
| **4** | 3b | H | $CH(CH_3)_2$ | 76% | **13** | 3k | $CH_3$ | $CH_2(CH_2)_2CH_3$ | 85% |
| **5** | 3c | H | $CH_2(CH_2)_2CH_3$ | 84% | **14** | 3l | $CH_3$ | $CH_2(CH_2)_3CH_3$ | 84% |
| **6** | 3d | H | $CH_2(CH_2)_3CH_3$ | 89% | **15** | 3m | $CH_3$ | $CH_2(CH_2)_4CH_3$ | 81% |
| **7** | 3e | H | $CH_2(CH_2)_4CH_3$ | 79% | **16** | 3n | $CH_3$ | $CH_2(CH_2)_5CH_3$ | 89% |
| **8** | 3f | H | $CH_2(CH_2)_5CH_3$ | 82% | **17** | 3o | $CH_3$ | $CH_2(CH_2)_{14}CH_3$ | 83% |
| **9** | 3g | H | $CH_2(CH_2)_{14}CH_3$ | 80% | **18** | 3p | $CH_3$ | $CH_2(C_6H_5)$ | 91% |

**Scheme 1.** Synthesis of biphenyl bis-sulfonamides (**2a–3p**).