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Short communication

Ionic liquid-enabled synthesis, cholinesterase inhibitory activity, and molecular docking study of highly functionalized tetrasubstituted pyrrolidines

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ABSTRACT

A small library of novel spiropyrrolidine heterocyclic hybrids has been prepared regioselectively in 1-butyl-3-methylimidazoliumbromide ([bmim]Br) with good to excellent yields using a [3+2] cycloaddition reaction. These synthesized compounds were evaluated as potential agents for treating Alzheimer's disease. Compound **4b** showed the most potent activity, with an IC_{50} of 7.9 ± 0.25 μM against acetylcholinesterase (AChE). The inhibition mechanisms for the most active compounds on AChE and butyrylcholinesterase (BChE) receptors were elucidated using molecular docking simulations.

1. Introduction

Alzheimer's disease (AD) is the main cause of dementia, affecting millions of people of a certain age worldwide. According to the World Alzheimer Report, 36 million people were living with dementia globally in 2010, which is predicted to increase to 66 million by 2030 and 115 million by 2050 [1]. AD prevalence sharply increases with age and is thought to arise from the steady loss of neurons, leading to slow memory deterioration, impairment of language skills, and the inability to perform routine activities [2,3].

Cholinesterases (ChEs) are vital in pharmaceutical research for the treatment of some AD symptoms. The two ChEs found in humans, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), are the major factors in AD complications [4,5]. These enzymes are both present in cholinergic synapses in the central nervous system (CNS), in parasympathetic synapses in the periphery, and in the neuromuscular junction. AChE is selective for ACh hydrolysis. All known AChE inhibitors are limited by their low bioavailability, short half-lives, narrow therapeutic efficacy, and toxicity. BChE hydrolyzes acetylcholine and other choline esters as a nonspecific cholinesterase [6]. These enzymes have unique binding pockets that are well-suited to interactions with small drug molecules. Consequently, the nature of enzyme catalysis chemistry makes ChEs amenable to inhibition by low-molecular-weight drug-like molecules. Therefore, the discovery and development of new inhibitors that efficiently inhibit ChEs is imperative in order to cure AD. Furthermore, AD has been included in the top ten death-causing diseases, which has stimulated chemists to develop new lead molecules as drug candidates.

Three-component reactions encompassing the [3+2] cycloaddition of nonstabilized azomethine ylides with an activated olefin [7–10] offer succinct access to highly functionalized pyrrolidine structural motifs in a stereospecific manner. Among five-membered heterocycles, spiropyrrolidines are important because their structural unit is a vital part of many natural products and biologically active small molecules that are considered valuable prototypes for pharmaceutical design. Therefore, the stereoselec-

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tive synthesis of functionalized pyrrolidines is of great importance in medicinal chemistry. Our earlier studies also showed that spiropyrrolidines are capable of inhibiting AChE and BChE enzymes, and are good candidates for AD treatment [11,12].

Absorption, distribution, metabolism, and excretion (ADME) prediction is usually carried out during the early stages of drug development (including drug discovery, drug design, and drug screening) to avoid failure during clinical trials [13]. The cytochrome P450 (CYP) enzyme family plays a vital role in the Phase-I metabolism of several drugs. In the human liver, 12 distinct cytochrome P450 (CYP) enzymes have been reported, which are all involved in detoxification mechanisms [14]. In general, AChE has two binding sites in the gorge, namely, the catalytic anionic site at the bottom of the gorge and the peripheral anionic site at the lip of the gorge [15]. However, hBChE has a peripheral anionic site (PAS) at the mouth of the gorge. The two amino acid residues of PAS, aspartic acid (Asp70) and tyrosine (Tyr332), play an important role in the binding of positively charged substrates [16].

As part of our work to identify novel potent cholinesterase inhibitors for AD treatment [17–24], we herein present preliminary results involving green synthesis, and AChE and BChE activities. Furthermore, molecular modeling analysis was performed to elucidate the binding interaction template of the most active inhibitors to the amino acid residues comprising the active sites of AChE and BChE enzymes.

2. Results and discussion

2.1. Chemistry

The dipolarophiles, **1a–j** were synthesized as reported previously by us [25]. Spiropyrrolidine heterocyclic hybrids **4a–j** were synthesized using the route shown in Scheme 1. The 1,3-dipolar cycloaddition reaction was performed in [bmim]Br by reacting **1a–j** with a novel azomethine ylide, generated in situ from acenaphthenequinone and phenylalanine, to afford functionalized spiropyrrolidines. Optimization was performed by reacting an equimolar mixture of **1f**, acenaphthenequinone, and phenylalanine under reflux in different solvents, including methanol, ethanol, methanol/dioxane, and dioxane, for 5 h. These reactions furnished the corresponding spiropyrrolidine (**4f**) in 65, 63, 60, and 63% yields, respectively. To increase the product yield and establish an alternative green chemical protocol, the same reaction was performed in [bmim]Br. This reaction furnished **4f** in an excellent yield of 90% after only 1 h, signifying that [bmim]Br was the appropriate solvent, the reaction time has also been considerably reduced with an increased yield. These optimized conditions were then applied to subsequent reactions by heating an equimolar mixture of the reactants in [bmim]Br (200 mg) in an oil bath at 100 °C for 1 h. After reaction completion, as monitored by TLC after successive time intervals, the cycloadduct was isolated and purified through flash column chromatography. [Bmim]Br was recovered and reused, and its efficiency was not considerably reduced in successive runs. The cycloaddition reaction progressed regio- and stereoselectively, affording stereoisomer **4** in good yields.

The structure of spiropyrrolidine **4** was derived using one- and two-dimensional NMR spectroscopic data. As a representative case, in the ^{1}H NMR spectra of **4f**, the H-4 proton appeared as a doublet at 4.05 ppm (J = 9.5 Hz), while its coupling partner, H-5, appeared as a multiplet at 4.77–4.85 ppm. The 3″–CH_2 protons appeared as two doublets at 2.55 ppm (J = 17.5 Hz) and 2.84 ppm (J = 18.0 Hz), whereas the two doublets of doublets at 3.02 ppm (J = 13.5, 6.0 Hz) and 3.16 ppm (J = 14.0, 7.0 Hz) were attributed to benzylic protons 6-CH_2. The two methoxy groups were appeared as two singlets at 3.68 and 3.78 ppm. The aromatic protons appeared as singlets, doublets, and multiplets at around 6.29–8.19 ppm. ^{13}C chemical shifts were assigned using DEPT 135 and HMQC experiments. Selected ^{1}H and ^{13}C NMR chemical shifts of **4f** are shown in Fig. 1. Structural elucidation of the other spiropyrrolidine heterocyclic hybrids was also assigned using similar straightforward considerations.

A rational mechanism for the construction of **4** is proposed in Scheme 2. The carbonyl group of **2** could form a hydrogen bond

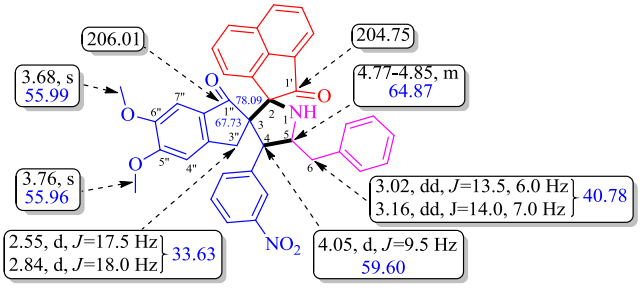
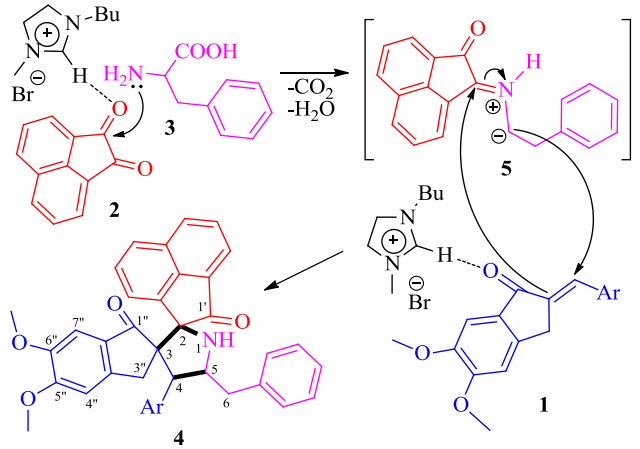
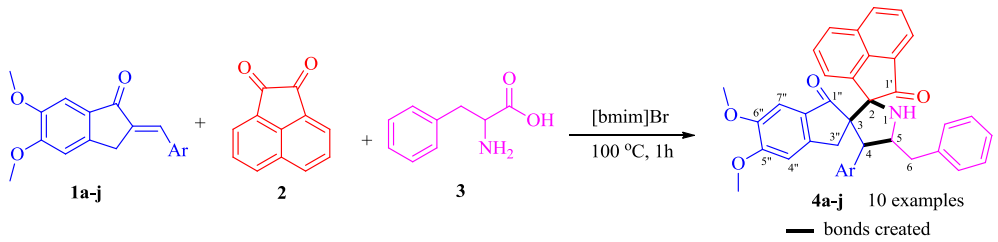


Fig. 1. Selected ^{1}H and ^{13}C NMR chemical shifts of **4f**.



Scheme 2. Plausible mechanism for the construction of tetrasubstituted spiropyrrolidines **4**.



Scheme 1. Synthesis of highly functionalized tetrasubstituted spiropyrrolidines **4a–j**.