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Discovery of potent carbonic anhydrase and acetylcholine esterase inhibitors: Novel sulfamoylcarbamates and sulfamides derived from acetophenones

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ABSTRACT

In this study, several novel sulfamides were synthesized and evaluated for their acetylcholine esterase (AChE) and human carbonic anhydrase I, and II isoenzymes (hCA I and II) inhibition profiles. Reductive amination of methoxyacetophenones was used for the synthesis of amines. Amines were converted to sulfamoylcarbamates with chlorosulfonyl isocyanate (CSI) in the presence of BnOH. Pd-C catalyzed hydrogenolysis of sulfamoylcarbamates afforded sulfamides. These novel compounds were good inhibitors of the cytosolic hCA I, and hCA II with K_i values in the range of 45.9 ± 8.9–687.5 ± 84.3 pM for hCA I, and 48.80 ± 8.2–672.2 ± 71.9 pM for hCA II. The inhibitory effects of the synthesized novel compounds on AChE were also investigated. The K_i values of these compounds were in the range of 4.52 ± 0.61–38.28 ± 6.84 pM for AChE. These results show that hCA I, II, and AChE were effectively inhibited by the novel sulfamoylcarbamates **17–21** and sulfamide derivatives **22–26**. All investigated compounds were docked within the active sites of the corresponding enzymes revealing the reasons of the effective inhibitory activity.

1. Introduction

Sulfamides are frequently studied organic compounds and they exhibit a wide range of biological activities for diverse targets.[1] The following drugs can be given as examples of sulfamide analogues: Doripenem (**1**)[2] an antibiotic; Quinagolide (**2**)[3] an anti-hyperprolactinemic agent; JNJ-26990990 (**3**)[4] and JNJ-26489112 (**4**)[5] anticonvulsants. (Fig. 1) It has been reported that sulfamide analogue **5** shows multifunctional properties (i.e., LDL receptor agonist profiles,[6] HCV replication inhibitory effect,[7] hypoglycemic[8] and antibacterial[9] activities) (Fig. 1). Sulfamide compounds are reported in the literature for different therapeutic actions, such as HIV-1 protease inhibition,[10] β-secretase activity,[11] protein tyrosine kinase inhibitory,[12] endothelin receptor antagonists activity,[13] anti-trypanosomal,[14] AChE inhibitory[15] and CA inhibitory properties.[16] On the other hand, Rivastigmine (Exelon, **6**) is a well known drug used in the treatment of neurodegenerative disorders such as dementia of Alzheimer's[17] and Parkinson's diseases[18] (Fig. 1). Rivastigmine (**6**) is cholinergic drug that inhibits AChE in an irreversible manner. For this reason, Rivastigmine has central nervous system selectivity over peripheral inhibition.[19]

CAs are metalloenzymes expressed in both prokaryotes and eukaryotes that catalyze the reversible conversion of carbon dioxide (CO_2) to bicarbonate ions (HCO_3^-) and protons (H^+).[20–23] CO_2 is the end product of aerobic metabolism. In mammals, CO_2 passes into the blood by secretion after transported to the lungs. CO_2 remains in erythrocytes for a while. During this time it reacts with H_2O. The product of this reaction is the carbonic acid (H_2CO_3). H_2CO_3 then loses an H^+ and it produces HCO_3^-.[24,25]

So far, six genetic families (α-, β-, γ-, δ-, ζ-, and η-CAs) encoding CAs were reported.[24] The mammalian carbonic anhydrase enzymes belong to the α-CA family and consist of sixteen active members that have different kinetic parameters, inhibitory properties, functions, and localization. α-CA family divides into sixteen isoforms including cytosolic (CA I, II, III, VII, and XIII), membrane-bound (CA IV, IX, XII, XIV, and XV), mitochondrial (CA VA and VB), and secreted (CA VI) forms. Three cytosolic forms, the CA related

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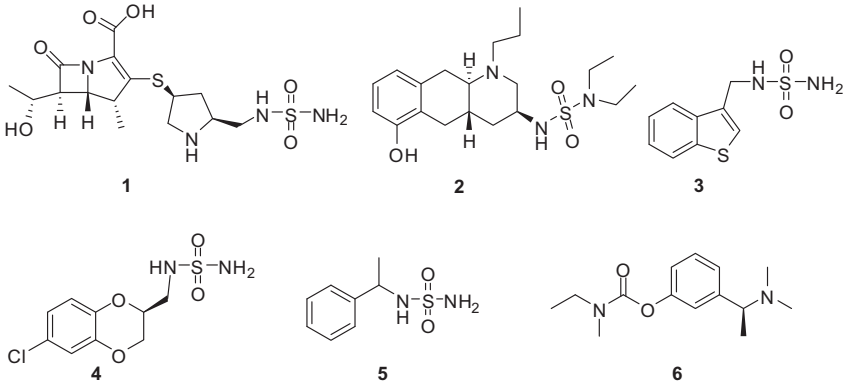


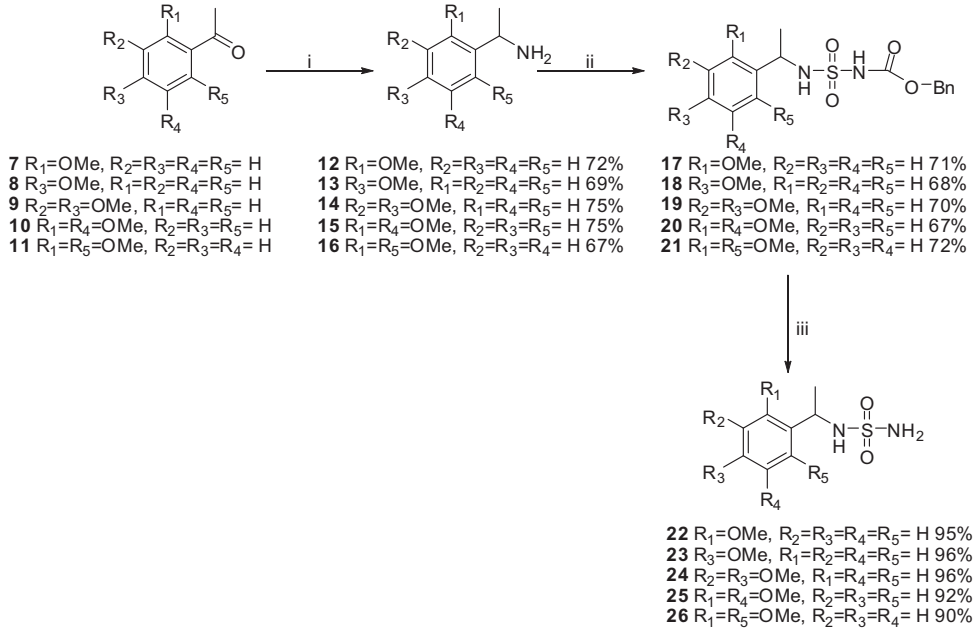
Figure 1. Some selected drugs **1**–**4**, **6** and biologically active sulfamides **5**.

proteins (CARP) (CA VIII, X and XI) have also been identified, but they are acatalytic.[26–29] These CA isoenzymes are targets for many diseases such as glaucoma, cancer, infertility, epilepsy, neurodegeneration, and obesity.

Together with sulfonamides and their isoesters, there are many other classes of CA inhibitors (CAIs) such as the dithiocarbamates, xanthates, coumarins, phenolics and polyamines. Sulfonamide derivatives are specific and potent CAIs and still attract much interest due to their pharmacological properties, facility of preparation, stability and ease of administration.[30–32] Recently, the inhibition of physiologically dominant isoenzymes hCA I and II was extensively studied.[33–35] It is well known that CAIs have some multi-functional applications as diuretics, antiepileptics, tumor diagnostic tools, or for the treatment of several other neurological minor disorders.[27]

Alzheimer's disease (AD) is the most common neurodegenerative disorder and it is the most frequent and predominant cause of dementia among the elderly people.[36] Reduction of AChE levels in the brain is the most considerable, biochemical change in AD.[15] Neuropathological argument has showed that cholinergic functions decrease in the basal forebrain and cortex in senile dementia of the AD. A significant correlation between decrease in cortical cholinergic activity and AD patients was found.[37] Accordingly, the increasing of cholinergic neurotransmission has been considered as one potential therapeutic approach against AD. Although the pathogenesis of AD is obstructed and involves numerous pathways, two major hypotheses are currently under consideration regarding the molecular mechanism: the cholinergic hypothesis and the amyloid cascade hypothesis.[38,39] Thus, the main focus in this study is to find selective AChE inhibition in order to relieve cholinergic deficits and improve neurotransmission. Donepezil, Rivastigmine and Galantamine are the most extensively studied AChE inhibitors (AChEIs). It was demonstrated that these AChEIs significantly improve cognitive function in AD.[40] In addition to these drugs; alternative and complementary drugs are also required to be developed.

As sulfamides exhibit important biological activities, CA and AChE inhibitory properties of hybrid molecules structurally related to the parasympathomimetic drug Rivastigmine (**6**) might be useful for further synthetic and biological applications. In that respect, we report here in the CA and AChE inhibitory properties of a series of sulfamides and sulfamoylcarbamates, which are hybrid molecules of Rivastigmine (**6**).



Scheme 1. Synthesis of sulfamides. Reagents and conditions: (i) $NH_4OAc/Zn/NaBCNH_3/NH_3$(aq), EtOH, 25–80 °C 36 h; (ii) CSI/NEt_3/BnOH, CH_2Cl_2 0–25 °C, 5 h; (iii) H_2/Pd-C, MeOH, 25 °C, 4 h.