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Synthesis, crystal structure determination, biological screening and docking studies of N^1-substituted derivatives of 2,3-dihydroquinazolin-4(1*H*)-one as inhibitors of cholinesterases

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ABSTRACT

Pursuing the strategy of developing potent AChE inhibitors, we attempted to carry out the N^1-substitution of 2,3-dihydroquinazolin-4(1*H*)-one core. A set of 32 N-alkylated/benzylated quinazoline derivatives were synthesized, characterized and evaluated for their inhibition against cholinesterases. N-alkylation of the series of the compounds reported previously (N-unsubstituted) resulted in improved activity. All the compounds showed inhibition of both enzymes in the micromolar to submicromolar range. Structure activity relationship (SAR) of the 32 derivatives showed that N-benzylated compounds possess good activity than N-alkylated compounds. N-benzylated compounds **2ad** and **2af** were found very active with their IC_{50} values toward AChE in submicromolar range (0.8 μM and 0.6 μM respectively). Binding modes of the synthesized compounds were explored by using GOLD (Genetic Optimization for Ligand Docking) suit v5.4.1. Computational predictions of ADMET studies reveal that all the compounds have good pharmacokinetic properties with no AMES toxicity and carcinogenicity. Moreover, all the compounds are predicted to be absorbed in human intestine and also have the ability to cross blood brain barrier. Overall, the synthesized compounds have established a structural foundation for the design of new inhibitors of cholinesterase.

1. Introduction

The cholinesterases consisting of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) belongs to serine hydrolases enzyme's family, which catalyzes the hydrolysis of the acetylcholine, neurotransmitter and subsequently facilitates termination of the nerve impulse in cholinergic synapses [1]. AChE is part of most tissues, but mostly found in autonomic ganglia, neuromuscular junctions, red blood cell membranes and brain cholinergic synapses [2,3]. AChE reduces cholinergic neurotransmission in the brain thus having significant role in cognitive impairment and memory associated with Alzheimer disease (AD) [4,5]. BChE is produced in the liver and commonly found not only in serum and glial cells, but also in smooth muscle cells, adipose tissue, intestine and white matter of the brain and neurons [6]. Various types of physiological processes, like hydrolysis of choline and non-choline esters, succinylcholine, acetylcholine and aspirin [9] have been associated with BChE [7–9]. Thus its activity plays an important role in anesthesia, drug abuse and neurotransmission. Due to the critical role of cholinesterases in maintaining and controlling several important physiological processes in human body, several disorders and diseases are associated with their activity and thus their functions and inhibition is becoming central targets in drug discovery research. Besides clinical use of cholinesterase inhibitors in senile dementia, ataxia, myasthenia gravis, Parkinson's disease and AD, their use in the management of several other conditions like type 2 diabetes and chronic pain may also be beneficial [10–14]. Inhibition of both AChE and BChE enzymes present in neurotic plaques and neurofibrillary tangles will increase ACh level that can interact with neuronal receptor [15]. So far four cholinesterase inhibitors namely tacrine (**1**), rivastigmine (**2**),

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donepezil (**3**) and galantamine (**4**) have been licensed for symptomatic treatment of AD (Fig. 1a). All of these have different pharmacological and pharmacokinetic profiles but all of them increase ACh level in the brain [16]. Other than this, researchers have developed multiple natural or synthetic origin cholinesterase inhibitors (ChEIs) [17,18].

Although anti-ChE moieties show a wide range of chemical diversity, generally different heterocyclic compound and their derivatives have shown potent inhibitory activity against AChE and BChE enzymes [19–24]. Amongst heterocyclic moieties, N-heterocyclic compounds have the potential to form hydrophobic interaction and nitrogen atom has the ability to donate or accept hydrogen atom and thus form strong hydrogen bonds. Nitrogen atom also shows dipole–dipole or ion–dipole interactions with amino acids in the enzyme gorge [25]. Various nitrogen containing heterocyclic compounds have shown good to excellent inhibition against cholinesterases. These heterocyclic compounds include imidazolidines, oxazolidines and benzoxazoles analogues, 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline derivatives, homo-and heterodimers obtained by coupling of suitable bioactive molecules or existing therapeutics (tacrine, donepezil, galantamine, memantine) [26–30]. To combat the multifactorial nature of AD, a variety of versatile tacrine-related multi-target drugs have gain immense attention. These multi-target tacrine hybrids have shown excellent inhibition due to its pharmacophoric features especially π-π interactions with Trp84 [31–35]. The structures of some tacrine hybrids are shown in Fig. 1b. Recently, our research group reported the identification of dihydropyrimidines (**4**–**5**, Fig. 1c) and 2,3-dihydroquinazolin-4(1*H*)-one derivative (**6**, Fig. 1c) as inhibitors of cholinesterases [22,36].

Quinazoline, a fused pyrimidine with a benzene ring **A** and a pyrimidine ring **B** (Fig. 2), have a number of diversity points where structural modification can be made. In previous study, we have synthesized a number of 2,3-dihydroquinazolin-4(1*H*)-ones with diversity points on ring A. The variations at benzene ring resulted in good inhibition of cholinesterases (Fig. 2). Pursuing the strategy of developing potent AChE inhibitors and to explore the diversity points on quinazoline core, we attempted to further optimize the N-1 position of 2,3-dihydro-quinazolin-4(1*H*)-one core. From our previous study, we have selected compounds containing unsubstituted phenyl ring fused with the pyrimidine ring having IC_{50} values in the range of 9.9–80.3 μM. This modification was achieved by N-alkylation/benzylation of 2,3-dihydroquinazolin-4(1*H*)-one core using alkyl/benzyl halides in DCM.

2. Result and discussion

2.1. Chemistry

A number of diverse quinazoline derivatives have been synthesized and evaluated for various biological activities but studies on the synthesis of 2,2-disubstituted and 1,2,2-trisubstituted quinazoline moieties are very limited. Few researchers have attempted synthesis of 2,2-disubstituted quinazoline derivatives using various condensation and catalytic methodologies [37–40]. However, synthesis and biological activities study of 1,2-disubstituted and 1,2,2-trisubstituted quinazoline derivatives are scantly reported in literature. Quite a few reports are present in literature about the synthesis 1,2-disubstituted quinazoline derivatives by using N-substituted substrate like N-phenyl anthranilic acid or other analogues [41]. But to the best of our knowledge, synthesis of 1,2,2-trisubstituted quinazoline derivatives have not been reported. Instead of using N-substituted substrates (for example 2-(benzylamino)benzamide) for cyclization into quinazoline ring, we tried an alternative and simple method based on selective

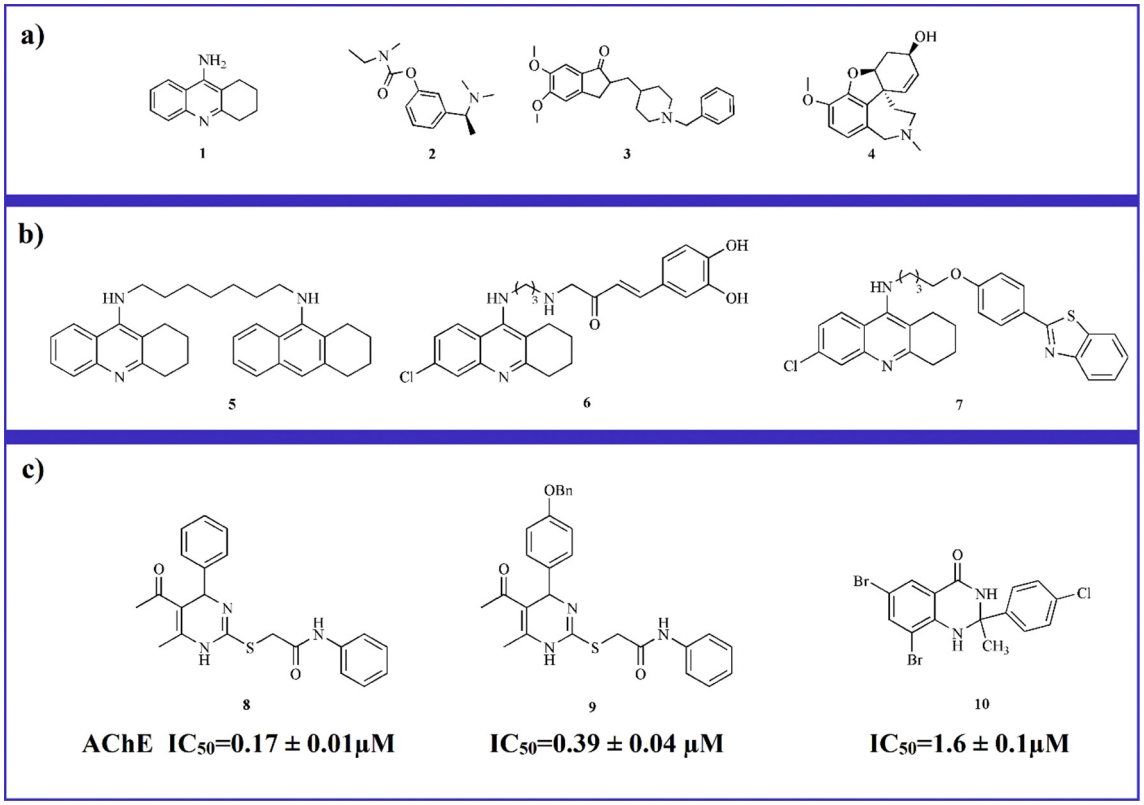

Fig. 1. (a) Chemical structure of approved drugs used for treatment of AD; (b) structures of some tacrine hybrids; bistacrine (**5**), tacrine-caffeic acid hybrid (**6**), tacrine-phenylbenzoheterocyclic hybrid (**7**); (c) Structures of our previously reported of 2,3-dihydroquinazolin-4(1*H*)-one and dihydropyrimidines as cholinesterase inhibitor.