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Conventional and microwave prompted synthesis, antioxidant, anticholinesterase activity screening and molecular docking studies of new quinolone-triazole hybrids

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ABSTRACT

The synthesis of ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylates (**4**, **5**) was performed via the reaction of corresponding anilines with diethyl ethoxymethylenemalonate under conventional and also microwave promoted conditions. The treatment of **4** and **5** afforded the corresponding hydrazides (**6** and **7**). These hydrazides were converted to the corresponding carbo(thio)amides (**9a-f** and **10a-e**) which were then subjected to an intramolecular cyclisation leading to the formation of quinolone-triazole hybrids (**11a-f** and **12a-e**). The newly synthesized compounds were screened for their biological activities such as antioxidant capacity (AC) and acetylcholinesterase Activity. Inhibition of cholinesterases is an effective method to curb Alzheimer's disease, a progressive and fatal neurological disorder. A series of some novel quinolone derivatives were designed, synthesized, and their inhibitory effects on AChE were evaluated. We obtained our compounds and determined their anticholinesterase activities according to the Ellman's method. **9b** and **10c** showed the best AChE inhibition with 0.48 ± 0.02 and 0.52 ± 0.07, respectively. Docking studies were performed for the most active compounds (**9b**, **10c**) and interaction modes with enzyme active sites were determined. As a result of these studies, a strong interaction between these compounds and the active sites of AChE enzyme was revealed.

1. Introduction

Quinolones are one of most important kind of synthetic antibacterial agents due to their well tolerability with excellent safety profile, favorable pharmacokinetic characteristics, broad antibacterial spectrum and good treatment effectiveness [1–3]. The quinolone structures include motifs exhibiting a wide variety of biological activities and they have been shown to possess various pharmacological activities such as anticonvulsant [4], antitumor [5] and antiviral [6]. These compounds have also been extensively used to treat genitourinary infections, prostatitis, respiratory diseases, gastroenteritis, sexually transmitted diseases, as well as skin and soft tissue infections [7,8]. Another biological activity of quinolones is ROS scavenging ability [9] and they have already been efficiently used for design of dual AChE inhibitor [10]. Acetylcholinesterase (AChE) is known as serine hydrolase enzyme managing on the hydrolysis of acetylcholine (ACh), which is a significant neurotransmitter for arrangement of cognition in animals [11–14]. Inhibition of AChE leads to the rise of ACh levels in cholinergic synapses [15]. Thus, cholinesterase inhibitors are used in the treatment of various neuromuscular disorders which occur as a result of reduced cortical and hippocampal levels of ACh such as Alzheimer's disease (AD) which is a complex neurodegenerative disorder characterized by synapse dysfunction, neuronal death, and loss of memory and learning ability [16–18]. Current treatment approaches for AD continue to be principally symptomatic, with the major therapeutic AD, known as the cholinergic hypothesis, and specifically on cholinesterase inhibition [19,20]. Various AChE inhibitors such as tacrine, donepezil, rivastigmine, and galantamine (Fig. 1) have been used contemporarily for the symptomatic treatment of AD [21–24]. In recent years, novel cholinesterase inhibitors from natural resources or synthetic ways, which have coumarin, benzofuran, berberine, β-carboline, benzophenone, ferulic acid, naphthyridine, triazine, and quinolone scaffolds as the main pharmacophoric groups, have been reported [25–29].

According to the X-ray crystallographic structure of AChE (PDB ID:4EY7), two main binding sites has been determined: the catalytic anionic site (CAS) including Trp86, Tyr130, Tyr133, Ser203,

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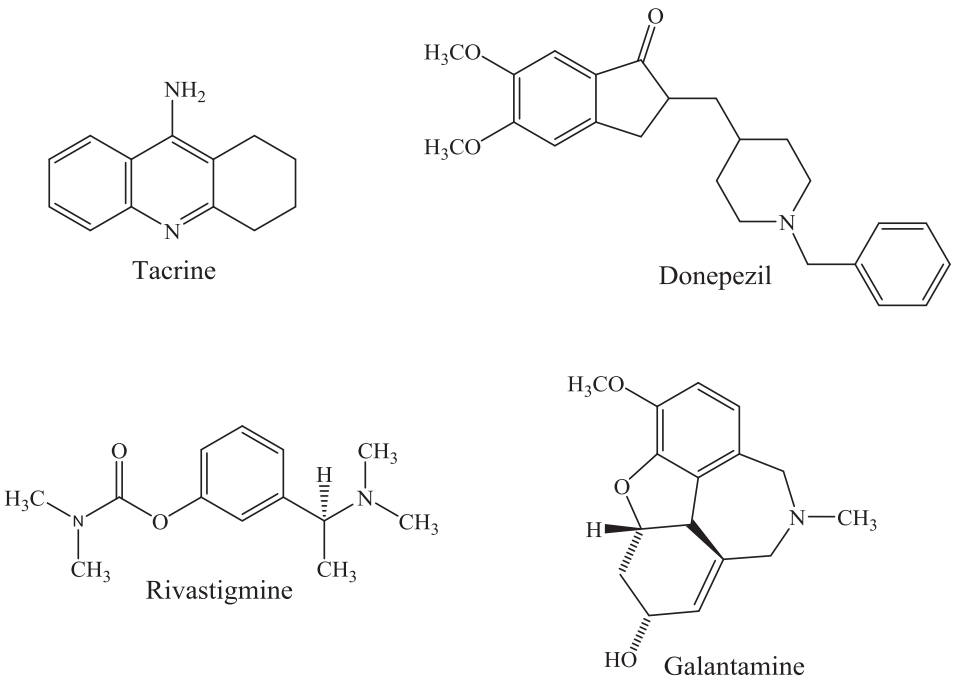

Fig. 1. Molecular structure of tacrine, donepezil, rivastigmine, and galantamine.

Glu334, Tyr337, Phe338, His447 and the peripheral anionic site (PAS) consisting of Tyr72, Asp74, Tyr124, Trp286, Tyr341 [30,31]. It has been reported that DNP interacts with both PAS and CAS and thus it is situated in the active site concordantly owing to the feature of dual binding site (DBS) [32,33]. Analyses of binding modes of the DNP indicate that the benzyl moiety is in a pi-pi interaction with the indole of Trp86 in the CAS. The formation of hydrogen bond between the oxygen atom of the carbonyl group in the 1-indanone and the amino group of Phe338 is a very significant interaction in terms of binding to the active site. The 1-indanone constitutes a pi-pi interaction with the indole of Trp286 in the PAS region. The piperidine has a position in the gorge to interact with Tyr337 and Tyr341 by doing a hydrogen bond. It also set up a van der Waals interaction with amino acids in both CAS and PAS [34,35]. Docking studies were performed for the most active compounds **9b** and **10c** interaction modes with enzyme active sites were determined. Docking studies revealed that there is a strong interaction between the active sites of AChE enzyme and these compounds. Ideally, a cholinesterase inhibitor is expected to effectively interact with these sites (Fig. 2). Using molecular docking approach, we tried to get insights into binding interactions of our derivatives in comparison with **9b**, **10c** in the active site of enzyme and understand the facts that underlie the relationships between structural modifications on these ligands and their efficacy.

Due to its multifactorial pathogenesis, the current strategy for the development of new drugs for AD is focusing on multipotent molecules acting in a complementary manner, in different neural and biochemical targets, which could be more efficacious for AD patients [36]. Many quinolone derivatives have been studied for their biological activity in AD. They are used as radical scavengers, such as vitamin E (a tocopherol), as copper or iron chelators such as clioquinol, or as inhibitors of AChE such as tacrine. Following our studies on the synthesis of quinolone carried out in our laboratory [37], we now report the synthesis of 4-oxo-1,4-dihydroquinoline-3-carbonyl)hydrazine carbothioamide, 4-oxo-1,4-dihydroquino line-3-carbonyl)hydrazine carboxamide 3-(5-mercapto-4H-1,2,4-t riazol-3-yl)quinolin-4(1*H*)-one and 3-(5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)quinolin-4(1*H*)-one. These new compounds were tested as AChE inhibitors and investigated antioxidant capacity. Finally, and thanks to molecular docking, we have identified the interactions with AChE.

2. Results and discussion

2.1. Chemistry

In the present study, the ecofriendly synthesis, acetylcholinenzyme inhibition and antioxidant activity screening, and molecular docking studies of new hybrid molecules was contemplated. The structures of newly synthesized compounds were established on the basis of physicochemical, elemental analysis and spectral data (FT IR, ^{1}H NMR, ^{13}C NMR and EI-MS).

Compounds **3**, **5** and **7** were synthesized in the following procedure [38]. The complete conversion of hydrazides **8** was observed after microwave irradiation at 100 W for 25 min. Synthesis of corresponding carbo(thio)amides (**9a-f**) and (**10a-e**) was accomplished by nucleophilic attack of the **7** and **8** hydrazide compounds to the alkyliso(thio) cyanates (Scheme 1). The reaction conditions were investigated in ethanol under reflux and also microwave irradiation conditions to maximize the yield of the product. To optimize reaction conditions, the synthesis of compound **9a** was chosen as model reaction and microwave (MW) irradiation was implemented at different power values of 50, 100, 150, 200 and 250 W (the progress of reaction was monitored by TLC) (Table 1). When compared to conventional method, microwave irradiation reduced the reaction time from 5 h to 10 min. It is notable to underline that shorter reaction time, lower microwave energy or very high microwave energy power give rise to lower conversion rate, while increasing reaction time or MW power resulted in fragmentation of the target product as revealed by TLC analysis. In the FT IR spectra, the signal originated from —C=S function of compounds **9a-d** and **10a-d**appeared between 1223 and 1263 cm^{-1}. In the ^{13}C NMR spectra of these compounds (**9a-f**, **10a-e**), —C=S or —C=O function resonated between 153.05 and 175.37 ppm. Further evidence for the formation of carbo(thio)