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Synthesis, molecular docking, acetylcholinesterase and butyrylcholinesterase inhibitory potential of thiazole analogs as new inhibitors for Alzheimer disease

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ABSTRACT

A series of thirty (**30**) thiazole analogs were prepared, characterized by ^{1}H NMR, ^{13}C NMR and EI-MS and evaluated for Acetylcholinesterase and butyrylcholinesterase inhibitory potential. All analogs exhibited varied butyrylcholinesterase inhibitory activity with IC_{50} value ranging between 1.59 ± 0.01 and 389.25 ± 1.75 μM when compared with the standard eserine (IC_{50}, 0.85 ± 0.0001 μM). Analogs **15**, **7**, **12**, **9**, **14**, **1**, **30** with IC_{50} values 1.59 ± 0.01, 1.77 ± 0.01, 6.21 ± 0.01, 7.56 ± 0.01, 8.46 ± 0.01, 14.81 ± 0.32 and 16.54 ± 0.21 μM respectively showed excellent inhibitory potential. Seven analogs **15**, **20**, **19**, **24**, **28**, **30** and **25** exhibited good acetylcholinesterase inhibitory potential with IC50 values 21.3 ± 0.50, 35.3 ± 0.64, 36.6 ± 0.70, 44.81 ± 0.81, 46.36 ± 0.84, 48.2 ± 0.06 and 48.72 ± 0.91 μM respectively. All other analogs also exhibited well to moderate enzyme inhibition. The binding mode of these compounds was confirmed through molecular docking.

1. Introduction

Alzheimer's disease is an irretrievable, complex neurodegenerative disorder characterized by progressive cognitive impairment, various neuropsychiatric and behavioral disturbances, and restrictions in activities of daily life. It is a pathologically complex disease implicating interactions between environmental and genetic risk factors [1]. Alzheimer's is an age related disease and is the most common reason of dementia in old people, being diagnosed after the age of 56, and affecting up to 10% of the population over the age of 65. The disease affects 30% or more of the population over the age of 80. In the developed world, AD is the fourth major cause of death after cardiovascular disease, cancer, and cerebral accidents. Worldwide there are approximately 35 million peoples with AD, and that number is expected to grow to 107 million by 2050 [2]. Alzheimer disease was reported to be associated with cardiovascular risk factors such as hypertension and increased serum cholesterol [3]. It involves the degeneration of cholinergic neurons and loss of cholinergic transmission. Since AD is a multipathogenic illness, a current drug-discovery strategy is to develop novel anti-Alzheimer agents with multiple potencies such as inhibition of both acetylcholinesterase and butyrylcholinesterase [4]. Acetylcholine plays an important role in cognitive functions particularly in memory. It reduced cholinergic neurotransmission in the brain which have an important role in cognitive impairment associated with Alzheimer's disease [5,6]. *BChE* (EC 3.1.1.8) is a sister enzyme of AChE [7]. Interest in *BChE* has been growing because of its possible role in Alzheimer disease and the introduction of anticholinesterase treatments for this disorder [8]. *BChE* enzymatic activity was higher in patients who had hypertension, hyperlipidemia, and high body weight and lower in patients who had suffered acute myocardial infarction or undergone treatment with beta blockers [9–11]. *BChE* inhibit the activity of the enzyme which

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affects the transmission of the neurotransmitter and makes patient discomfort including dizziness, blurred vision, vomiting, fever and even death [12,13]. *BChE* specific inhibition is unlikely to be associated with adverse events and may show efficacy without remarkable side effects [14]. Therefore *BChE* may be considered as an important target for novel drug development to treat Alzheimer disease. In the future, the development of specific *BChE* inhibitors and the continued use of cholinesterase inhibitors may lead to improved clinical outcomes [15].

The heterocyclic compounds are reported to posses various biological activity [16]. Thiazole moiety is the key pharmacophore and intermediate for synthesizing pharmaceuticals and in the field of agro-chemicals [17–19]. Thiazole are important class of heterocyclic compounds found in many potent biologically active molecules such as thiobendazol (anthelmintic drug) [20], riluzolr (anticonvulsant drug) [21] and talipexzol (antiparkinsonian drug) [22]. Its application also found in drug development for the treatment of inflammation [23]. Recently thiazole analogs have been also reported as antiglycating agent, anti-diabetic and as a potent inhibitor for cholinesterase [24–26].

Our research group is continuously doing an effort in search of lead molecules [27]. Herein we are going to report thiazole derivatives as new class of Acetylcholinesterase and butyrylcholinesterase inhibitors.

2. Results and discussion

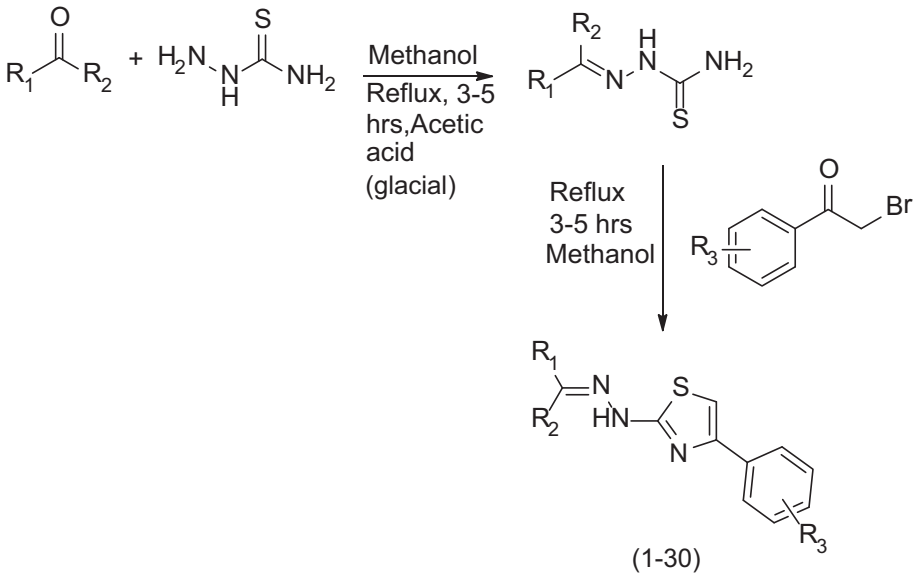
2.1. Chemistry

Different acetophenone/benzaldehyde (1 mmol) were reacted and refluxed with thiosemicarbazide (1 mmol) in methanol in the presence of catalytic glacial acetic acid for 3–5 h. After completion of reaction the mixture were filtered and washed with hexane to yield pure product. The obtained products (1 mmol) were then reacted and refluxed with (1 mmol) of methoxy or chloro substituted phenacyl bromide for 3–5 h. After reaction completion the mixture was filter and wash with hexane to yield pure products (**1–30**) [23,28,29]. Different spectroscopic techniques, such as EI-MS, ^{1}H NMR and ^{13}C NMR were used to determine the structure of all analogs (see Scheme 1 and Table 1).

2.2. Acetyl cholinesterase and butyrylcholinesterase inhibition

Analogs **1–30** showed acetylcholinesterase inhibition with IC_{50} values ranging between 21.3 ± 0.08 and 452.1 ± 0.27 μM as compared with standard eserine with IC_{50}, 0.04 ± 0.0001 μM. Seven analogs **15**, **20**, **19**, **24**, **28**, **30** and **25** exhibited good acetylcholinesterase inhibitory potential with IC_{50} values 21.3 ± 0.50, 35.3 ± 0.64, 36.6 ± 0.70, 44.81 ± 0.81, 46.36 ± 0.84, 48.2 ± 0.06 and 48.72 ± 0.91 μM respectively. Analog **15** was found the most potent among the series. This compound has two hydroxyl groups on one phenyl ring and one chloro group on other phenyl ring. The presence of these two hydroxyl group seems to be play an important role in this inhibition. The hydroxyl might be involved in hydrogen bonding. Analog **20** was found to be second active among the series. This compound illustrate activity have one methoxy group on one phenyl ring and also methoxy group on other phenyl part. Compound **19** have two chloro groups on one phenyl ring and one methoxy group on other phenyl ring. Analog **30** have two hydroxyl groups on one phenyl ring. Similarly other active analogs have either EWG or EDG on phenyl ring, whose position, nature and arrangement on phenyl ring greatly affect the inhibition.

Analogs **1–30** also showed a variable degree of butyrylcholinesterase inhibition with IC_{50}values ranging between 1.59 ± 0.01 and 389.25 ± 1.75 μM as compared with standard eserine (IC_{50}, 0.85 ± 0.0001 μM). Seven analogs **15**, **7**, **12**, **9**, **14**, **1** and **30** exhibited potent butyrylcholinesterase inhibitory potential with IC_{50} values 1.59 ± 0.01, 1.77 ± 0.01, 6.21 ± 0.01, 7.56 ± 0.01, 8.46 ± 0.01, 14.81 ± 0.32 and 16.54 ± 0.21 μM respectively. Compound **15** was also found to be the most potent among the series. This compound has two hydroxyl groups on one phenyl ring and one chloro group on other phenyl ring. The presence of these two hydroxyl group seems to be play an important role in this inhibition. The hydroxyl group is might be involved in hydrogen bonding. Analog **7** was found to be second most active among the series. The compound have anthracene moiety and chlorinated phenyl ring. The activity is may be due to arene-interaction. Analog **12** have one hydroxyl group on one phenyl ring and one chloro group on other phenyl ring. Its potential is less than compound **15**; this might be due less number of hydroxyl groups. Analog **9** having secondary amine group on one phenyl part and chloro group on the other phenyl part. Analog **14** illustrate activity have



Scheme 1. Synthesis of thiazoleanalogs (**1–30**).