



Design and discovery of Novel Thiazole acetamide derivatives as anticholinesterase agent for possible role in the management of Alzheimer's



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ABSTRACT

A novel series of thiazole acetamides was synthesized in excellent yields and characterized with the aid of various spectroscopic and elemental analysis. These compounds were evaluated for in vitro acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activities for possible benefit in Alzheimer's disease (AD). Among the synthesized compound, **6d** was identified as the most potent compound of AChE ($IC_{50} = 3.14 \pm 0.16 \mu M$) with a selectivity index (SI) of 2.94 against BuChE. These compounds were further tested for inhibition of A β aggregation and β -secretase, where it showed potent inhibition which confirmed its multifactorial benefits in AD. The toxicity and docking study were also carried out to exemplify the pharmacological profile of compound **6d** as prospective lead molecule against AD.

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Across a globe, the greater number of elder population was affected by progressive, never-ending, neurodegenerative disorder known as Alzheimer's disease (AD).^{1–3} It is characterized by a loss of memory and cognitive abilities affecting about 6% of the population worldwide aged over 65. Studies suggest that, the loss of cholinergic neurons in the hippocampus and the cerebral cortex of the central nervous system (CNS) are the ultimate cause of cognitive and behavioral abnormalities that characterize AD.^{4–6} Therefore, early therapeutic approaches to treat AD were aimed at escalating the availability of the cholinergic neurotransmitter acetylcholine (ACh). The levels of ACh could be maintained by two types of agents, viz., drugs directly acting on cholinergic receptor or drugs preventing its degradation via inhibiting the activity of acetylcholinesterase (AChE) enzyme. The latter class of drug, that is, AChE inhibitors (AChEIs) is considered superior over directly acting ACh ligands for the symptomatic relief of AD by enhancing the cholinergic action.^{7,8}

Thiazoles are an important class of heterocyclic molecules exhibiting numerous pharmacological activities, for instance, antimicrobial⁹, anticancer¹⁰ and antimalarial¹¹ including anticholine esterase activity.¹² More recently, acotiamide hydrochloride, a thiazole based selective AChEI for the treatment of functional dyspepsia has been identified and now being in advanced stages of clinical studies.¹³

Therefore, on the basis of above, we are encouraged to design and develop Novel Thiazole acetamides as anticholinesterase inhibitors for potential benefit in AD.

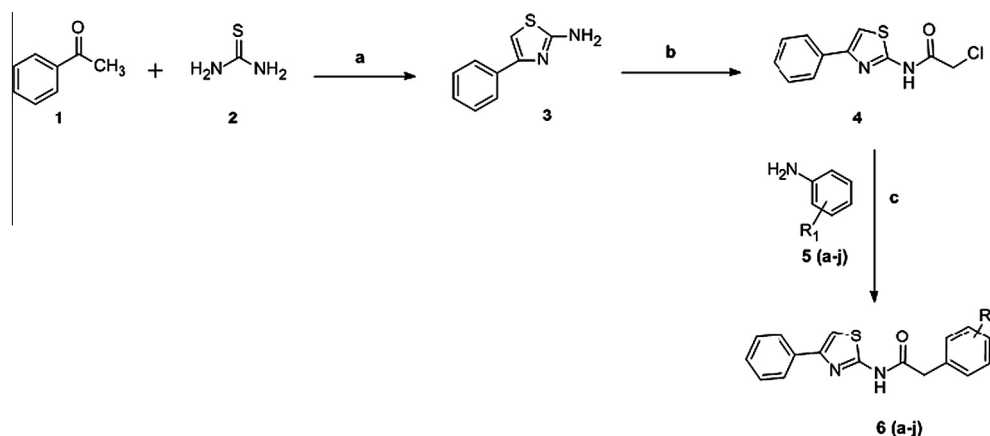
The development of target analogues **6 (a–j)** were realised in an efficient synthetic manner as depicted in Scheme 1. The substituted benzaldehyde (**1**) was allowed to react with thiourea to afford phenyl thiazole (**3**) in efficient yield via cyclo-condensation reaction. This reaction was carried out in the presence of Bromine which leads to the formation of α -haloketones and reaction generally referred as Hantzsch thiazole synthesis. Moreover, in a second step, the chloro acetyl chloride was used to replace the free amine of the above synthesized thiazole to afford compound **4**. This resultant compound was then reacted with distinguished anilines **5 (a–j)** to furnish target analogues **6 (a–j)**. Here, various electron donating and withdrawing substituent were introduced on the R¹ positions to determine its potential effect as anti-choline esterase.

The structure of various title derivatives **6 (a–j)** was ascertained by spectral analysis. The FT-IR peaks of title compounds showed at 3368–3385 cm^{-1} (strong, broad) show characteristic of amide hydrogen (–CONH–). All compounds exhibits stretching vibration between 1658 to 1678 cm^{-1} which attributable to C=O group. All compounds displayed characteristic carbon, carbon double bonds (C=C) peak at 1559–1571 cm^{-1} in its expected region. Furthermore, the ¹H NMR ¹³C NMR and MS signals of the title compounds were also observed in their expected region.

The bioactivities of the organic medicinal agents (OMAs) have been greatly dependent upon physicochemical properties.

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Scheme 1. Synthesis of Thiazole acetamides derivative. Reagents and conditions: (a) Br₂, Reflux; (b) DCM, Et₃N, 0 °C – rt, 4 h; (c) ACN, K₂CO₃, Reflux 4–8 h.

Therefore, the developed thiazole acetamides analogues were rigorously analyzed by Molinspiration, a web based software. It was used to predict parameter such as MiLogP, TPSA and druglikeness.¹⁴

The MiLogP (octanol/water partition coefficient) is able to envisage the ability of the molecule to cross the cell membrane. This methodology is based on the sum of fragment based contributions and correction factors for the compounds analyzed. Molecular Polar Surface Area or Total Polar Surface Area (TPSA) is calculated as a sum of fragment based contributions in which surface areas correspond to polar fragments centered to N- and O- and by hydrogen atoms attached to them are to be considered.¹⁵ It has been deemed as a very efficient descriptor illustrating the drug absorption (including intestinal absorption, bioavailability, Caco-2 permeability) and blood brain barrier permeability. This method is based on contribution of group obtained by comparing the sum of fragment contributions to “real” 3D volume for a training set of about 12,000 drug-like molecules. Moreover, the semiempirical AM1 method was used for the optimization of the 3D molecular geometries for a training set.

The ability of a molecule to iterate for adopting the best possible conformation in binding pocket was determined by the Number of Rotatable Bonds. It has been directly related with an oral bioavailability of drugs and defined as any single bond except the aromatic, bonded to non-terminal non-hydrogen atom. Due to high rotational energy barrier, amide C–N bonds are not considered.¹⁶ The results of the rigorous analysis of compounds **6 (a–j)** in terms of molecular properties which depicts pharmacokinetics tolerability on the basis of above discussed parameters has been shown in Table 1. It was found that, the entire set of molecules obeyed Lipinski rule of five recommendations suggesting to have good bioavailability necessary for new chemical entities (Nviolations = 0). As shown by MiLogP value, these molecules were also

able to cross the cell membrane which is a key parameter for transportation across and in turn is needed for the generation of bioactivity. Moreover, it will be suitable for drug absorption owing to the acceptable TPSA value.¹⁶

BuChE was found in elevated concentration in AD and responsible for hydrolyzing the acetyl choline, thus, inhibition of BuChE was also considered as a fruitful target for symptomatic relief in ADs. Consequently, the inhibitory effect of target analogues was analyzed for both AChE and BuChE using Ellman method. Rivastigmine was used as standard in this comparison test. The inhibitory potency (IC₅₀) of tested compounds along with selectivity index has been outlined in Table 2. According to the results, the entire set of the synthesized compound showed considerable inhibition of both the enzymes. It has been found that, compound **6a**, bearing no substituent showed least activity against the tested enzymes. Whereas, on the introduction of the methyl as a substituent (**6b**) render compound much more active in regard of inhibitory potency and SI. On changing the substitution pattern, from *para* to *ortho*, the activity was decreased marginally. The highest inhibitory potency was reported by the compound **6d** having *p*-methoxy against the tested enzymes along with high SI. Whereas, its isomeric counterpart, compound **6e** exhibit less pronounced activity than the parent. The activity was significantly abolished in the presence of an electron withdrawing group. Particularly, in the case of compound **6f** and **6g**, marked reduction in activity was observed with minimal difference. On replacing the nitro with chloro, the activity was declined more than twofold with a mild reduction in SI. No significant difference was observed in the case of compound **6j** against both the tested enzymes with less selectivity for AChE. It is surprising to note that, none of the synthesized compound exhibited activity similar or better than Rivastigmine. However, the structure activity relationship (SAR) suggests that, presence of electron donating group seemed to be suitable for

Table 1
Molecular properties of compounds **6 (a–j)**

Compound	miLogP	TPSA	Natoms	MW	nON	nOHNH	nviolations	nrotb	Volume
6a	3.65	41.99	21	294.38	3	1	0	4	261.60
6b	4.10	41.99	22	308.41	3	1	0	4	278.17
6c	4.05	41.99	22	308.41	3	1	0	4	278.17
6d	3.70	51.22	23	324.40	4	1	0	5	287.15
6e	3.66	51.22	23	324.40	4	1	0	5	287.15
6f	3.61	87.81	24	339.38	6	1	0	5	284.94
6g	3.56	87.81	24	339.38	6	1	0	5	284.94
6h	4.33	41.99	22	328.82	3	1	0	4	275.14
6i	4.28	41.99	22	328.82	3	1	0	4	275.14
6j	3.81	41.99	22	312.37	3	1	0	4	266.54

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