RESEARCH ARTICLE

Promising Drug Discovery for Choline Derivatives via Ugi Reaction and their Inhibition Activity on AChE Enzyme

Zinah A. Al-shareeda, R. A. Abramovich, O. G. Potanina, Hasan M. Alhejoj, Ivanov U. V.

Peoples Friendship University of Russia (RUDN University), Moscow, Russia

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ABSTRACT

A great focus was given to multi-component reactions in the last two decades because many compounds were synthesized through them and approved biological and pharmacological properties. The two famous reactions are Passerini (3-CR) and Ugi (4-CR). From this point, we started our study to modify choline derivatives and to study their inhibitory effect on AchE enzyme (acetylcholinesterase enzyme). We synthesized four different compounds by Ugi reaction (2b,2c,2d), all of them were new after that, they were tested for the inhibitory activity through the screening kit k-197 all of them gave activity, but the strength of activity was different the most active one was compound 2b and the others gave inhibitory effect but not in the same potency than the relative activity% (RA%) and relative inhibitory% (RI%). Donepezil was used as standard, and linear plots were drawn to compare activity with donepezil.

Keywords: AChE, Alzheimer disease, Bis amides, Carbamates, Inhibition, MCRs, NMR, Screening.

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INTRODUCTION

A great focus was given to multi-component reactions in the last two decades because many compounds were synthesized through them and approved biological and pharmacological properties. The two famous reactions are Passerini (3-CR) and Ugi (4-CR); many drugs were synthesized through this reaction, for example, which led to the emergence of many essential drugs to treat several diseases. For instance, Crixivan® I (Indinavir™, MK 639), made by Merck, is an important HIV protease inhibitor.[1-3]

The Ugi reaction contributes to the short synthesis of the piperazine derivative that is the main starting compound in the production of Crixivan® Also, philanthotoxin-12 analogs show potential non-competitive inhibitory effects on various types of inotropic receptors in the central nervous system have been synthesized *via* the Ugi reaction.[4] The principle of Ugi reaction is the reaction of a carboxylic acid with aldehyde or ketone and an amine in the presence of isocyanides. That is why sometimes it's called the isocyanides-based reaction. Due to the high flexibility of the Ugi reaction with different functional groups, a wide range of linear bis-amides and pseudo-peptides (linear or cyclic) can be obtained, and post-modifications can be achieved to synthesize versatile heterocyclic compounds with unusual structures and a wide range of biological activity.[5] Many studies were done to develop drugs used for Alzheimer's disease because it's a complicated neurodegenerative disease increasing within years. Broad drugs nowadays are used like donepezil and galantamine and others with various potencies. Both of them are considered reversible inhibitors.[6] New studies showed that bis amides also are efficient in inhibiting AchE enzyme.[7] Fourteen alkyl and aryl Thiocarbonate derivatives of choline were synthesized and studied as potential acetylcholinesterase inhibitors (AChE). The inhibitors are competitive with the substrate, and the AChE activities do not hydrolyze them. Certain of these new compounds may provide direction for the development of new drugs that have anticholinesterase activity and may be used to treat Alzheimer's disease.[8] The AChE anionic site is responsible for binding the substrate quaternary ammonium group with cation-π interactions. Due to this, it also enables inhibitor binding to the enzyme. And the enzyme has the esoteric site, which is responsible for ester cleavage.[9] Usually, modifications are done either with existing drugs already in the library or by trying to make new ones.

MATERIALS AND METHODS

This part of work was divided into two parts

- A-synthesis part
- B- the inhibitory activity testing part

**Author for Correspondence: habibbaty@gamil.com*

Part A: Synthesis Part

The methods were used in this study for the synthesis were multi component reaction Ugi (4-CR) (Figure 1).

Part B: The Inhibitory Activity Testing Part

The inhibitory assay was carried out by using the screening kit k-197. This kit was bought from Biovision (an American company), and the microplate reader was from the Biorad laboratories. Then the relative inhibitory % and relative activity were calculated%.[10]

This test was conducted for the four new compounds by using BioVision's Acetylcholinesterase Inhibitor Screening Kit can be used screen for potential inhibitors of AChE activity. It utilizes the ability of an active human AChE enzyme to hydrolyze the provided colorimetric substrate and generating a yellow chromophore that can be detected by measuring absorbance at 412 nm. In the presence of the potent reversible AChE inhibitor donepezil, enzyme activity is suppressed, preventing chromophore generation. The assay kit is adapted to a 96-well format and provides a rapid, simple, and reliable test for high-throughput screening of AChE inhibitors.[10] The test was carried for 40 minutes, and the donepezil was used as a standard. This kit is very hazardous and should be stored at a temperature of -20°C.

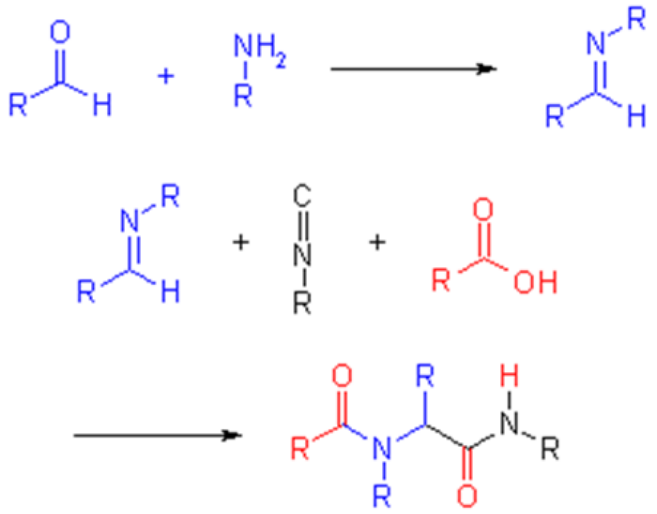

Figure 1: UGI four-component reaction (UGI-4CR)

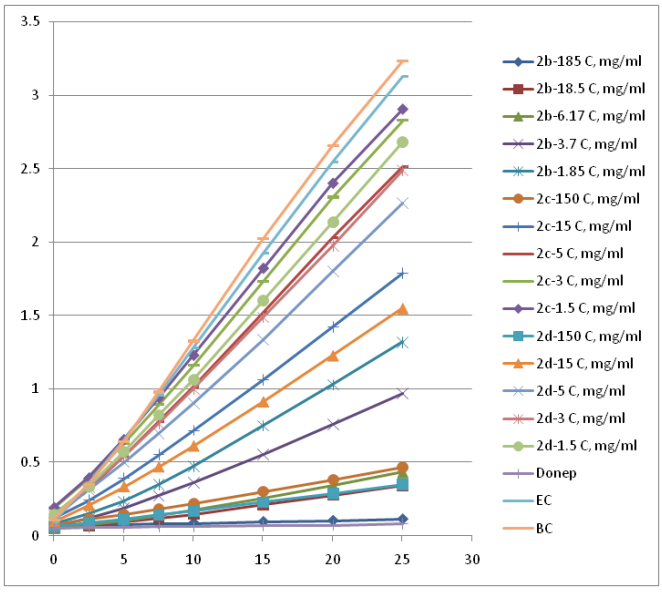

Figure 2: The inhibitory activity of the compounds in different concentrations

RESULTS

The compounds were synthesized successfully, and at the same time, the four resulting compounds showed that they were not hydrolyzed by the enzyme AChE, which means that they act as inhibitors (Figure 2).

DISCUSSION

So in our study, we tried to focus on modifying the choline structure by trying to save the quaternary ammonium site,[11] which is also important for the inhibitory activity, and trying to complicate the ester site[12] to get new compounds that have the inhibitory activity on the AChE enzyme. Still, this time, using the multicomponent reactions to get these compounds, and the activity was tested using the screening kit k-197 [10] from an American company called Biovision company. The microplate reader was done in Bio-rad laboratories.

Like that, all of them had an effect, but the inhibitory activities were dissimilar. The most powerful compound was b. It gave RA% and RI% in very close percentages to the standard donepezil, which is 98%. And the second one was compound 2a. The reason is the main quaternary ammonium site, which many studies have proved. Also, the bis amide group in other studies showed that these functional groups have good inhibitory effects[7] And studies also proved that choline derivatives also had a role in inhibition.[8]

CONCLUSION

Cholinesterases are important biological targets responsible for regulating cholinergic transmission, and their inhibitors are used to treat Alzheimer's disease. To design new cholinesterase inhibitors, different structure-based design strategies were followed, including modifying compounds from a previously developed library and a fragment-based design approach. The Ugi reaction approved that there is a new gate for drug discovery. Many studies were done, and this reaction synthesized many drugs and that's why it gave a great focus toward polymer chemistry and drug synthesis.

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