

RESEARCH ARTICLE

The Ability of Choline Derivatives Synthesized by Multi-component Reactions in the Inhibition of AChE Enzyme

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ABSTRACT

Multi-component reactions (MCRs) are strong synthetic tools in which more than two starting materials are coupled together with a purpose to form the multi-functionalized compounds in a one-pot process. In this procedure, they used an additional step without changing the solvent, the so-called sequential-addition procedure, to limit the number of synthetic steps while increasing the complexity and the molecular diversity, which are highly step-economical reactions. The Ugi reaction, one of the most common multi-component reactions, has recently fascinated chemists with the high diversity brought by its four- or three-component-based isonitrile. The Ugi reaction has been introduced in organic synthesis as a novel, efficient and useful tool for the preparation of libraries of multifunctional peptides, natural products, and heterocyclic compounds with stereochemistry control.

Keywords: AChE, Alzheimer disease, Bis amides, Carbamates, Inhibition, Multi-component reactions (MCRs), Nuclear magnetic resonance (NMR), Screening.

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INTRODUCTION

The synthesis of choline derivatives by multi-component reactions and test their inhibitory effect on the enzyme acetylcholinesterase by using the screening kit K-197.

In this review, we highlight the recent advances of the Ugi reaction in the last two decades from 2000–2019, mainly in the synthesis of linear or cyclic peptides, heterocyclic compounds with versatile ring sizes, and natural products, as well as the enantioselective Ugi reactions.¹ Alzheimer's disease is an irreversible, progressive brain disease that slowly destroys thinking skills and eventually even the ability to carry out the simplest tasks.

Drugs are prepared in different ways, and many attempts have been done to develop the existing drugs. Many types of research showed that the use of choline chloride didn't play a role in treating the disease.²

One of the most famous ways to treat Alzheimer disease is the use of choline esterase inhibitors like donepezil which is the most widely used drug, so in our research, we are going to use this drug as a standard to compare it with our new synthesized drugs the test was done by using screening kit known as k-197.³ In this research, we synthesized our

components by using multi-component reactions Passerini and Ugi reactions. Passerini's reaction was firstly discovered in 1921. It's a three-component reaction that involves aldehyde or ketone, carboxylic acid, isocyanide.⁴ Meanwhile, Ugi is a four multi-component reaction in which primary or secondary amine is involved and aldehyde or ketone, carboxylic acid, and isocyanide.⁵ The Ugi four-component reaction (U-4CR) gives peptide-like structures known as bis-amides or peptomers, classified as peptidomimetics, and have promising pharmacological properties.⁶ U-4CR reactions have proven their efficiency in the synthesis of these structures with the least number of steps and lowest cost, ensuring the synthesis of the target structure using different aliphatic or aromatic isonitriles, with carboxylic acid, carbonyl compound, or amine derivatives with structural diversity to synthesize α -aminoacyl amides.⁷

Many studies that had been done showed that bis amide functional group played a role in inhibiting the action of acetylcholinesterase enzyme (AChE).⁸ Fourteen alkyl and aryl thiocarbonate derivatives of choline were synthesized and studied as potential acetylcholinesterase inhibitors (AChE). Twelve of the compounds inhibited AChEs. Certain of these new compounds may provide direction for the development

of new drugs that have anticholinesterase activity and may be used for the treatment of Alzheimer's disease.⁹

MATERIAL AND METHOD

The methods were used in this study for the synthesis were multi-component reactions like Passerini and Ugi. 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 was calculated.³

The Inhibitory Assay

The screening kit k-197 tested the two compounds;³ the first compound that Passerini prepared didn't show any activity while the second prepared by Ugi showed an inhibition effect. The procedure was carried in Biorad labs.

RESULTS

The compounds were prepared successfully, but the activity was different. The first compound did not show any activity while the second one showed an activity (Figure 1).

DISCUSSION

The first compound by Passerini reaction didn't show any activity despite many studies showing that carbamate group has an effective inhibitory effect on AChE enzyme. One of the drugs used as AChE inhibitor is rivastigmine.^{10,11}

While the second compound, which Ugi prepared, showed a little inhibitory activity, which is obvious because bis amides have good inhibitory activity, according to a study.⁸ The inhibitory activity that was shown in compound b gives us a great start toward synthesizing more new components by utilizing Ugi reaction in spite that Passerini is also promising, but the compound may be hydrolyzed because of the current situation of covid-19 that didn't give the ability to work in labs and because of the kit has not arrived early it was arrived after one year many causes give the reason to the inactivity of

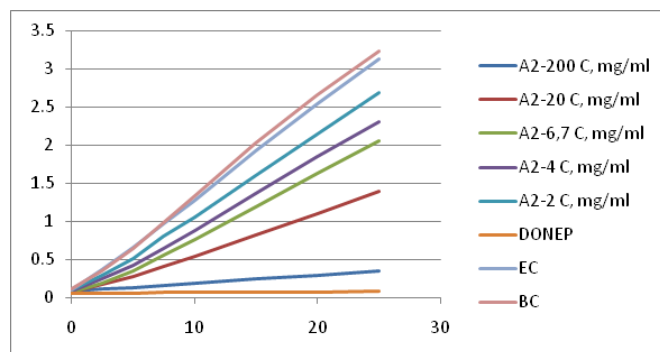


Figure 1: Inhibitory activity in different concentrations of compound 2

compound because many studies made sure that compound 1 should have the activity because it has the carbamate group which is considered as the potent functional groups that inhibit AChE enzyme, in contrast getting results from compound 2. The inhibitory effect is little, but it is promising, and this is shown in many studies that the bis amides also have inhibitory activity on esterase.

CONCLUSION

Multi-component reactions great step for looking forward to trying synthesizing new compounds, and it gave a spotlight to treat many neurodegenerative diseases. It will open the gate to new compounds to be prepared by them, which is a great focus toward polymer chemistry which is considered as novel chemistry nowadays due to the large numbers of drugs which are prepared by these methods.

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