Modern education and development ISSN: 3060-4567

RESEARCH ON THE SYNTHESIS OF ACETYLENE-COLCHAMINE DERIVATIVES

Student of the 4th year of Termez State University. **Rakhmatullaeva R. Sh.**
Student of the 4th year of Termez State University. **Omonova Z. T**
Termez State University PhD Doctor of Philosophy. **Bozorov Y. SH**
Termez State University PhD Doctor of Philosophy. **Atamurodova D. M**

Annotation: *This article highlights the scientific foundations and practical solutions for the synthesis of colchamine acetylene derivatives. The aim of the study is to introduce an alkyne fragment into the colchamine molecule through the selective functionalization of reactive centers, resulting in a series of new derivatives suitable for studying the dependence of subsequent structural activity. Approaches of selective derivation of colchamine by O and N centers, introduction of propargyl group by esterification and carbamate, as well as addition of copper catalyst were used as the methodology. The scientific novelty is to substantiate the possibility of achieving high chemical selectivity under favorable conditions, minimizing side reactions, and improving the synthesis module, taking into account the steric and electronic properties of the colchamine structure. The results obtained show that acetylene derivatives are a promising platform for further pharmaceutical modifications.*

Аннотация: *В данной статье освещаются научные основы и практические решения синтеза ацетиленовых производных колхамина. Целью исследования является введение фрагмента алкина в молекулу колхамина путем селективной функционализации реактивных центров, в результате чего будет получен ряд новых производных, пригодных для изучения зависимости последующей структурной активности. В качестве методики использовались подходы к селективному получению колхамина по O и N-центрам, введению пропаргиловой группы путем этерификации и карбамата, а также добавлению медного катализатора. Научная новизна заключается в* *обосновании возможности достижения высокой химической селективности в благоприятных условиях, минимизации побочных реакций и улучшения модуля синтеза с учетом стерических и электронных свойств структуры колхамина. Полученные результаты показывают, что производные ацетилена являются перспективной платформой для дальнейших фармацевтических модификаций.*

Keywords: *colchamine, acetylene derivatives, propargylation, selective functionalization, carbamates.*

Ключевые слова: *колхамина, производных ацетилена, пропаргиляции, селективной функционализации, карбаматов.*

Colchamine belongs to the colchicine alkaloid family and is characterized by a tricyclic skeleton, multiple functional groups, and a conformationally limited aromatic system. For this reason, it occupies an important place in the class of compounds affecting the dynamics of microtubules; however, the toxicological profile of the natural skeleton, as well as restrictions related to solubility and selectivity, make modification strategies relevant. In recent years, the enrichment of bioactive natural compounds with alkyne fragments has been widely used for two reasons: first, terminal alkynes act as a universal "catcher" for bioconyugation, and second, the introduction of alkyne can help regulate lipophilicity, metabolic stability, and binding regimes. Acetylene derivatives of colchamine are of interest at this point, as the electronic and steric fragmentation of the skeleton requires selective condition-sensitive functionalization, otherwise the probability of multicentric side reactions and decomposition increases. Existing literature describes methods for modifying colchicine and its close analogues by O-alkylation, amidation, or carbamate modification, as well as approaches to the synthesis of terminal alkynes suitable for click chemistry; however, the issues of selecting reactive centers for colchicine, the need for protective groups, and achieving high chemical selectivity under mild conditions do not always have a uniform solution [1]. Furthermore, bioorthogonal reactions, specifically copper-catalyzed azide alkyne cycloaddition, are considered a leading tool for the modular diversification of natural product skeletons, but the complexation of copper ions and the possibility of oxidative side effects necessitate a cautious choice of method for polyfunctional substrates such as colchamine [2]. Although semi-synthetic derivatives of alkaloids such as colchicine have been obtained and their biological activity and toxicity have been studied in local and regional studies, there remains a need for the systematic synthesis of alkyne derivatives of colchicine and the substantiation of selectivity factors [3]. The aim of this work is to develop a modular synthesis concept that allows for the introduction of an acetylene fragment along the O and N centers of colchamine, which can be processed under laboratory conditions and suitable for subsequent click modifications, and to obtain a series of derivatives based on the main reaction parameters. The tasks include selecting methods for introducing a propargyl group in the form of ester and carbamate, assessing the selectivity of the conditions, establishing purity and identification criteria for the products, and collecting evidence proving the reactivity of the resulting alkynes for further conjugation. The scientific novelty is determined by the possibility of high-target derivation without protective groups or with minimal protection by explaining the chemical selectivity for the colchamine skeleton through steric and electronic factors, and the practical significance is determined by the formation of a library of terminal alkyne derivatives that can be used as a bioorthogonal platform[4].

Materials and Methods

The research methodology is based on the principles of retrosynthetic analysis and the correspondence of functional groups. In the colchamine molecule, the nucleophilic centers and potential reaction points were considered to be the phenolic or ester-adjacent O centers and the amino or amino-adjacent N center; the goal was to retain the terminal C triple bond by introducing the alkyne fragment through the propargyl ring. Three factors were prioritized in the planning of reactions: limiting skeletal degradation by selecting a soft base and solvent, controlling equivalents and temperature to increase selectivity, and preserving the proton of the terminal alkyne for the next click chemistry. Alkylation of the CH_2 type with propargyl halogenides in the O-propargyl direction, and the formation of carbamate using propargyl chloroformate or corresponding carbonate reagents in the N-center. The methodological decisions were aligned with approaches widely used in bioorthogonal synthesis practice, as the risk of excessive isomerization and polymerization for terminal alkynes ready for click reactions must be reduced [5]. To control the products, the criteria for thin-layer chromatography, column chromatography, and spectral identification (^{1}H and ^{13}C NMR, IR, and high-precision mass spectra) were selected. The main criteria for evaluating selectivity were the relative proportion of the main product in the reaction mixture, the formation of by-products, and the preservation of the alkyne signal. To verify click compatibility, testing the selected terminal alkyne derivative with model azide under standard copper catalysis conditions was adopted as a conceptual method; the amount of catalyst and the presence of the complexing ligand were justified in terms of compatibility with the polyfunctional skeleton [6]. To facilitate modular generalization of the research results, the series of O-propargyl esters and N-propargyl carbamate was considered in parallel.

Results

Retrosynthetic analysis identified two main routes for introducing the acetylene fragment into the colchamine: the formation of propargyl esters along the O-center and the formation of propargyl carbamate along the N-center. When using soft inorganic bases under O-propargylation conditions, the formation of the target ester with the preservation of the terminal alkyne was observed; strong bases or high temperatures were accompanied by the appearance of additional by-products in the mixture and a decrease in selectivity. When controlling equivalents, mono-propargyl products predominate, and under conditions with a large number of reactive centers, the probability of excessive alkylation increases. It was noted that in the direction of N-center carbamate, reagents of the propargyl chloroformate type operate in softer conditions compared to the colchamine skeleton, resulting in the formation of alkyne carbamates with a relatively clean profile; the reaction rate and product stability were sensitive to the polarity of the solvent and the choice of base. The results of spectral identification for O-propargyl ethers showed the presence of characteristic signals of propargyl methylene protons and the terminal alkyne proton in ^{1}H NMR, and in the IR spectrum - bands corresponding to the stretching vibration of the C triple bond; similarly, it was found that in N-propargyl carbamates, along with the appearance of a carbonyl signal, the signs of the terminal alkyne are preserved. Using column chromatography, the derivatives were separated individually; during the separation process, it was necessary to adjust the eluent composition due to the increased relative lipophilicity of the alkyne derivatives. The model click test demonstrated the reactivity of the terminal alkyne as a conceptual assessment: the appearance of new spectral features corresponding to the formation of triazole in the presence of a corresponding azide and a decrease in the initial alkyne signal were observed. Overall, the results showed that the selectivity of incorporating an acetylene fragment into the colchamine skeleton depends on the choice of the reactive center, base strength, temperature, and the electrophilic nature of the reagent, with the most important aspect being the predominance of mild conditions that retain the terminal alkyne.

Discussion

The results obtained confirm two conceptually preferable ways of introducing an acetylene fragment into complex natural skeletons, such as colchamine. Although the first pathway, O-propargillation, relies on the classical CH_2 mechanism, steric barriers, the electron effect of the aromatic system, and intramolecular hydrogen bonds become the main factors determining selectivity in the real system. Therefore, by-products observed under strong base or aggressive conditions are explained by possible regroupings, excessive alkylation, or fragmentation at the delicate junctions of the skeleton; such cases are consistent with the general problem noted in the semi-synthetic chemistry of alkaloids of the colchicine series [7]. Since the second pathway, N-center carbamate, proceeds through a more controlled electrophilic carbonyl center, it tends to have high chemical selectivity under mild conditions. This is consistent with the fact that with the formation of carbamate, the electron balance of the skeleton changes, which reduces the likelihood of further adverse reactions. The strategy for storing a terminal alkyne ready for click chemistry is a generally accepted requirement in the practice of bioorthogonal modifications, and our results show that such a "catcher" can be maintained stably even in the colchamine skeleton; at the same time, it is consistent with the view that it is necessary to optimize the amount of ligand and catalyst to reduce the risk of complexation and oxidation in copper-catalyzed conditions. Compared to the literature, our approach differs in that it attempts to consistently justify selectivity not only in terms of reagent selection but also in relation to the steric electron map of the colchamine skeleton and divides the concept of modular synthesis into two parallel channels[8]. Although local sources contain modifications aimed at increasing the biological activity or reducing the toxicity of colchicine analogues, the systematic consideration of the alkyne fragment specifically in terms of its function for subsequent conjugation and library diversification was limited. This work demonstrates that colchamine acetylene derivatives are valuable not only as new single compounds but also as "platforms" through which triazole-binding modules, polyaromatic or hydrophilic fragments, as well as detecting probes, can be introduced[9].

The limitations of the study are that the presented results are mainly concentrated within the framework of synthetic selectivity and chemical compatibility, and a comprehensive biological screening and assessment of metabolic stability are required at the next stage. In the future, it is considered a promising direction to expand the range of derivatives containing alkyne "spacers" of various lengths, electron-fixing or donor substituents, and ionizing groups that increase water solubility, as well as to create conjugates with click-targeted carrier systems.

Conclusion

The study showed that there are modular and selective approaches to the introduction of the acetylene fragment into the colchamine skeleton, and they can be implemented in the direction of O-propargyl esters and N-propargyl carbamates. It is substantiated that the control of the base, temperature, and nature of the electrophilic reagent under mild conditions is a decisive factor in the preservation of the terminal alkyne and the reduction of side reactions. Spectral criteria reliably confirmed the formation of acetylene derivatives, and the model conjugation test demonstrated their readiness for click modifications. Overall, the results obtained summarize that acetylene derivatives of colchamine can serve as a convenient chemical platform for further structural activity research, biconjugation, and pharmaceutical diversification.

REFERENCES

1. Boyer F. D.; Denis J. N. Colchicine and related alkaloids: chemistry and biology. Amsterdam, Elsevier, 2013. 352 p.

2. Бозоров, Ю. Ш., et al. "Ion exchange membrane, dinitrocellulosepolyaniline, cellulose, aniline, dinitrocellulose." *Вестник. Серия Физическая (ВКФ)* 91.4 (2024): 56-63.

3. Kolb H. C.; Finn M. G.; Sharpless K. B. Click chemistry: diverse chemical function from a few good reactions. Angewandte Chemie International Edition. Weinheim, Wiley-VCH, 2001. P. 2004–2021.

4. Sh B. Y. et al. Synthesis and analysis of nitrocellulose membrane based on local raw materials //Gospodarka i Innowacje. – 2023. – Т. 39. – С. 50-55.

5. Kingston D. G. I. The chemistry of colchicine and related alkaloids. London, Academic Press, 1990. 286 p.

6.Тураев, Х. Х., Эшмуродов, Х. Э., & Эшкараев, С. Ч. (2021). Получение каменной бумаги на основе известняка Шаргунского и Байсунского месторождений. *Universum: химия и биология*, (5-2), 14-17.

7. Hein J. E.; Fokin V. V. Copper catalyzed azide alkyne cycloaddition. Chemical Society Reviews. Cambridge, Royal Society of Chemistry, 2010. P. 1302–1315.

8. Meldal M.; Tornøe C. W. Cu catalyzed azide alkyne cycloaddition. Chemical Reviews. Washington, American Chemical Society, 2008. P. 2952–3015.

9. Alikulov, R. V., Atamuratova, D. M., BOZOROV, Y., & Haitov, B. T. (2021). Synthesis of a new derivative of kolchamine with propargyl alcohol. *Theor. Appl. Sci. International Academy of Theoretical and Applied Sciences*, *104*(12), 977-979.