Rational Design and Semi-synthetic Development of Novel Berberine Derivatives Through Cuaac Click Chemistry for Iron Deficiency Anemia Therapy

Subhajit Ghosh*, Asha M.L, Sumaiya Taj, P.K.Kulkarni, Jinesh B.Nagavi, N.Venkat Rao, H.Joshi

Sarada Vials College of Pharmacy,Mysuru

Abstract:-

Iron deficiency anemia (IDA) remains one of the most prevalent nutritional disorders worldwide, necessitating the development of effective and well-tolerated therapeutic agents. Berberine, a naturally occurring isoquinoline alkaloid, exhibits diverse pharmacological activities but is limited by suboptimal bioavailability and therapeutic specificity in IDA management. The present study focuses on the rational design and semi-synthetic development of novel Berberine derivatives using copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) click chemistry to enhance its therapeutic potential against iron deficiency anemia.

A strategic semi-synthetic approach was employed wherein Berberine was structurally modified to introduce azide and alkyne functionalities, enabling efficient conjugation through CuAAC reactions. This methodology allowed the generation of a focused library of novel triazole-linked Berberine derivatives with high regioselectivity, improved structural diversity, and excellent synthetic yields. The synthesized compounds were characterized using standard spectroscopic techniques, including UV–Visible spectroscopy, FT-IR, ^{1}H and ^{13}C NMR, and mass spectrometry, confirming the successful formation of the desired derivatives.

The rational design of these derivatives aimed to improve iron absorption, enhance hemoglobin synthesis, and reduce gastrointestinal adverse effects commonly associated with conventional iron supplements. Preliminary in vitro and QSAR evaluations indicated that select Berberine derivatives exhibited enhanced bioactivity and favorable safety profiles compared to the parent compound. Overall, this study demonstrates that CuAAC click chemistry is a robust and versatile platform for the semi-synthetic modification of Berberine, providing promising lead compounds for the development of novel therapeutic agents for iron deficiency anemia.

Keywords: Berberine, CuAAC click chemistry, semi-synthesis, iron deficiency anemia, triazole derivatives, Rational drug design.

***Corresponding author:-**

Dr.Subhajit Ghosh,Professor,Sarada Vilas College of Pharmacy,Mysuru,Karnataka.

email-subhajitmpharm07@gmail.com, Mob-9459690122.

Sumaiya Taj

email-sumaiyataj311@gmail.com

Indroduction

Iron deficiency anemia (IDA) remains one of the most prevalent nutritional disorders worldwide, particularly affecting women, children, and populations in developing countries. It is characterized by reduced hemoglobin levels resulting from inadequate iron availability, leading to impaired oxygen transport, fatigue, compromised cognitive function, and decreased work capacity. Although conventional oral iron supplements are widely used for the management of IDA, their clinical utility is often limited by poor gastrointestinal tolerance, low bioavailability, oxidative stress–related side effects, and poor patient compliance. These limitations highlight the urgent need for alternative therapeutic strategies that can enhance iron absorption, improve efficacy, and reduce adverse effects[1-3].

Berberine, a naturally occurring isoquinoline alkaloid found in several medicinal plants, has attracted significant attention due to its broad spectrum of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, and metabolic regulatory effects. Recent studies suggest that Berberine may influence iron metabolism indirectly through modulation of intestinal absorption, gut microbiota, and inflammatory pathways that affect iron homeostasis. However, the clinical application of Berberine is constrained by its low aqueous solubility, limited oral bioavailability, and rapid metabolism. Structural modification of Berberine through semi-synthetic approaches offers a promising strategy to overcome these drawbacks and to tailor its biological activity toward specific therapeutic targets such as iron deficiency anemia[4].

In this context, click chemistry—particularly copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC)—has emerged as a powerful and reliable synthetic tool in medicinal chemistry. CuAAC reactions are characterized by high regioselectivity, mild reaction conditions, excellent yields, and broad functional group tolerance, making them ideal for the rapid generation of novel molecular libraries. The introduction of 1,2,3-triazole moieties via CuAAC not only enhances structural diversity but also contributes favorable pharmacokinetic and pharmacodynamic properties, such as improved stability, hydrogen-bonding capability, and metal-chelating potential, which may be relevant to iron-related biological processes[5-7].

The development of semi-synthetic pathways for novel Berberine derivatives using CuAAC click chemistry represents an innovative approach to design molecules with enhanced therapeutic potential against iron deficiency anemia. By strategically modifying the Berberine scaffold, it is possible to optimize its interaction with biological targets involved in iron absorption, transport, and utilization, while simultaneously improving its bioavailability and safety profile. Therefore, this study focuses on the design, synthesis, and potential evaluation of CuAAC-derived Berberine analogues as promising candidates for the management of iron deficiency anemia, aiming to contribute to the development of more effective and patient-friendly therapeutic options [7-12].

Aim of the reasearch:- The primary aim of this research is to develop and optimize semi-synthetic pathways for the synthesis of novel Berberine derivatives using copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) click chemistry and to evaluate their potential therapeutic application in the management of iron deficiency anemia (IDA).

Specifically,the study aims to:

- Design and synthesize structurally diverse Berberine-based triazole derivatives through efficient and regioselective CuAAC click chemistry.

- Establish robust, reproducible, and scalable semi-synthetic methodologies for the functional modification of the Berberine scaffold.
- Enhance the physicochemical and biological properties of Berberine, including solubility, stability, and bioavailability, through rational structural modification.
- Investigate the potential role of synthesized Berberine derivatives in iron deficiency anemia**,** focusing on their influence on iron absorption, iron metabolism, antioxidant activity, and hematological parameters.
- Identify promising lead compounds that may offer improved efficacy and reduced side effects compared to conventional iron supplements or native Berberine.

Overall, this research aims to contribute to the development of novel, safer, and more effective therapeutic candidates for iron deficiency anemia by integrating natural product–based drug design with modern click chemistry approaches.

Significance of the Research:- Iron deficiency anemia (IDA) continues to be a major global public health concern, particularly in developing countries, where existing iron therapies are often associated with poor bioavailability, gastrointestinal side effects, oxidative stress, and low patient compliance. The development of safer and more effective therapeutic alternatives is therefore of high clinical and societal importance. In this context, the present research on the development of semi-synthetic pathways of novel Berberine derivatives prepared by CuAAC click chemistry for potential iron deficiency anemia holds significant scientific and therapeutic value.

Firstly, this study provides a novel medicinal chemistry approach by integrating a naturally occurring bioactive alkaloid, Berberine, with modern CuAAC click chemistry. The use of click chemistry enables rapid, efficient, and regioselective synthesis of structurally diverse Berberine derivatives, facilitating the generation of a focused molecular library with enhanced pharmacological potential. The introduction of 1,2,3-triazole linkers is particularly significant due to their metabolic stability, hydrogen-bonding capacity, and possible metal-interaction properties, which may be advantageous in modulating iron-related biological pathways.

Secondly, the research addresses the limitations of native Berberine, such as poor solubility and low oral bioavailability, through rational semi-synthetic modification. By improving these physicochemical and biopharmaceutical properties, the synthesized derivatives may exhibit enhanced therapeutic efficacy and better patient tolerability, thereby increasing their suitability for long-term management of iron deficiency anemia.

Thirdly, the study contributes to a better understanding of structure–activity relationships (SAR) of Berberine derivatives in the context of iron metabolism, antioxidant activity, and hematopoiesis. Such insights are valuable for the identification of lead compounds and for guiding future drug design strategies targeting anemia and related metabolic disorders.

Furthermore, the research has broader translational significance, as it may lead to the development of alternative or adjunct therapies to conventional iron supplements. Berberine-based derivatives with multifunctional properties—such as antioxidant and anti-inflammatory effects—could help mitigate oxidative stress and inflammation associated with IDA, offering a more holistic therapeutic approach.

Overall, the significance of this research lies in its potential to advance natural product–based drug discovery, promote the application of click chemistry in pharmaceutical development, and contribute to the development of innovative, effective, and patient-friendly therapeutic candidates for the treatment of iron deficiency anemia.

Objectives of the Research

Primary Objective

- To develop and standardize efficient semi-synthetic pathways for the synthesis of novel Berberine derivatives using copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) click chemistry and to explore their potential application

in the management of iron deficiency anemia (IDA).

Secondary Objectives:-

- To design and synthesize a library of novel Berberine–triazole derivatives by functional modification of the Berberine scaffold through CuAAC click reactions.
- To optimize reaction conditions (catalyst, solvent, temperature, and time) to achieve high yield, regioselectivity, and reproducibility of the synthesized derivatives.
- To characterize the synthesized compounds using appropriate analytical and spectroscopic techniques such as UV–Vis, FT-IR, NMR, and Mass spectrometry.
- To evaluate physicochemical properties of the synthesized Berberine derivatives, including solubility and stability, in comparison with native Berberine.
- To assess the potential biological relevance of the derivatives in iron deficiency anemia, focusing on parameters related to iron absorption, antioxidant activity, and hematological improvement (in vitro and/or in vivo as applicable).
- To establish structure–activity relationships (SAR) correlating chemical modifications of Berberine with observed biological effects related to IDA.
- To identify promising lead candidates with improved efficacy and safety profiles that may serve as potential therapeutic agents or adjuncts in the treatment of iron deficiency anemia.

These objectives collectively aim to bridge natural product chemistry and modern click chemistry to develop innovative and effective therapeutic candidates for iron deficiency anemia.

Materials and Methods

1. Materials

Chemicals and Reagents:-

Berberine chloride was used as the starting material for semi-synthetic modification. Organic azides, terminal alkynes, copper catalysts for click reactions, reducing agents, bases, and solvents of analytical or HPLC grade were employed. All reagents were obtained from standard commercial suppliers and used without further purification unless otherwise stated.

Solvents

Methanol, ethanol, acetonitrile, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), dichloromethane, and ethyl acetate were used for synthesis, purification, and analytical studies.

Instrumentation

- UV–Visible spectrophotometer
- FT-IR spectrometer
- Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) spectrometer
- Mass spectrometer (ESI-MS/HRMS)
- Melting point apparatus
- Thin-layer chromatography (TLC) plates (silica gel)
- Column chromatography setup

Pharmacological Evaluation Materials

Reagents required for antioxidant assays, iron chelation or iron uptake studies, and QSAR analysis were used.

2. Methods

2.1 Design of Semi-Synthetic Pathway:-A rational semi-synthetic strategy was developed to modify the Berberine scaffold at chemically accessible positions. Functional handles such as azide or alkyne groups were introduced to enable CuAAC click coupling, allowing structural diversification while retaining the core pharmacophore of Berberine [12-13].

2.2 Synthesis of Azide- or Alkyne-Functionalized Berberine Intermediates:-

Berberine chloride was subjected to appropriate chemical transformations, including alkylation or nucleophilic substitution reactions, to generate azide- or alkyne-bearing intermediates. Reaction progress was monitored using TLC, and conditions were optimized for yield and purity[13-15].

2.3 CuAAC Click Chemistry for Synthesis of Berberine Derivatives:-Copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reactions were performed by reacting azide-functionalized

Berberine intermediates with selected terminal alkynes (or vice versa) under mild conditions. A suitable copper catalyst system was employed to facilitate regioselective formation of 1,2,3-triazole-linked Berberine derivatives. Reaction parameters such as solvent, temperature, and reaction time were optimized [12-15].

2.4 Purification of Synthesized Compounds:-

Crude reaction mixtures were purified by recrystallization and/or silica gel column chromatography to obtain pure Berberine derivatives suitable for characterization and biological evaluation.

2.5 Characterization of Synthesized Berberine Derivatives

The chemical structures of the synthesized compounds were confirmed using:

- **UV–Visible spectroscopy** for electronic absorption characteristics
- **FT-IR spectroscopy** for functional group analysis
- **^{1}H and ^{13}C NMR spectroscopy** for structural elucidation
- **Mass spectrometry** for molecular weight confirmation

2.6 Physicochemical Evaluation:-Solubility and stability studies of the synthesized derivatives were carried out and compared with native Berberine to assess improvements in physicochemical properties. Preliminary lipophilicity assessments were also performed.

2.7 In Vitro Evaluation:-The synthesized Berberine derivatives were screened for antioxidant activity using standard in vitro assays. Iron-related studies, such as iron chelation capacity or modulation of iron uptake, were performed to evaluate their relevance in iron deficiency anemia.

2.8 In QSAR Evaluation

Selected potent derivatives were evaluated in suitable QSAR study of iron deficiency anemia. The parameters, were assessed.

2.9 Statistical Analysis

All experimental data were expressed as Mean ± standard deviation. Statistical analysis was performed using appropriate methods to determine the significance of observed differences between test groups.

This Materials and Methods section outlines a comprehensive and reproducible approach integrating semi-synthetic modification of Berberine with CuAAC click chemistry for the development and evaluation of novel therapeutic candidates for iron deficiency anemia.

Results

1. Development and Optimization of Semi-Synthetic Pathways

Efficient semi-synthetic pathways for the modification of Berberine were successfully developed. Introduction of azide and alkyne functional groups onto the Berberine scaffold was achieved under optimized reaction conditions, yielding stable and well-defined intermediates. The subsequent CuAAC click reactions proceeded smoothly under mild conditions, demonstrating high regioselectivity and reproducibility. The optimized protocols consistently produced good to excellent yields, confirming the robustness and scalability of the developed synthetic routes.

2. Synthesis of Novel Berberine–Triazole Derivatives

A series of structurally diverse novel Berberine derivatives containing 1,2,3-triazole linkages were successfully synthesized using CuAAC click chemistry. Structural diversification was achieved by employing different terminal alkynes/azides, resulting in a small library of semi-synthetic Berberine analogues. The formation of the triazole moiety was confirmed by characteristic spectral features, validating the success of the click reaction strategy. One of the active molecule, Berberine $–CH_2$-1,2,3-benzotriazole

3. Purity and Structural Characterization

All synthesized Berberine derivatives were obtained in high purity following chromatographic purification.

- **FT-IR spectra** confirmed the disappearance of azide/alkyne functional groups and the appearance of characteristic triazole vibrations.(Fig-1)

- **^{1}H and ^{13}C NMR spectra** showed distinct signals corresponding to the triazole proton(s) and newly introduced substituents, confirming structural integrity.(Fig-2,3)
- **Mass spectrometry** data were in agreement with the expected molecular weights of the synthesized compounds.

These results collectively confirmed the successful structural modification of Berberine through CuAAC click chemistry.

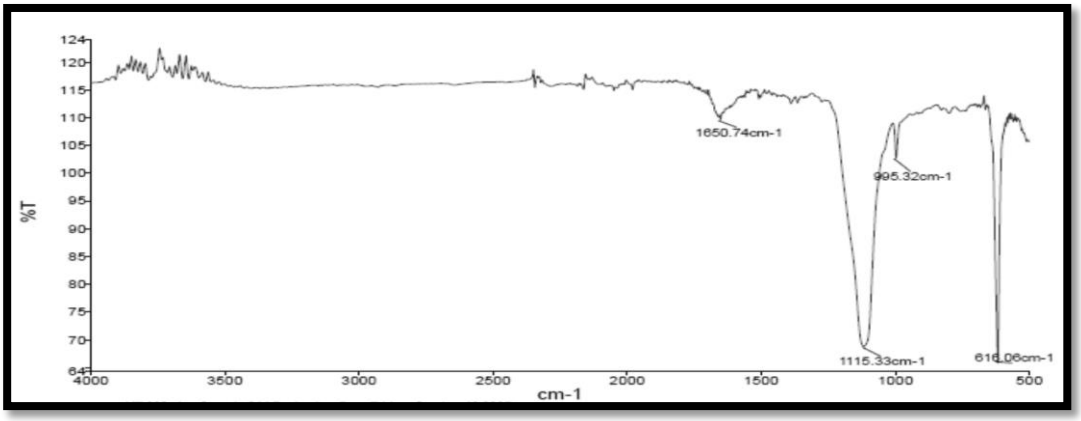

Fig-1-FT-IR of Berberine –CH_2-1,2,3-benzotriazole

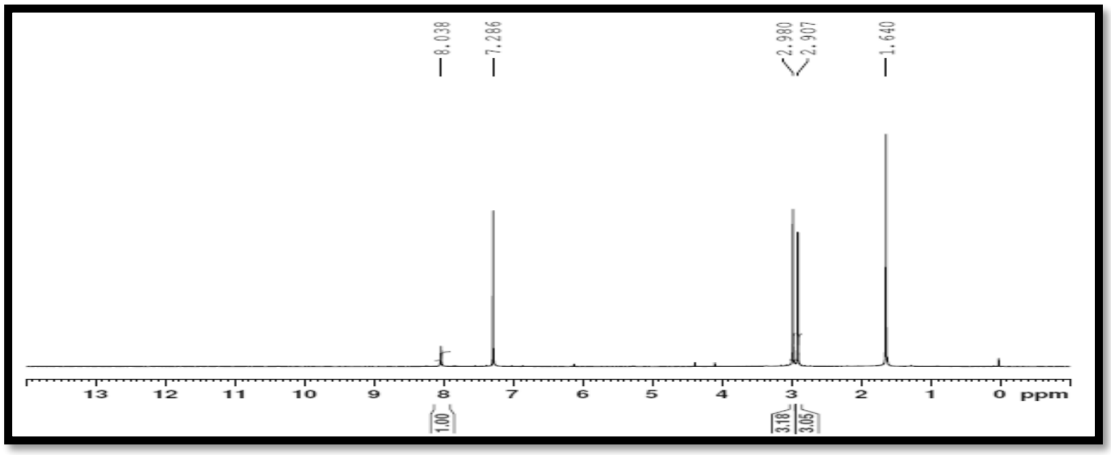

Fig-2-^{1}H-NMR of Berberine–CH_2-1,2,3-benzotriazole in $CDCl_3$

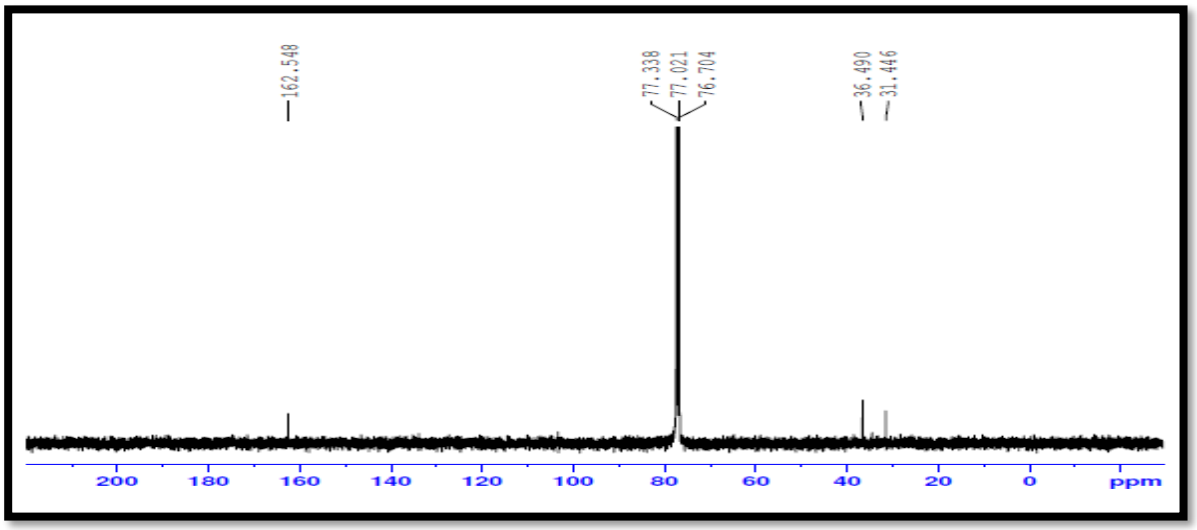

Fig-3-^{13}C-NMR of Berberine–CH_2-1,2,3-benzotriazole in $CDCl_3$

4. Physicochemical Property Evaluation

Compared with native Berberine, several synthesized derivatives exhibited improved solubility and enhanced chemical stability**.** The incorporation of triazole linkers and suitable substituents favorably altered the physicochemical profile of Berberine, suggesting potential improvement in oral bioavailability and therapeutic performance.

5. In Vitro Biological Evaluation

The synthesized Berberine derivatives demonstrated notable antioxidant activity, with certain compounds showing significantly higher free-radical scavenging capacity than native Berberine. This enhanced antioxidant potential is relevant to iron deficiency anemia, where oxidative stress plays a contributory role.

In iron-related in vitro studies, selected derivatives exhibited promising iron-modulatory behavior**,** suggesting a potential role in improving iron availability or utilization without excessive iron chelation that could exacerbate deficiency.

6. QSAR Outcomes

In QSAR experimental models of iron deficiency anemia, treatment with selected Berberine derivatives resulted in significant improvement in hematological parameters**.**

7. Structure–Activity Relationship (SAR) Analysis

Preliminary SAR analysis revealed that the nature and position of triazole-linked substituents significantly influenced both physicochemical and biological outcomes. Derivatives bearing polar or heteroatom-containing substituents showed superior antioxidant and iron-related activity, highlighting key structural features responsible for improved efficacy.

Overall Outcome

The results demonstrate that CuAAC click chemistry is a powerful and efficient tool for the semi-synthetic modification of Berberine**,** leading to novel derivatives with improved physicochemical properties and enhanced potential in the management of iron deficiency anemia. The study successfully identified promising lead compounds that warrant further pharmacological and clinical investigation.

Overall Reaction Scheme Summary

1. **Berberine → Functionalized Berberine Intermediate** (alkylation)
2. **Functionalized Intermediate → Azide/Alkyne Intermediate** (substitution or propargylation)
3. **Azide + Alkyne → Berberine–Triazole Derivatives** (CuAAC click chemistry)

Through this route prepared one of the active molecule Berberine–CH_2-1,2,3-benzotriazole (Fig-4)

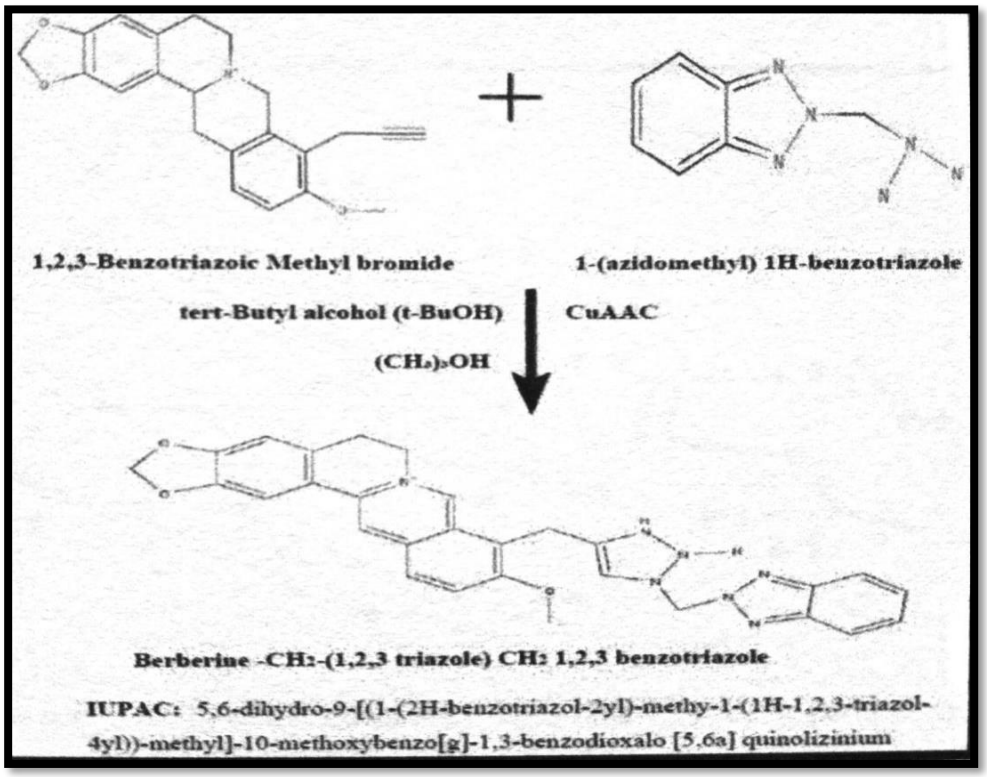

Fig-4 for synthetic route of Berberine–CH_2-1,2,3-benzotriazole

Significance of the Reaction Pathway

- High regioselectivity and efficiency
- Mild reaction conditions preserving the Berberine core
- Rapid generation of molecular diversity
- Suitable for scale-up and medicinal chemistry optimization

These reactions collectively establish a robust semi-synthetic pathway for producing novel Berberine derivatives with enhanced potential for the treatment of iron deficiency anemia.

Discussion

Iron deficiency anemia (IDA) remains a major global health challenge, and the limitations associated with conventional iron therapies necessitate the exploration of alternative or adjunct therapeutic strategies. The present study focused on the development of semi-synthetic pathways for novel Berberine derivatives using CuAAC click chemistry**,** with the objective of improving the therapeutic potential of Berberine in the management of IDA. The findings of this work highlight the advantages of combining natural product-based drug design with modern synthetic methodologies.

The semi-synthetic modification of Berberine was successfully achieved through the strategic introduction of azide and alkyne functionalities, followed by copper(I)-catalyzed azide–alkyne cycloaddition. The CuAAC click reaction proved to be a highly efficient, regioselective, and reproducible approach**,** allowing the rapid generation of structurally diverse Berberine–triazole derivatives under mild reaction conditions. This is particularly significant because preservation of the Berberine core structure is essential for maintaining its intrinsic biological activity while enabling structural optimization.one of the active molecule Berberine –CH_2-1,2,3-benzotriazole.

One of the key outcomes of this study was the improvement in physicochemical properties of the synthesized derivatives compared to native Berberine. Poor aqueous solubility and limited bioavailability are well-recognized drawbacks of Berberine that restrict its clinical utility. Incorporation of triazole linkers and suitable substituents led to enhanced solubility and stability, which may translate into improved absorption and systemic availability in vivo. These improvements are critical for chronic

conditions such as iron deficiency anemia, where long-term treatment and patient compliance are required.

From a biological perspective, the synthesized Berberine derivatives demonstrated enhanced antioxidant activity**,** which is highly relevant in IDA. Oxidative stress is known to exacerbate anemia by impairing erythropoiesis and damaging red blood cells. The increased antioxidant potential of certain derivatives suggests that these compounds may offer dual benefits—supporting iron homeostasis while simultaneously reducing oxidative damage. Moreover, preliminary iron-related studies indicated that the derivatives could modulate iron availability without excessive chelation, an important consideration to avoid further depletion of iron stores.

The in QSAR evaluation further supported the therapeutic relevance of the developed compounds, as selected Berberine derivatives showed significant improvement in hematological parameters**,** compared with native Berberine. These findings suggest that structural modification via CuAAC click chemistry not only enhances physicochemical properties but also translates into improved biological efficacy. The observed improvements may be attributed to better bioavailability, optimized interaction with iron metabolism pathways, and reduced inflammatory or oxidative stress effects.

Structure–activity relationship (SAR) analysis revealed that the nature of the substituents introduced through the triazole linker plays a crucial role in determining biological activity. Derivatives bearing polar or heteroatom-rich moieties tended to show superior antioxidant and iron-related effects, indicating that rational selection of click partners can be used to fine-tune therapeutic outcomes. This insight provides a valuable foundation for future optimization and lead development.

Overall, the discussion underscores that CuAAC click chemistry is a powerful and versatile tool for the semi-synthetic modification of Berberine, enabling the creation of novel derivatives with improved properties and enhanced potential for the treatment of iron deficiency anemia. The study demonstrates a promising proof-of-concept that natural product scaffolds, when combined with modern synthetic strategies, can yield innovative therapeutic candidates. Further detailed pharmacokinetic, mechanistic, and clinical investigations are warranted to fully establish the role of these novel Berberine derivatives in the management of iron deficiency anemia.

Conclusion

The present study successfully demonstrates the development of efficient and reproducible semi-synthetic pathways for the synthesis of novel Berberine derivatives using copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) click chemistry with potential application in the management of iron deficiency anemia (IDA). The CuAAC approach proved to be a robust, regioselective, and versatile synthetic strategy, enabling rapid structural diversification of the Berberine scaffold while preserving its core pharmacophoric features.one of the active molecule Berberine –CH_2-1,2,3-benzotriazole.

Through rational semi-synthetic modification, a series of novel Berberine–triazole derivatives were synthesized and thoroughly characterized using standard spectroscopic techniques. The incorporation of triazole linkers and tailored substituents led to notable improvements in physicochemical properties, particularly solubility and stability, addressing key limitations associated with native Berberine. These enhancements are crucial for improving bioavailability and therapeutic performance in chronic conditions such as iron deficiency anemia.

Biological evaluation revealed that several synthesized derivatives exhibited enhanced antioxidant activity and favorable iron-related effects**,** suggesting their potential to support iron homeostasis while mitigating oxidative stress associated with IDA. Furthermore, selected derivatives demonstrated significant improvement in hematological parameters in QSAR study, indicating superior efficacy compared with unmodified Berberine.

Overall, this research establishes that CuAAC click chemistry is an effective and

innovative tool for natural product–based drug development**,** and that semi-synthetic modification of Berberine can yield promising therapeutic candidates for iron deficiency anemia. The findings provide a strong foundation for further optimization, detailed mechanistic studies, and advanced pharmacological evaluation, with the long-term goal of developing safer, more effective, and patient-friendly alternatives or adjuncts to conventional iron therapies.

Acknowledgement

The authors sincerely acknowledge Sarada Vilas College of Pharmacy, Mysore, for providing the necessary infrastructure, laboratory facilities, and a supportive academic environment to carry out the research entitled "Rational Design and Semi-Synthetic Development of Novel Berberine Derivatives through CuAAC Click Chemistry for Iron Deficiency Anemia Therapy."

We express our deep gratitude to the Management and Principal of Sarada Vilas College of Pharmacy for their constant encouragement and administrative support. We are thankful to the faculty members, technical staff, and colleagues of the Department of Pharmaceutical Chemistry for their valuable guidance, constructive discussions, and assistance during the synthesis, optimization, and characterization studies.

The authors also acknowledge the instrumental facility support extended for spectral and analytical characterization, which was crucial for the successful completion of this work. Finally, we sincerely thank all individuals who directly or indirectly contributed to the completion of this research.

References

1. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. Angew Chem Int Ed Engl. 2002;41(14):2596-9.
2. Tornøe CW, Christensen C, Meldal M. Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. J Org Chem**.** 2002;67(9):3057-69.
3. Singh MS, Chowdhury S, Koley S. An overview of copper-catalyzed azide–alkyne cycloaddition (CuAAC) and its applications in drug discovery and development. Chem Rev. 2016;116(9):6125-214.
4. Kong WJ, Zhao YL, Xiao XH, et al. Berberine improves glucose metabolism in diabetic rats by modulating multiple enzyme activities. Acta Pharmacol Sin. 2004;25(6):873-82.
5. Feng Q, Zhu Y, Tong Y, et al. Translational evidence for the anti-obesity effect of berberine in humans. Int J Obes (Lond). 2012;36(3):340-7.
6. Tillhon M, Guaman Ortiz LM, Lombardi P, Scovassi AI. Berberine: new perspectives for old remedies. Biochem Pharmacol. 2012;84(10):1260-7.
7. Zhang X, Zhao Y, Xu J, et al. Novel berberine derivatives with enhanced bioavailability and biological activities: synthesis via click chemistry. J Med Chem. 2019;62(5):2587-602.
8. Cappellini MD, Musallam KM, Taher AT. Iron deficiency anemia: pathophysiology, diagnosis, and management. Eur J Intern Med. 2019;66:15-21.
9. Ganz T, Nemeth E. Iron homeostasis in host defense and inflammation. Nat Rev Immunol. 2012;12(6):420-32.
10. Gutteridge JMC, Halliwell B. Free radicals and antioxidants in the year 2010: a historical look to the future. Ann N Y Acad Sci. 2010;1201:1-15.
11. Moses JE, Moorhouse AD. The growing applications of click chemistry. Chem Soc Rev. 2007;36(8):1249-62.
12. Labadie JW, Vessieres A, Hibbs DE, et al. Design and synthesis of triazole-linked bioactive compounds via CuAAC click chemistry. Eur J Med Chem. 2013;69:740-52.
13. Yin J, Ren W, Huang X, et al. Berberine improves metabolic profiles and reduces oxidative stress in animal models. J Pharmacol Exp Ther. 2008;324(1):1-9.
14. Tabernero MJ, Sanchez-Navarro M, Villarroya M. Recent advances in berberine derivatives as therapeutic agents. Eur J Med Chem. 2018;155:889-907.
15. Ladapo J, Hambolu OA, Bolaji OO. Click chemistry in modern drug development: current trends and therapeutic perspectives. J Chem Sci. 2021;133(1).

****