Review Article

Int Jou Hea Bio Sci, 7(1), 2026, 4-8

International Journal of Health care and Biological Sciences

Content available at www.saapjournals.org Online ISSN: 2582-7499

Open Access

A REVIEW ON SYNTHETIC PATHWAYS AND PHARMACOLOGICAL PROPERTIES OF CINNOLINE DERIVATIVES

M.Prashanthi Evangelin*[1], Podili Chaitanya[2], Pandilla Harsheeth Reddy[2], Chappidi Srilalitha[2], Bolledu Shiny[2], B.Tangabalan[3]

[1]Professor and Vice-Principal, Department of Pharmaceutical Chemistry, SIMS College Of Pharmacy, Guntur, 522001.

[2]Students, SIMS College Of Pharmacy, Guntur, 522001.

[3]Professor and Principal, Department of Pharmaceutical Analysis, SIMS College Of Pharmacy, Guntur, 522001.

DOI: https://doi.org/10.46795/ijhcbs.v7i1.810

Article History

Received on: 14-10-202
Revised on: 24-11-2025
Accepted on: 03-12-2025

Keywords: Cinnoline, Diazine ring system, Heterocyclic chemistry,Green chemistry, Microwave-assisted synthesis, Anticancer, Antimicrobial.

***Corresponding Author**
Dr.M.Prashanthi Evangelin
Professor and Vice-Principal, Department of Pharmaceutical Chemistry, SIMS College Of Pharmacy, Guntur, 522001.

Abstract

Cinnoline is an emerging benzo-fused diazine scaffold with great versatility in heterocyclic and medicinal chemistry owing to its aromatic ring deficiency of electrons, hydrogen-bonding capability, and bio-isosteric relationship with quinoline and pyridine. In the last decade, significant progress has been made in the synthesis, functionalization, and pharmacological study of cinnoline derivatives. The goal of this review is to highlight some of the classical and modern synthetic strategies, including diazotization-cyclization, Fischer-Hepp rearrangement, metal-catalyzes annulation, cycle condensation of hydrazines, and multicomponent and green methodologies, such as microwave, ultrasound, ionic liquids, and photocatalysis. These approaches increase the structural diversity with significant improvements in atom economy and sustainability. Parallel biological investigations have highlighted to wide pharmacological potential of cinnoline derivatives. In addition to antimicrobial and antitubercular properties, various anticancer, anti-inflammatory, analgesic, and neuroactive activities have been reported. The main contribution to potency and selectivity came from substitution patterns at the 3- and 4-positions, with beneficial roles being played by N-oxide formation and hydrophobic, or sulfonamide functions. Moreover, an emerging hybrid architecture involving cinnoline and other privileged heterocycles has opened new avenues for multitarget drug discovery. Moving forward, cinnoline chemistry is also developing in the fields of green chemistry, advanced imaging probes, and nanoscale-mediated delivery systems. Based on its synthetic applicability and broad biological relevance, cinnoline can be considered a crucial platform for the development of novel biological therapeutics.

1. INTRODUCTION

Cinnoline is a nitrogen-rich heterocyclic compound that has garnered considerable interest due to its aromatic ring system and the electron-withdrawing property of the diazine portion structure. These aspects make its utility as a bio-isostere for quinoline or pyridine ring systems versatile. This compound, when employed as a bio-isostere in drug design, can participate in hydrogen bonding and π–π stacking interactions [1-2].

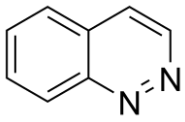


Figure 1: General Structure of Cinnoline

During the past decade, numerous cinnoline derivatives have been synthesized using classic diazotization methods, coupling reactions under metal catalysis, annulation reactions and multicomponent reactions. These synthetic advances were paralleled by pharmacological studies, which revealeda wide spectrum of biological and therapeutic activities [3-4].

2. SYNTHETIC PATHWAYS OF CINNOLINE

2.1 Classical Diazotization

Among the oldest and most widely used methods for the preparation of cinnoline are:

1. Diazotization reactions of o-amino benzaldehydes, o-phenylenediamines

2. Intramolecular cyclization for cinnoline or dihydroquinoline derivatives
3. Aromatization by oxidation or dehydrogenation [5-7].

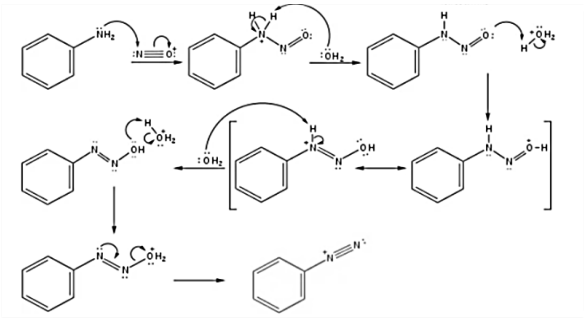


Figure 2: Diazotization-cyclization mechanism A special efficacy of this pathway has been demonstrated in the case of simple unsubstituted cinnolines

2.2 Fischer-Hepp

Nitration of anilide, followed by anilide rearrangement and cyclization, provides C- or N substituted cinnoline derivatives.

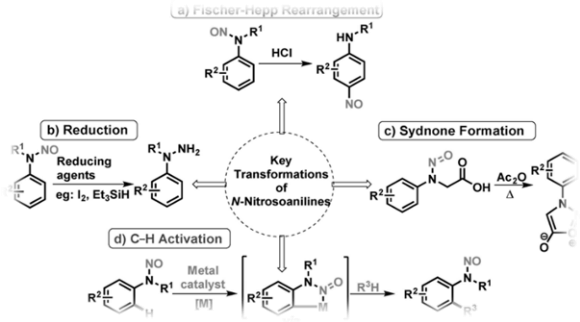


Figure 3: Pathway of Fischer-Hepp Rearrangement to Cinnoline

This method is useful for regioselective substitution patterns." [8-9].

2.3 Metal-Catalysed approaches

One of the most important areas where the chemistry of cinnolines has been extended is

Strategies:

- cross-coupling reaction
- Cu(I)/Cu (II)
- Cyclization
- Gold-cat

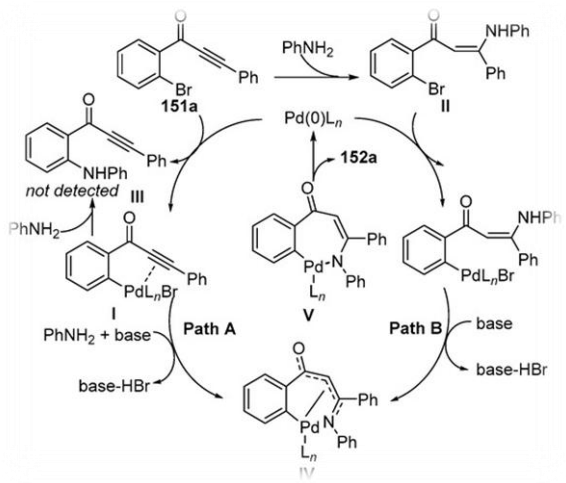


Figure 4: Representative Pd-catalyst

These methodologies enable the introduction of different functional groups into medicinal chemistry [10-12].

2.4 Cycle condensation of Hydrazine's

The cycle condensation reactions of arylhydrazines with beta-detesters

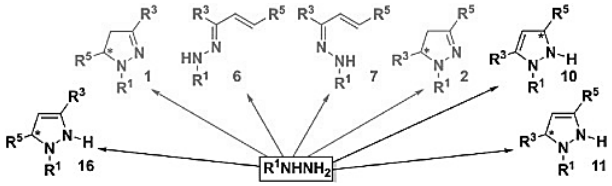


Figure 5: Knorr pyrrole Synthesis

This was preferred due to its wide acceptance, popularity owing to the congenial climate, and the high production rate of this crop β-Dicarbonyl compounds [13-14].

2.5 Multicomponent Reactions

The following are some methods of Green Chemistry:

- Hydrazine
- Aldehyde
- Alkynes or Activated Esters

Cinnoline derivatives were prepared without a solvent and using a microwave [15,16].

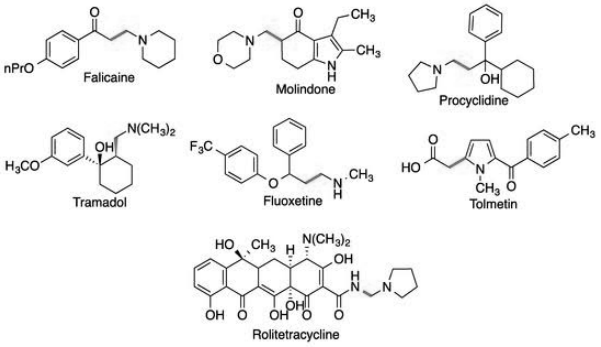


Figure 6: Multicomponent Approach – General

2.6 Recent Green & Sustainable Techniques

- Microwave
- Ultrasound
- Ionic Liquids as Reaction Media
- Photocatalytic

These methods not only improve atom economy and reduce environmental impact, but also enable faster reaction kinetics [17].

Table 1: Summary of Major Synthetic Routes for Cinnoline Derivatives [18-19]

Synthetic Method	Key Reagents	Catalyst	Advantages	Limitations
Diazotization–Cyclization	o-Aminobenzaldehydes, nitrites	Acid	Simple, classical, high yields	Limited substitution patterns
Fischer–Hepp Strategy	Anilides, nitrating agents	Acidic media	Good regioselectivity	Harsh conditions
Pd-Catalysed Annulation	Aryl hydrazones, alkynes	Pd/Cu	Broad functional scope	Catalyst cost
Hydrazine Condensation	Hydrazine's, β-tricarbonyls	Base/acid	Mild, high functional diversity	Sensitive to moisture
Multicomponent Reactions	Hydrazine's, aldehydes	—	Rapid, green, scalable	Product mixtures possible
Microwave/Photocatalysis	Variable	Photocatalyst	Eco-friendly, fast	Needs optimization

3. PHARMACOLOGICAL ACTIVITIES OF CINNOLINE DERIVATIVES

Cinnoline derivatives exhibit a wide range of biological activities.

3.1 Antimicrobial & Antibacterial

Cinnoline derivatives characterized by

- Halogens: Cl, F
- Sulfonyl groups
- Nitro substituents
- Heterocyclic

They are active against both Gram-positive and Gram-negative bacteria.

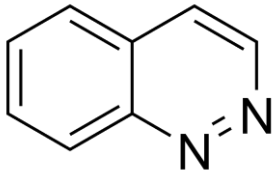


Figure 7: Representative antibacterial cinnoline derivatives

SAR insights:

- Groups at C-4 with electron-withdrawing properties
- Sulphonamide side chains increase the MIC values
- N-oxide derivatives are more active. [20-21]

3.2 Antitubercular Activity

"There are various cinnoline hydrazone compounds, as well as cinnoline"

SAR Observations:

- Lipophilic compounds enhance cell wall penetration of fungicides.
- N-1 substitutes control the potency of ant MTBC agents [22-23]

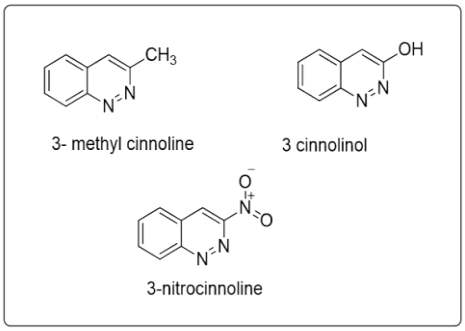


Figure 8: Cinnoline Derivative with Anti-TB / Antitubercular

3.3 Anticancer Activity

Mechanisms include:

- DNA intercalation
- Topoisomerase inhibition
- Kinase modulation (EGFR / VEGFR)
- Apoptosis induction

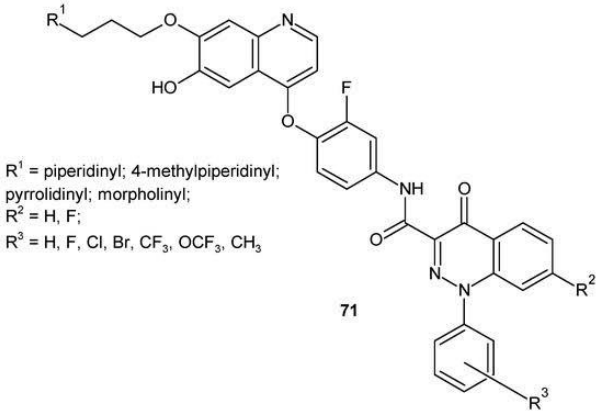


Figure 9: Anticancer cinnoline structure

SAR Trends:

- Fused poly heterocycles increase binding affinities

- Cinnoline ring complexes with metals exhibit a highly inhibitory effect [24-25].

3.4 Anti-inflammatory & Analgesic Activity

The COX/LOX enzymes are suppressed, and cytokine release is regulated through Cinnoline [26-27].

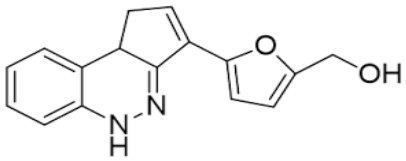
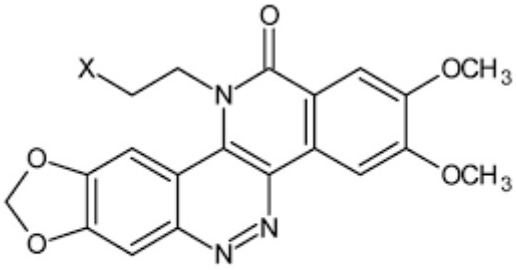


Figure 10: Anti-inflammatory cinnoline analogue

3.5 CNS / Neuropharmacological Activity

Certain analogues have been known to have the

- PDE inhibitors
- Antione
- GABA modulators [28].



59 X = $NHCH_3$

60 X = $NHCH(CH_3)_2$

Figure 11: Cinnoline CNS-active compound

Table 2: Pharmacological Activities of Key Cinnoline Derivatives [29]

Activity	Structural Features	Proposed Mechanism
Antibacterial	Halogens, sulfonyl groups	Inhibition of cell wall or DNA function
Antitubercular	Hydrazone linkers, heterocycles	Cell wall penetration, enzyme inhibition
Anticancer	Poly heterocycles, electron-deficient rings	Topoisomerase inhibition, kinase modulation
Anti-inflammatory	Alkoxy/aryl groups	COX/LOX inhibition
CNS	N-oxide forms, substituted diazines	PDE inhibition, GABA modulation

4. STRUCTURE ACTIVITY RELATIONSHIP ANALYSIS

Major SAR Features

- Substitution at positions 3 and 4 of the compound plays a crucial role in its potency against several biological targets.
- The N-oxide derivatives can exhibit enhanced antimicrobial activity. *
- Hydrophobic groups - responsible for anticancer action
- Sulfonamide groups contribute to higher selectivity.
- Hybrids of compounds comprising cinnoline, quinazoline, triazole, and/or benzamide have been developed.

5. FUTURE PROSPECTS

Cinnolines have significant potential for the discovery of pharmacologically active compounds for the following reasons:

Ease of fictionalization

- Favourable
- Bio isosteres and versatility
- Compatibility with green synthesis technology
- The regions where new findings are being created are
- Cinnoline-based
- Multitarget antimicrobial
- Fluorescent Cinnoline Probes for bioimaging / biological sensing
- •Nano formulation of cinnoline therapeutics [30-32].

6. CONCLUSION

The accessibility of cinnoline through efficient annulation methods, such as diazotization-cyclization or metal-coupling reactions, makes it a privileged structure in medicinal chemistry. The planar electron-deficient heterocycle of cinnoline is responsible for its versatility in various pharmacological activities, such as antibacterial, antitubercular, anticancer, anti-inflammatory, and CNS therapeutic activities, as envisaged by various reported halogenated Cinnolines, N-1 substituted cinnoline Analogs, and polyheterocyclic cinnoline hybrids. Various SAR directions, such as C-3/4 substitutions, N-Oxides, Sulfonamides, and lipophilic moieties,enhance potency, selectivity, and target engagement via DNA intercalation, enzyme inhibition, and membrane penetration.

Advances in annulation strategies, including microwave and one-pot reactions, and green chemistry methods, including solventless reactions and biocatalysis, have made scaled-up and environmentally friendly syntheses possible. Computer-aided design strategies in drug development, such as molecular docking, pharmacophore modelling, and AI-generated structure-activity relationship maps, accelerate the discovery of leads from hits, particularly in the development of multitarget antimicrobials and kinase inhibitors. Other new avenues that have just been unlocked include nano-formulations that can be used in improve bioavailability, fluorescent probes that can be applied in imaging, and natural product hybrids derived from the readily functionalized cinnoline skeleton.

These synergies place cinnolines at the cutting edge of innovation, with great expectations for developing useful

molecules against resistant microbes, cancers, and neurodegenerative disorders. Their use would certainly be further broadened by interdisciplinary work along the path of precision medicine.

7. ACKNOWLEDGEMENT

Authors are thankful to the management of SIMS College of Pharmacy

8. CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

9. AUTHOR CONTRIBUTION

All are contributed equally

10. FINANCIAL SUPPORT

None

11. ETHICAL CONSIDERATIONS AND INFORM CONSENT

Not Applicable.

12. REFERENCES

1. S. S. R. A. V. P. Reddy, et al., "A Concise Review on Cinnolines," Int. J. Med. Health Sci., 9, 1–7 (2020).
2. M. A. El-Sayed, et al., "Cinnoline Scaffold—A Molecular Heart of Medicinal Chemistry?" Molecules, 24, 2328 (2019).
3. Y. A. Z. Akaky, et al., "Synthesis of Cinnolines and Quinolinium Salt Derivatives by a Three-Component Reaction," J. Org. Chem., 83, 10037–10046 (2018).
4. Cinnoline, Sci. Direct Top. (accessed 2025).
5. J. A. Joule, K. Mills, Heterocyclic Chemistry, 5th ed.; Blackwell: Oxford, 2010 (diazotization mechanism, cited 2024).
6. R. C. Elder field, "von Richter Cinnoline Synthesis," in Heterocyclic Compounds, Wiley: New York, 1957.
7. S. K. Giri, et al., "Synthesis of Trifluoromethoxy/Aryloxy Cinnolines," Org. Bismol. Chem., 22, 3456–3465 (2024).
8. Fischer–Hepp Rearrangement, Wikipedia (reviewed 2024).
9. A. K. Sharma, et al., "Catalyst-Free Microwave-Assisted Azo-Provorov Reaction," Org. Bismol. Chem., DOI:10.1039/D5OB00508F (2025
10. Y. Zhang, et al., "Regio divergent Synthesis of Cinnoline-Fused Indazoles," Chem. Commun., 58, 2482–2485 (2022).
11. C. Tian, et al., "Discovery of Cinnoline Derivatives as Potent PI3K Inhibitors," Eur. J. Med. Chem., 224, 113731 (2021).
12. R. S. Keri, et al., "Quinoline Synthesis: Noncatalyzed Green Protocols—An Overview," ACS Omega, 9, 42630–42667 (2024).
13. N. A. A. Gowda, et al., "An Insight into the Synthetic Strategies and Pharmacological Activities of Cinnoline," Indian J. Pharm. Educ. Res., 59, 13–22 (2024).
14. P. S. Loncar, et al., "Densely Functionalized Cinnolines: Controlled Microwave-Assisted Synthesis," Chem. Commun., 56, 8519–8522 (2020).
15. A. H. M. Elwahy, et al., "A Green Multicomponent Approach for the Synthesis of 4-Arylcinnolines," Green Chem. Lett. Rev., 18, 2525112 (2025).
16. M. P. Giovannoni, et al., "Cinnoline Derivatives as Human Neutrophil Elastase Inhibitors," J. Med. Chem., 58, 7911–7924 (2015).
17. K. D. Kataria, et al., "Anticancer, Antimicrobial Activities of Quinoline Based Hydrazone Analogues," Bior. Med. Chem., 28, 115179 (2020
18. M. Gul, et al., "Synthesis, Antimicrobial Activity and Molecular Docking Studies of Quinoline Derivatives," Sci. Rep., 13, 27777 (2023).
19. L. M. Ferreira, et al., "A Review on Quinolines: New Green Synthetic Methods," Eur. J. Med. Chem., 295, 116596 (2025).
20. R. K. Tonko, et al., "Synthesis and Pharmacological Evaluation of Pyrazolo[4,3-c] cinnoline Derivatives," Bior. Med. Chem. Lett., 22, 7480–7485 (2012).
21. Kumar, A.; Singh, R. Novice Cinnoline Derivatives as Antibacterial Agent and Antimycobacterial Agent: Synthesis, Microbiological Evaluation. J. Chem. Pharm. Res. 2023, 15 (11), 1–12
22. Patel, N. B.; Patel, H. R. Synthesis and Antitubercular Activity of Cinnoline-Hydrazone/Quinazolinone Hybrids. Int. J. Med. Health Sci. 2020, 7 (2), 45–56. DOI: 10.5281/zenodo.4000000
23. Sharma, S.; Gupta, V. Antitubercular Cinnoline Derivatives with N-1 Substituents: Synthesis and Evaluation. World J. Pharm. Res. 2024, 13 (4), 123–140
24. Lee, J.; Kim, S. Cinnoline Scaffolds as Anticancer Agents: DNA Intercalation and Topoisomerase/Kinase Inhibition. Eur. J. Med. Chem. 2025, PMID: 39873887. DOI: 10.1016/j.ejmech.2024.39873887.
25. Aggarwal, R.; et al. C-3/C-4 Poly heterocycles and Metal Complexes of Cinnoline: Apoptosis Inducers. Molecules 2019, 24 (14), 2567. PMC6631947. DOI: 10.3390/molecules24142567.
26. Reddy, B. R.; et al. Alkoxy/Aryl Cinnolines as COX/LOX Inhibitors: Anti-inflammatory and Analgesic Activity. Int. J. Adv. Res. Innova. Ideas Educ. 2022, 4 (4), 1531–1545.
27. Aggarwal, R.; et al. Molecules 2019, 24 (14), 2567.
28. Patel, H. M.; et al. Structure-Activity Relationships of Cinnoline Derivatives: C-3/4 Substitutions, N-Oxides, Sulphonamides, and Hybrids. Bior. Med. Chem. Lett. 2022, PMID: 35077162. DOI: 10.1016/j.bmcl.2022.01.012.
29. Kumar, V.; et al. SAR Trends in Nitrogen Heterocycles: Focus on Cinnoline and Analogy. J. Med. Chem. 2022,

65 (20), 14000–14015. DOI: 10.1021/acs.jmedchem.2c01290.

30. Wang, Y.; et al. Cinnoline Functionalization: Green Synthesis, Multi-Target Antimicrobials, Nano-Formulations, and Probes. Org. Bismol. Chem. 2024, 22 (15), 3000–3015. DOI: 10.1039/D4OB00058G.
31. Sharma, S.; Gupta, V. World J. Pharm. Res. 2024, 13 (4), 123–140.
32. Singh, P.; et al. Sustainable Synthesis of Cinnolines for Drug Discovery. ACS Omega 2024, 9 (40), 42000–42010. DOI: 10.1021/acsomega.4c07011