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REVIEW ARTICLE
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A Concise Review on Cinnolines

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Abstract
Cinnoline (1, 2 benzodiazine or pyridine) is a novel aromatic bioactive heterocyclic compound which have wide range of pharmacological profiles like antimicrobial activity like antibacterial, antifungal, anti-inflammatory, antihelminthic activity, anti molluscicidal activity, antimalarial, anti-tuberculosis, anti tumor activity etc.Cinnoline has a heterocyclic system, which is fused six member ring containing two nitrogen atoms with special structural activity have been showed special interest in chemical or synthetic research field. This review critically discusses about the synthesis, wide range of activities and applications of Cinnoline aromatic compound. Apart from that, this review is also enlisted the various reported literature based on advanced synthesis and application of Cinnoline in various biological activities.
Keywords: 1 2 benzodiazine, cyclization reaction, cinn-tillating synthesis, biological activities

1 | INTRODUCTION

Cinnoline is a 1,2-diazanaphthalene or benzo[c]-1,2-diazine (Hantsch- Widmann system), $C_8H_6N_2$ is a nitrogenous organic base, obtained from certain complex diazocompounds. Their system is an isosteric relative to either quinoline or isoquinoline. The synthesis of its nucleus was first carried out by V. Richter in1883, after whom this heterocyclic system is named. (1) Cinnoline and its derivatives have received considerable interest due to their wide range of pharmacological profiles e.g; antibacterial, antitumor, antifungal, and anti-inflammatory activities. Certain compounds of the cinnoline series have antithrombotic and antituberculosis properties and also exhibit anaesthetizing and sedative activity, in addition to their use as agrochemicals. (2) Cinnoline is a pale yellow solid, m.p. 39°C, a six-membered heterocyclic compound having two hetero atoms in the ring having pKa of 2.64. They are reactive by virtue of the presence of a benzene ring and the electrophillic attack takes place in this ring. (3)

Supplementary information The online version of this article (https://doi.org/10.15520/ijmhs.v10i03.2829) contains supplementary material, which is available to authorized users.

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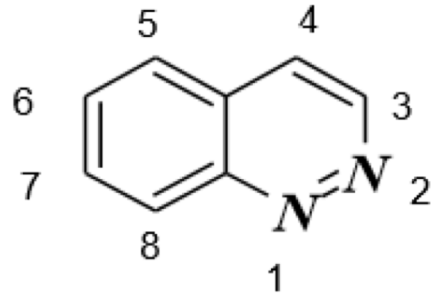


FIGURE 1:

SYNTHESIS OF CINNOLINE DERIVATIVES:

The chemistry of compounds of the cinnoline series is a vigorously developing branch of organic chemistry in so far as the compounds exhibit a broad range of biological activity. In recent years a large number of papers have appeared on research into the biological activity of compounds of the cinnoline series.

The cinnoline ring was first synthesized by Richter during the diazotization of ortho-aminophenylpropionic acid and cyclization of the obtained arenediazonium salt.

ARYLHYDRAZONES AND ARYLHYDRAZINES AS PRECURSSORS OF CINNOLINE:

This approach is the most universal since it makes it possible to obtain derivatives of cinnoline with various types of substituents at various positions and includes methods in which the cinnoline system is formed at various positions of the pyridazine ring. As a rule, ring closure occurs during an attack of the amino group at a CC, CO or CN multiple bonds.

An example of the production of cinnoline through the formation of the N (2)- C (3) bond is the classical method for the synthesis of 3-hydroxycinnolines- the Neber-Bossel method. During the diazotization of (2-aminophenyl), hydroxyacetates and reduction of the diazonium salt the obtained hydrazine undergo cyclization to 3-hydroxycinnoline when boiled in HCl. Substituents in the aromatic ring have an appreciable effect on the course of cyclization, and in the case of the unsubstituted and 4-chloro-substituted ring, the yields of the desired compounds are 60 and 70% respectively.

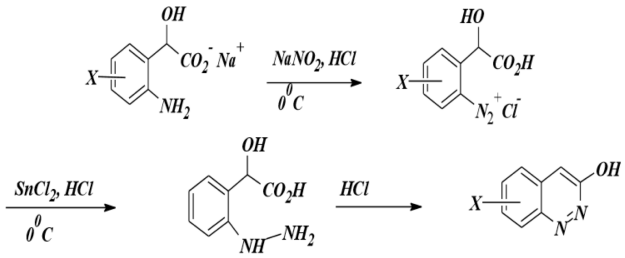


FIGURE 2:

While studying the chemistry of the anion-activated CF_3 group Kiselev's group showed that the hydrazones obtained from orthotrifluoromethylarylhydrazines and benzaldehydes undergo cyclization by the action of a base, forming a pyridazine ring.

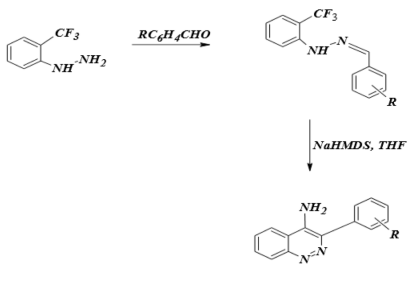


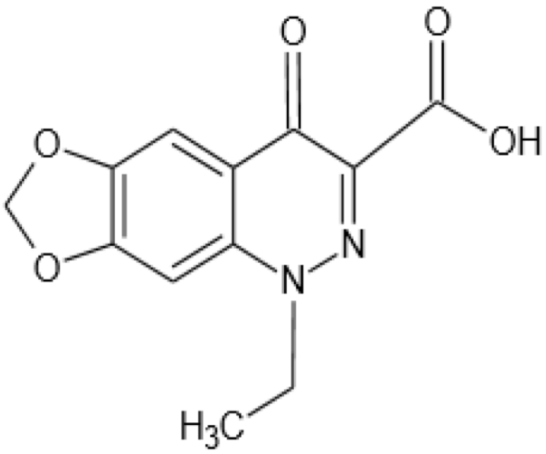
FIGURE 3:

CYCLIZATION OF ARENEDIAZONIUM SALTS :

This group of methods includes the first examples of the synthesis of the cinnoline system: Richter, Widman-Stoermer, and Borsche – Herbert cyclizations.

In the middle of the last century, the Borsche and Herbert reaction were widely used as the method for the production of 4hydroxycinnolines. The method involves diazotization of ortho-aminoacetophenones followed by cyclization of the obtained arenediazonium salt. The reaction is fairly universal and makes it possible to obtain a wide range of cinnoline derivatives containing substituents at various positions of the ring; yields here amount to 70-90%. Diazotization is carried with $NaNO_2$ in hydrochloric, sulphuric or formic acids. (4)

Various literature reviews collected shows that cinnoline nucleus is having antimicrobial, anti-inflammatory, anti-cancer, antithrombocytic,



Cinnoxacin

FIGURE 4:

anti-tuberculosis, analgesic, antidepressant, anti-convulsant, sedative activities.

BIOLOGICAL ACTIVITIES:

Antibacterial activity Kalyani G, Srinivas Bethi, Sastry K.V, Vijaya Kuchana; 2017 designed (5) and synthesized a series of novel cinnoline fused Mannich bases by the condensation reaction of 4-methyl-3-acetyl cinnoline with different secondary aromatic and aliphatic amines. The biological potential of newly synthesized compounds are evaluated for their antibacterial activity against Staphylococcus aureus (Gram positive), and Escherichia coli (Gram negative) bacteria. Compounds having larger hydrophobic substitutions such as di phenyl and di cyclohexane groups at amino group creating bulkier region resulted in relatively higher antibacterial against S. aureus and E. coli when compared to Streptomycin. (6)

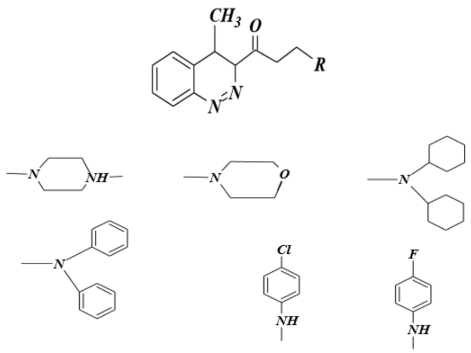


FIGURE 5:

FIGURE 6:

S. Hurmath Unnissa and Divya Rajan; 2016 synthesized a series of Pyridazine derivatives by diazotization of substituted anilines followed by Friedel-Crafts acylation and coupling to form corresponding hydrazones which on Intramolecular cyclization forms 3acetyl-substituted Benz pyridazine-4(1H)-one. Further condensation reaction by treatment with hydrazine hydrate yields the expected 3'-methy-substituted –pyrazolo[4,3-C] Cinnoline derivatives. All the synthesized compounds were checked for drug likeliness using Molinspiration software and toxicity prediction studies were conducted using Protox and Gusar software and found to be efficatious and Sreening for antimicrobial activity studies. Evaluation of the results from anti-bacterial studies showed that synthesized Pyridazine derivatives exhibit moderate to good antibacterial with a zone of inhibition were found to be in the range of (5-30mm) as compared to standard ciprofloxacin(10μg/disc). The MIC of synthesized compounds for antibacterial activity was found to be in the range of 1.2 to 5.2 μg/ml. (7)

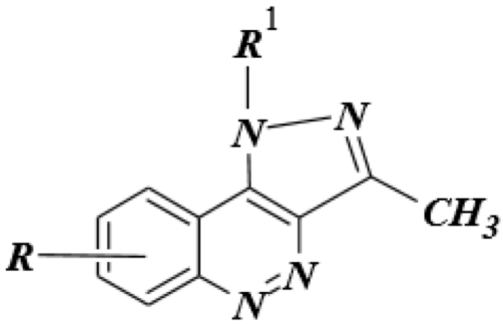


FIGURE 7:

Jyoti Chaudhary, Khusbu Patel, Dr.C.N.Patel; 2014 synthesized novel series of Cinnoline with Pyrazoline or without Pyrazoline condensed derivatives for anti-bacterial activity. Compound 3-chloro-4-fluoro aniline on coupling diazotization and cyclic condensation reaction to yield 3- acetyl-7-chloro-6-fluoro cinnoline-4(1H)-one. Compound undergoes Claisen-Schmidt condensation with aromatic benzaldehyde to

afford the corresponding 7-chloro-6-fluoro-3-[-3-substituted phenylprop-2-enoyl] cinnoline-4(3H)-one in good yields. Cyclocondensation of compounds with phenyl hydrazine yields 7-chloro-6-fluoro-3- [5(substituted phenyl)1-phenyl-4,5-dihydro-1H-pyrazol-3-yl] cinnoline-4(3H)-one. The newly synthesized compounds have been characterized by IR, 1HNMR and Mass spectral studies. All the newly synthesized compounds were screened for their antibacterial activity against Gram Positive S. aureus and B. subtilis and Gram Negative E. coli bacteria by cup plate method at different concentrations ranges from 100 to 500μg/ml. The study revealed that electron withdrawing group in cinnoline without pyrazoline compounds and hydroxy series in cinnoline with pyrzoline compounds have increased antibacterial activity against gram positive and gram negative bacteria. (8)

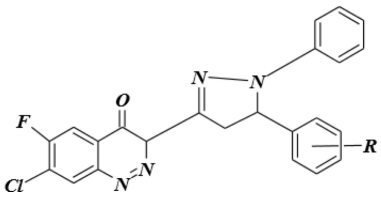


FIGURE 8:

Cinnoline itself is toxic and shows antibacterial activity against Escherichia coli . None of its derivatives have been found in nature. The synthesis of its nucleus was first carried out by V. Richter in 1883, after whom this heterocyclic system is named (9). Although its derivatives have been reviewed in many books and journals, only some of them reported biological properties (10–12). This review includes papers and patents after 1945 because earlier data are scarce. In 1957, Jacobs in his review on cinnoline and related compounds pointed out that this ring system was the least known of the condensed, bicyclic aromatic heterocycles containing two nitrogen atoms. Since then a significant interest in the synthesis of compounds possessing the cinnoline ring system has developed. Some cinnolines have been screened and have received approval as bioactive drugs or are still under clinical trials. Of all substituted cinnolines, which have been prepared, mainly amino cinnolines are known to have biological activity. With the view of discovering a new antimalarial drugs such as chloroquine analogs, the derivatives of 4-aminocinnolines 2 were synthesized by Keneford et al. Biological tests demonstrated that some of them showed significant activity . A year later in 1948, Kornfeld synthesized a series of 1,2-dihydrocinnolines to investigate compounds with possible estrogen-like activity, but the compound 3 exhibited only a weak estrogen activity.

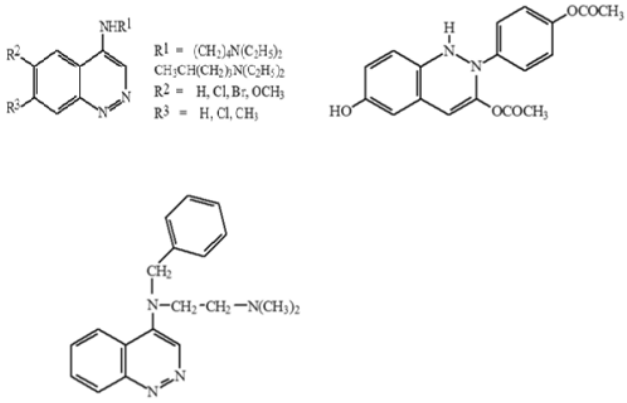


FIGURE 9:

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