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A concise review on cinnoline and its biological activities

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ABSTRACT

Cinnoline is an aromatic heterocyclic compound having a wide range of pharmacological actions like antibacterial, antifungal, anti-inflammatory, anti-tuberculosis, antiepileptic, antidepressant, antitumor, antihypertensive, antianxiety activities. Cinnoline is a fused six membered ring with two nitrogen atoms as heteroatoms which is an isosteric derivative to quinolone or isoquinoline. This heterocyclic nucleus is the least condensed one and is having a special interest in the synthetic research field. This review discusses the biological activities of cinnoline compounds with different substitutions.

Keywords— *Cinnoline, Cyclization, Biological activities*

1. INTRODUCTION

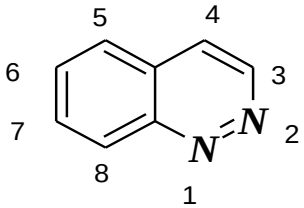
Medicinal Chemistry is a discipline at the intersection of chemistry and pharmacology that involves the identification, synthesis, and development of new chemical entities that are suitable for medical or pharmaceutical use. It deals with the design and synthesis of new molecules, ascertain how they interact with biological macromolecules (such as proteins or nucleic acids), elucidate the relationship between their structure and biological activities, determine their absorption and distribution throughout the body and evaluate their metabolic transformations. [1]

Drug design is an integrated advancing discipline, in which a biologically active molecule is produced by chemical synthesis followed by an evaluation of its activity and toxicological studies with the limitation of trial-and-error screening. [2]
Heterocyclic compounds are the cyclic organic compounds which contain at least one hetero atom, the most common hetero atoms are the Nitrogen, Oxygen, and Sulphur but heterocyclic rings containing other hetero atoms are also widely known. Heterocyclic compounds considered one of the vital classes of organic compounds, which are used in many biological fields, due to its activity in multiple illnesses. There are a lot of heterocyclic compounds which are having application in many common diseases and are used as antimicrobial herbicides, urinary antiseptics, and anti-inflammatory agents. Heterocycles have been found a key structural in medical chemistry and also they are frequently found in large percent in biomolecules such as enzyme, vitamins, natural products and biologically active compounds including antifungal, anti-inflammatory, antibacterial, antioxidant, anticonvulsant, anti-allergic, enzyme inhibitors, herbicidal activity, anti-HIV, antidiabetic, anticancer activity, insecticidal agents. [3]

1.1 CINNOLINE

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.[4]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. [5]

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. [6]



1.2 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.

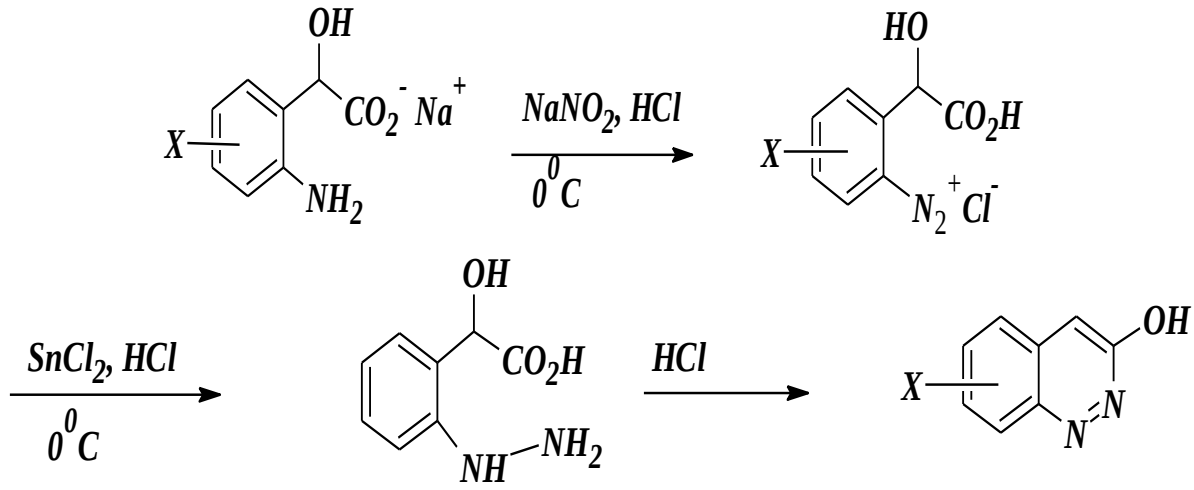
The cinnoline ring was first synthesized by Richter during the diazotization of *ortho*-amino-phenylpropionic acid and cyclization of the obtained arenediazonium salt.

2. 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.

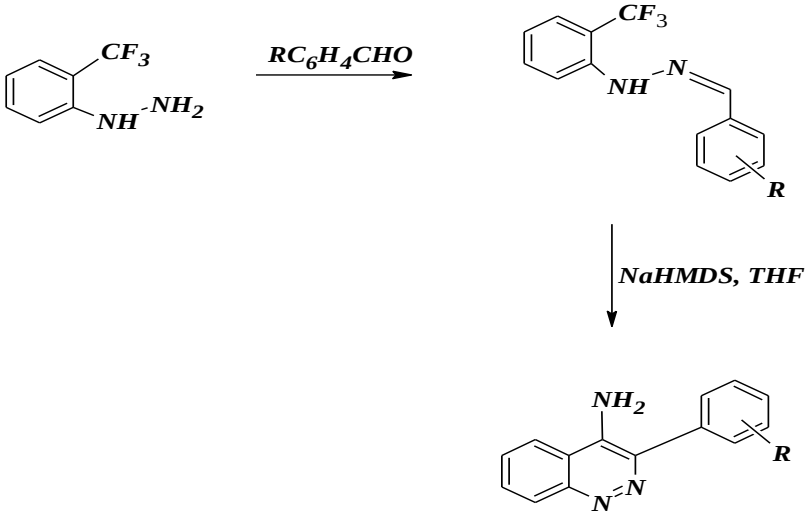
a) An example of the production of cinnoline through the formation of the N (2)- C (3) bond is the classical method for the synthesis of 3-hydroxycinnolines-the Neber-Bossel method. During the diazotization of (2-aminophenyl), hydroxyacetates and reduction of the diazonium salt the obtained hydrazine 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.

b)



X=H, Cl

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

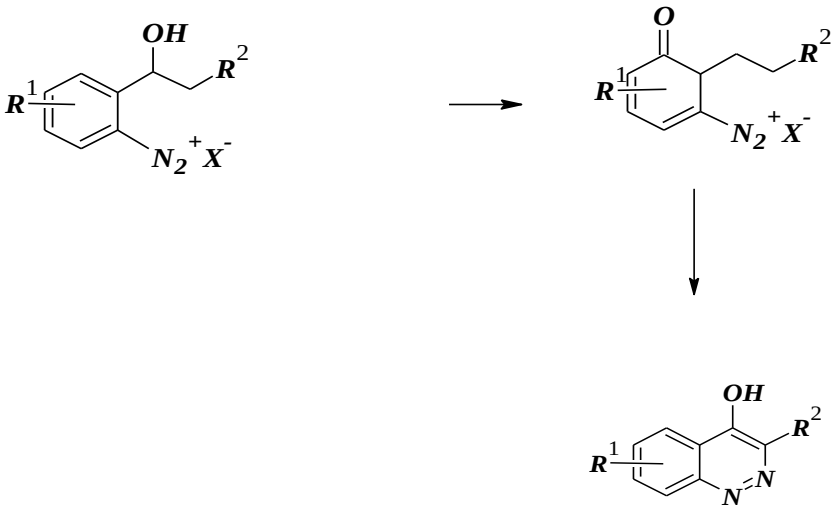


R=H, F, Cl, Me, OMe, Pyr

3. CYCLIZATION OF ARENEDIAZONIUM SALTS

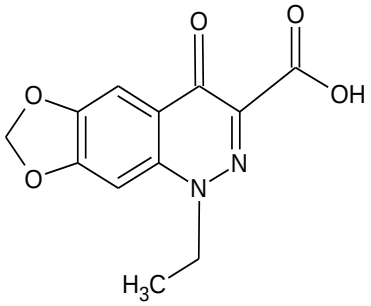
This group of methods includes the first examples of the synthesis of the cinnoline system: Richter, Widman-Stoermer, and Borsche – Herbert cyclizations.

In the middle of the last century, the Borsche and Herbert reaction were widely used as the method for the production of 4-hydroxycinnolines. 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.[7]

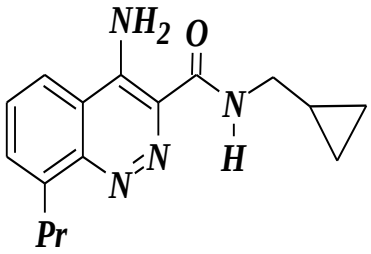


R2 = H, Hal, Alk, Aryl

Significant commercial interest in the development of benzopyridazine derivatives, particularly pharmaceutical uses of pyridazines and cinnolines is shown by a large number of patents filed in this area. Their ring system is an isosteric relative to either quinolone or isoquinoline, therefore, in many cases the synthesized compounds were designed as analogs of previously obtained quinolone or isoquinoline derivatives; for example, cinoxacin (1) is a cinnoline analogue of the quinolone antibacterials used for urinary tract infections and ICI-D-7569(2) is an anxiolytic agent. [5]



Cinnoxacin



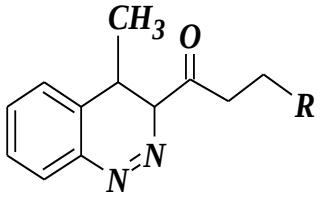
ICI-D-7569

Various literature reviews collected shows that cinnoline nucleus is having antimicrobial, anti-inflammatory, anti-cancer, antithrombocytic, anti-tuberculosis, analgesic, antidepressant, anti-convulsant, sedative activities.

4. BIOLOGICAL ACTIVITIES

4.1 Antibacterial activity

Kalyani G, Srinivas Bethi, Sastry K.V, Vijaya Kuchana; 2017 designed 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. [19]



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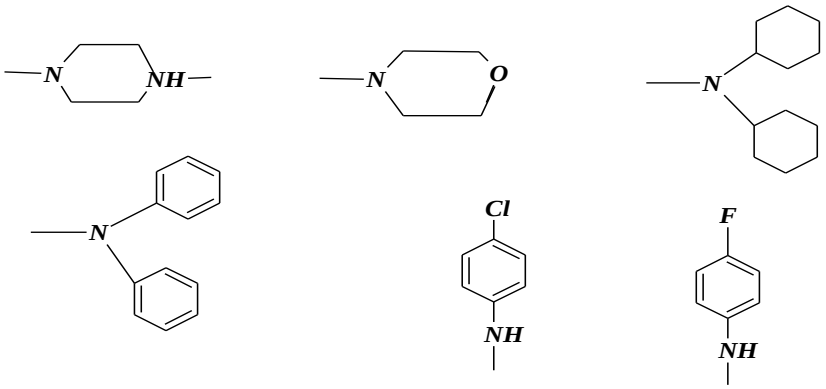
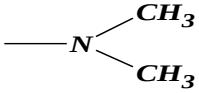
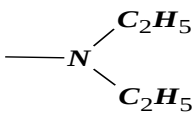
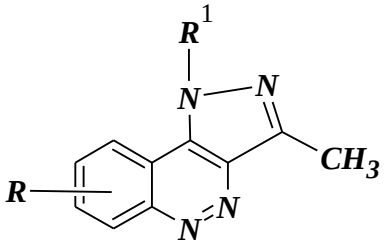


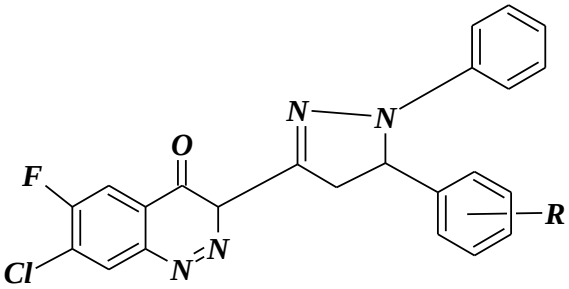



S. Hurmath Unnissa and Divya Rajan; 2016 synthesized a series of Pyridazine derivatives by diazotization of substituted anilines followed by Friedel-Crafts acylation and coupling to form corresponding hydrazones which on Intramolecular cyclization forms 3-acetyl-substituted Benz pyridazine-4(1H)-one. 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. [20]



PZ-1: R = Cl, R_1=H PZ-3: R= F, R_1= C_6H_5 PZ-5: R=SO_2NH_2, R_1= H
PZ-2: R= Cl, R_1 = C_6H_5 PZ-4: R=NO_2, R_1=H PZ-6: R=SO_2NH_2, R_1= C_6H_5

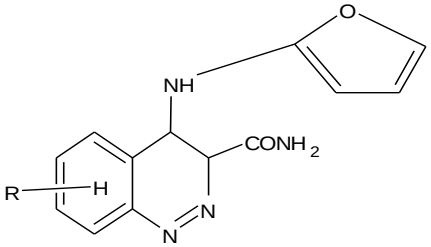
Jyoti Chaudhary, Khusbu Patel, Dr.C.N.Patel; 2014 synthesized novel series of Cinnoline with Pyrazoline or without Pyrazoline condensed derivatives for anti-bacterial activity. Compound 3-chloro-4-fluoro aniline on coupling diazotization and cyclic condensation reaction to yield 3- acetyl-7-chloro-6-fluoro 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, ^{1}HNMR 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. [21]



R = 4-OCH_3, 4-Cl, 2-OH, 4-OH, 4-NO_2, H

4.2 Anti-inflammatory activity

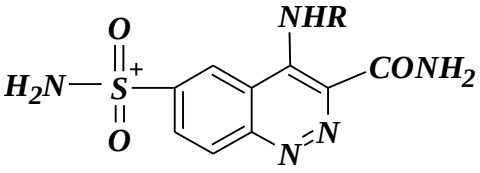
Mishra Pankaj, Saxena Vikas, Kesheri Minu, Saxena Abhishek; 2015 synthesized a series of substituted cinnoline furan derivatives followed by diazotization using substituted anilines and then treated with cyanoacetamide. The resulting compound was refluxed with chlorobenzene and aluminum chloride and then with 2-chloro furan. The compounds which are halogen mainly Chloro substituted were showed potent antibacterial, anti-inflammatory and anti-fungal activity than other compounds. Methyl substituted compound also showed more potent antimicrobial and anti-inflammatory activity. [22]



R = 2-nitro, 4-nitro, 4-chloro,4-bromo, 3,4-dinitro, 2-methyl, 3-chloro, 2-fluoro, 2,3-dichloro, 3-nitro

Anurag Singh, Dr.LVG Nargund; 2015 synthesized 6-sulphonamido-cinnolines and their purification and characterization reaction and were screened for antibacterial, anti-oxidant and *invitro* anti-inflammatory activity using bovine serum albumin denaturation model. Sulphanilamide was treated with sodium nitrite in presence of Conc. HCl at 0-5°C to form diazonium salt, which on treatment

with cyanoacetamide gave aryl hydrazine (cyano)acetamide. It was allowed to react with anhydrous $AlCl_3$ in the presence of chlorobenzene to form 4-amino-6-sulphonamido-3-cinnolo carboxamides. This on treatment with formamide gave sulphonamido-cinnolino-pyramidine. 6-suphonamide cinnoline derivatives identified and characterized by physical methods like melting point, TLC and spectral method UV, IR, NMR data. The newly synthesized compounds were investigated for their microbial susceptibility using *invitro* model for against *Bacillus subtilis* (gram positive) *E. coli* (gram negative). The compounds were also subjected for bovine serum albumin denaturation which was considered as *invitro* anti-inflammatory activity model. Substituted pyrimidine ring in cinnoline molecule demonstrated good activity. Cinnoline schiff's base derivatives against Bovine Serum Denaturation present electron donating group like (OH) at *ortho* and *meta* position demonstrated very good activity. [23]



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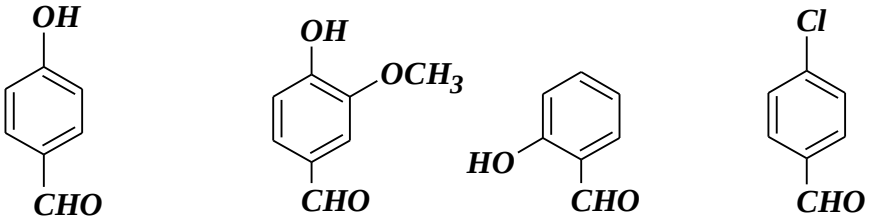

4.3 Analgesic activity

Rajiv.K. Tonk, Sandhya Bawa, Gita Chawla, Suresh Kumar, Himanshu Gupta and Obaid Afzal; 2012 synthesized new series of compounds containing pyrazole moiety clubbed with the 1,2-diazanaphthalene ring, structurally related to celecoxib and naproxen. The compounds were evaluated for anti-inflammatory activity and the compounds showed marked anti-inflammatory activity were further tested for their analgesic, ulcerogenic and lipid peroxidation effect using naproxen as a reference drug. The result showed that the compounds containing groups Chlorine, Fluorine, phenyl, o-hydroxy pheny and p-methoxy phenyl exhibited good anti-inflammatory and analgesic activity with minimum gastric irritation. Compounds having chlorine and o-hydroxy phenyl and chlorine and p-methoxy phenyl emerged as a potent analgesic agent (with percentage protection of 68.72 and 67.68).

4.4 Antiepileptic activity

Moghal Zubair Khalid Baig *et al* synthesized cinnoline containing quinoxaline and cinnoline containing benzoxazine moieties. A series of 4-methyl-3-(quinoxalin-2-yl) cinnoline and 3-(4-methyl cinnolin-3yl)-2H-benzo[b][1,4]oxazine were synthesized from 4-methyl-3-acetyl cinnoline treated with o-phenylenediamine and o-amino phenol respectively. Mild to moderate antiepileptic activity was observed for all the synthesized compounds. The cinnoline derivatives with electron donors, more polarity nature substitutes (-OH, -COOH) have more potency over cinnoline derivatives with electron withdrawers and less polar nature substitutes (-Cl, $-NO_2$) towards antiepileptic activity.

4.5 Anti-tubercular activity

Hurmath Unnissa S, Ravi.T.K, and Sonia George; 2015 synthesized a series of 3-(5-substituted-1,3,4-oxadiazol-2-yl)-6-substituted cinnoline-4-ol and 5-(4-hydroxy-6-sustituted cinnolin-3-yl)-1,3,4-oxadiazole-2(3)-thione were synthesized from 4-hydroxy-6-substituted cinnoline-3-carbohydrazide. All the compounds were screened for their antifungal and anti-tubercular activity. The synthesized compounds were tested for activity against *Mycobacterium tuberculosis* $H_{37}Rv$ using Microplate alamar blue assay method. Compound ox-1 to ox-9 inhibited the growth of *Mycobactrium tuberculosis*.

4.6 Anti-tumor activity

Eman D.Awad *et al*; 2012 synthesized a series of 6-substituted – 4-methyl-3-(4-arylpiperazin-1-yl)cinnolines via intramolecular cyclization of the respective 1-(2-arylhydrazano)-1-(4-arylpierazin -1-yl)propan-2-ones mediated by polyphosphoric acid(PPA). The amidrazones themselves were synthesized via direct interaction of the appropriate hydrazonoyl chlorides with the corresponding N-substituted piperazine in the presence of trimethylamine. The anti-tumor, anti-bacterial and antifungal activity of the synthesized compounds were evaluated. The anti-tumor activity was characterized by cell viability assays using the tetrazolium dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) Cultures of MCF-7 breast cancer cells were treated first. Compounds 10b, 10d, and 8b showed potent anti-MCF-7 activity and were able to reduce the viability after 72 h to less than 50%.

4.7 Antidepressant activity

Kuppuswamy Nagarajan, Joy David, and Rashmi.K.Shah; 1975 synthesized a series of 5-oxo-1,4,5,6,7,8-hexahydrocinnolines and examined for their CNS activity. 1-(2-diethylaminoethyl)-3-(p-fluorophenyl)-5-oxo-7,7-dimethyl-1,4,5,6,7,8-hexahydrocinnolines and 1-(2-dimethylaminoethyl)-3-phenyl-5-oxo-7,7-dimethyl-1,4,5,6,7,8-hexahydrocinnoline had sedative and anti-convulsant properties and were also active in tests used characterize antidepressants.

The review article mentioned that the new group cinnoline condensed system, structurally related to earlier patented compounds, was also described by Takada *et al*. The synthesized pyrazolo [4,3-c] cinnolin-3-one analogues inhibited binding of ^{3}H-diazepam to the benzodiazepine receptor in rat cortex. The same activity was also reported in the Japanese Patent No.61161285. One of the synthesized compounds showed that the condensed pyrazolocinnoline systems are useful as psychotropic agents

5. CONCLUSION

The above given data clearly establish that cinnoline nucleus is having a wide range of biological activities like antibacterial, anti-inflammatory, analgesic, antitumor, antiepileptic activity, antidepressant activity, antituberculosis activity. This review was prepared with an intention to highlight the biological activities of cinnoline nucleus with different substitutions for further synthesis of novel cinnoline derivatives and its evaluation for certain pharmacological activities. Good antibacterial activities are possessed when electron withdrawing substituents are attached. Substitutions of cinnoline with chlorine and fluorine gives antibacterial activity. Halogen substituted cinnolines increase the anti-inflammatory activity as well as analgesic activity. Electron donating groups like (-OH, -COOH) increases antiepileptic activity when compared with electron withdrawing group substituted cinnolines. Fluorine and bromine substitutions increase the antitumor activity of cinnolopiperidine category compounds. Thus cinnoline nucleus with different substituents possesses different pharmacological activities. Hence this heterocyclic nucleus can be chosen for further investigational processes.

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