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Review Article

An Insight into the Synthetic Strategies and Pharmacological Effects of Cinnoline Derivatives

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ABSTRACT

The cinnoline ring is a new aromatic heterocyclic connected with two nitrogen atoms in a 6 membered ring and compounds containing this ring have been shown to have a wide variety of pharmacological effects. This review study extensively explains the synthetic strategy by which researchers have produced cinnoline derivatives reported to have numerous pharmacological effects, including antitubercular, antibacterial, anticancer, antimolluscidal, etc., The cinnoline moiety is a highly powerful lead that may give a range of pharmacological effects and this study provides brief information on the various synthesis techniques and pharmacological activity of reported cinnoline analogs that support this claim. This succinct review summarizes the several known cinnoline analogs, outlining their respective synthesis strategies and pharmacological activity and conclusively showing that the cinnoline moiety is a potent lead capable of producing a wide range of therapeutic actions. This article's literature review will serve as a springboard for further research into the synthesis of cinnoline derivatives, which in turn will aid in the creation of cinnoline-based compounds with improved pharmacokinetic and pharmacodynamic characteristics.

Keywords: Cinnoline, Aromatic, Synthesis, Pharmacokinetic, Heterocyclic, Pharmacological effects.

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INTRODUCTION

Heterocyclic compounds are those that include nitrogen, oxygen, or sulfur in addition to carbon.[1] The field of organic chemistry could not function without these substances. Numerous natural items include range of biological and pharmacological properties.[2-5] Cinnamicacid is a heterocyclic aromatic molecule also known as 1,2 diazanapthalene and benzo[c],1,2 diazine.[6,7] Figures 1 and 2 depict the basic structure and the structure based on the position of functional groups respectively.[8]

Cinnoline and its derivative are reported to possess various pharmacological activities antibacterial, antifungal, antituberculosis, anti-inflammatory, antitumor,[9-14] CNS depressant,[15] antiparasitic,[16,17] anti-infective,[18] antithrombotic, antihypertensive,[19] anti-molluscicidal,[20] Liver X Receptor inhibitor,[21] antipyretic, analgesic, insecticidal[22-24] and antirheumatic activities.[25,26] Furthermore, antiproliferative effects of cinnoline derivatives were found in 1997.[27] The sedative, anti-ulcer, anti-allergic and anti-fibrotic effects of cinnoline acyl derivatives are also noteworthy.[28] A cinnoline's central core may be processed into fluorescent material or dyes.[29,30]

Cinnoline has isosteric qualities with quinoline and isoquinoline, two other compounds with the chemical formula $C_8H_6N_2$. It is the diazo compound from which cinnoline and its derivatives are formed.[31] In 1883, Von Ritcher successfully synthesized cinnoline's nucleus. It has a melting point of 24-25°C,[32,33] and a light-yellow color when solid. Pthalazines may be synthesized by the cyclo-condensation of ortho-diacyl benzenes with hydrazine,[34] whereas cinnolines can be made from the intramolecular cyclization of ortho-alkenyl or ortho-alkynyl aryldiazonium salts. Similarly, 2,2'-dinitro biphenyls may be reduced to generate cinnolines.[35]

Among natural compounds, it was discovered that extracts of Cichorium endivia produced a new compound, 2-furanmethanol-(5'→11)-1,3-cyclopentadiene-[5,4-c]-1*H*-cinnoline (as seen in Figure 3) which was also reported to possess hepatoprotective effects. It was also reported in the study that *Cichorium endivia* L. Extract (CEE) constituent protects hepatic tissue from oxidative damage *in vitro* and *in vivo*, potentially due to the

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presence of -furanmethanol-(5'→11)-1,3-cyclopentadiene-[5,4-c]-1*H*-cinnoline and also does not cause acute oral toxicity.[36]

Table 1 provides information on many commercially available pharmaceuticals with a basic cinnoline nucleus having various actions. Cinnoxacin showed good antibacterial activity against gram-negative bacteria.[37] Sinofem acts as a plant regulator.[38] Schatz *et al.* (1968) discovered cinnopentazone[39] which showed the best anti-inflammatory properties. Merck *et al.* (1996) synthesized a drug; the trade name cinnofuradione[40] was introduced in medical practice.

Derivatives of cinnoline have been approved for use in agriculture and medicine because of their purported efficacy as microbicides, pollen suppressants, herbicides and fungicides.[41] Substituted analogues of 1,4-dihydro-4-oxo-1-phenyl-cinnoline-3-carboxylic acid depicted a new class of pollen suppressant agents for wheat (*Triticum aestivum* L.) as shown in Figure 4 Consequently, it is reasonable to infer that the cinnoline nucleus is a starting point for several medications that may target different kinds of receptors for the treatment of many disorders.[42] Figure 5 displays a selection of drugs containing a cinnoline nucleus, each of which has a unique pharmacological effect.

This review study highlights the many synthesis routes and pharmacological activities of the cinnoline moiety, which may pave the way for the inclusion of the same in drug design and the subsequent identification of novel lead compounds as Figure 5.[43-61]

General Methods of synthesis of cinnoline

Diazotization Reaction

By diazotizing o-amino phenyl propiolic acid in water at 70°C yields diazonium chloride. Cyclization of the intermediate molecule results in the isolation of 4-hydroxycinnoline-3-carboxylic acid with good yield while it was heated over its melting point, carbon dioxide was released and 4-hydroxycinnoline was produced.[62]

Alkalization reaction

Quinoxalin {2,3-c} cinnoline is easily synthesized from a number of 2-amino-3(2-nitrophenyl) quinoxalines through cyclization with metabolic KOH (heated). 2-aminoquinoxalines were cyclized and alkoxylated at the benzylic carbon by removing water, resulting in acetylated product.[63]

Cinn-tillating synthesis

Retro synthetic routes (cinn-tillating synthesis) of cinnoline were designed by tandem cupper catalyzed annulation to give hydrazine nucleophile.[64]

Synthesis and Biological Activity of Cinnoline Derivatives

Antimicrobial Activity

Recent decades have seen a dramatic rise in the prevalence of microbial infections, making them a major challenge for the healthcare system. Because of this, finding novel antimicrobial drugs is a challenging undertaking, but one that is necessary at present.[65] To create the cinnoline derivative, Vikas *et al.* (2009) diazotized substituted anilines and coupled them with cyanoacetamide in an aqueous ethanolic solution containing sodium acetate to form the appropriate hydrazone as shown in Figure 6. Intramolecular cyclization of the hydrazone with anhydrous $AlCl_3$ in chlorobenzene yielded the substituted phenyl 4-amino cinnoline 3-carboxamide (5a-i). For the synthesis of substituted 4-(p-amino phenyl sulphonamide) cinnoline 3-carboxamides 7a-i, the cinnoline derivatives obtained (5a-i) were reacted with p-acetamido benzene sulphonyl chloride, DMF and ammonia. The produced compounds were evaluated for their antimicrobial activity against both strains of bacteria (gram-positive and gram-negative) by utilizing the disk-diffusion technique. The findings indicated that sulphonamide derivatives of cinnoline (7b, 7g, 7h) had high antibacterial activity and it was determined that the range of the width of the zone of inhibition was between 17-22mm as compared to the standard antibiotic norfloxacin.[66]

To create cinnoline derivatives, Lettreuch *et al.* (2020) added a 2-nitrophenyl hydrazine derivative to methyl pyruvate in the presence of concentrated HCl at room temperature. The scheme for synthesis is shown in Figure 7 for the production of Z-2 nitrophenyl hydrazone. An additional reaction between the hydrazone derivatives and 1 equivalent of sodium dithionite produced the corresponding amine. Also, a new 3-methylcinnoline-4 (1H)-one derivative is made by reducing them with 10 equivalents of sodium dithionite.

S. aureus, S. epidermidis, B. Subtilis and *E. coli* were used to assess the antimicrobial activity of the synthesized compounds (gram negative bacteria). Mixture 4j has shown maximum bactericidal activity, with a zone of inhibition diameter value of 32 mg/mL.[67]

New thiazinothieno cinnoline compounds (b, c, d) (shown in Figure 8) were synthesized by Ahmed *et al.* (2019) by the reaction of 9-amino benzo[f, h]thienol[2, 3-c] cinnoline 8-carbonitrile with carbon disulfide, formamide and ammonium isothiocyanate. *Escherichia coli, Staphylococcus aureus, Bacillus subtilis and Klebsiella pneumoniae* were used to test the efficacy of compounds b, c and d produced for antimicrobial activity. The disc diffusion test was used to evaluate their efficacy against bacteria. Maximum Inhibitory Concentration (MIC) values were compared to assess antibacterial efficacy. Comparing the MIC values of several compounds against *E. coli*, it was observed that compound (c) had the greatest antibacterial activity, with a

value of 45 g/mL (compared to 7.25 g/mL for the conventional medication tetracycline).[68]

Antitumor Activity

Cancer treatment is a major challenge for contemporary medicine.[65] Yuounong *et al.* (2002) synthesized novel cinnoline analog by the method shown in Figure 9. Compound 2 was synthesized from the reaction of N, N-dimethyl formamide and orthophosphoric acid to obtain intermediates which were further treated with o-dinitrobenzene which served as a coupling reagent. The compounds obtained via this reaction were also reacted with DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone) gave naphthalene derivative which was reduced to 2(o-aminophenyl) 6,7-dimethoxynapthalene, Then, the diazotization of obtained compound produced the final product.

As compared to the conventional medication vinblastine, for which the IC_{50} value was determined to be 0.001 M, the synthesized molecule exhibited the strongest action against HeLa.[69]

N, N"-([1,1'-Biphenyl]-4,4'-diyl) bis (2-oxopropane hydrazonoyl chloride) was produced by Malath *et al.* (2018) by diazotizing 1,1' -biphenyl-4,4' diamine as in Figure 10. Compound 2 was dissolved in water-based ethanol and 3-chloropentan-2,4-dione was added. After obtaining the product, it was thoroughly washed and dried in the air. It had been recrystallized from amidrazones in dimethylformamide. In the presence of triethylamine, compound 2 reacted with N-substituted piperazine or cyclic secondary amines to yield compound 3. Compound 3 was then cooked in phosphoric acid at 130-140°C for 6-12 hr in order to generate 4,4'-dimethyl-3,3'-bis (4-substituted

Table 1: Chemical Structure of some commercially available drugs having cinnoline moiety.[37-40]

Sl. No.	Structure of drugs	Name of drugs	Uses of drugs	Mechanism of Action
1.	2	Cinnoxacin	Antibiotic	Inhibition of DNA gyrase, a type II topoisomerase and topoisomerase IV.
2.	2	Sinofem	Pesticide	By causing a sodium/potassium imbalance preventing normal transmission of nerve impulses.
3.	2	Cinnopentazone	Anti-inflammatory	Inhibition of bacterial cell wall synthesis.
4.	2	Cinnofuradione	Analgesic	Inhibits smooth muscle cell contraction in the vasculature by blocking L-and T-type voltage-gated calcium channel.

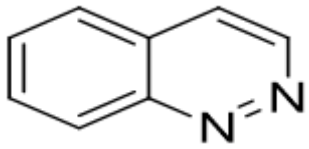


Figure 1: Structure of cinnoline.

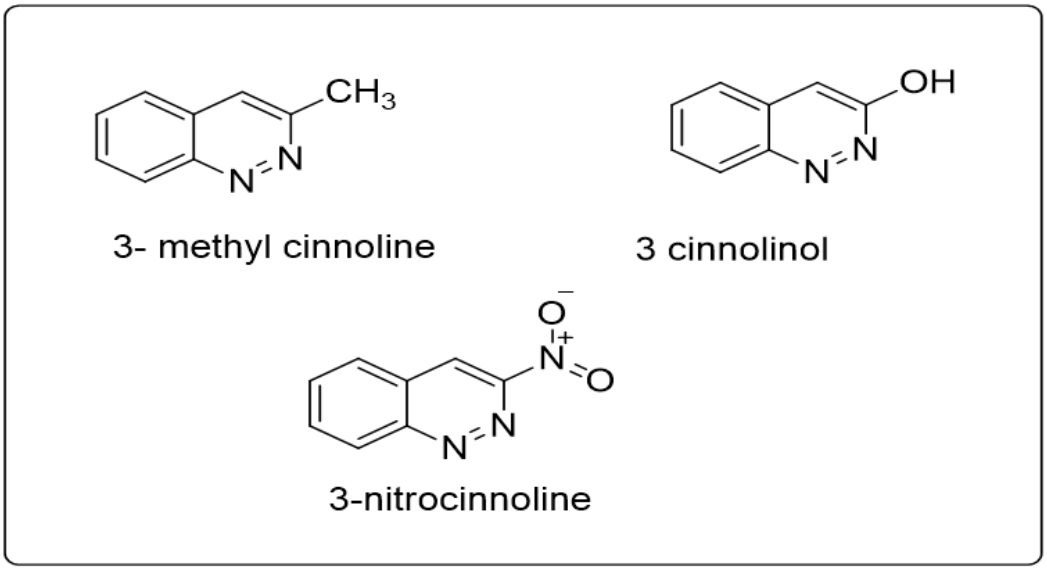


Figure 2: Structure of cinnoline based on the position of their functional group.

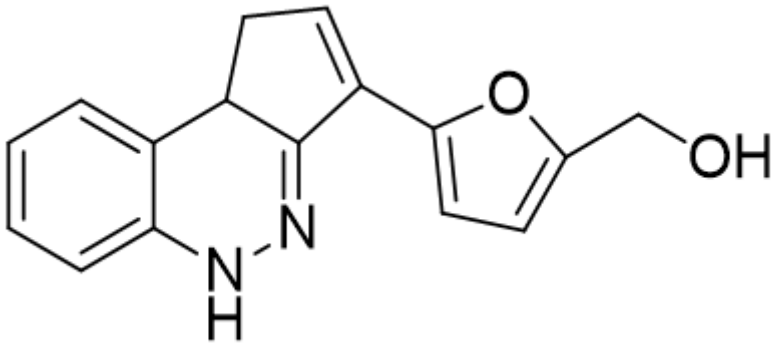


Figure 3: Structure of 2-furanmethanol-(5′→11)-, 3-cyclopentadiene-[5,4-c]-1H-cinnoline.

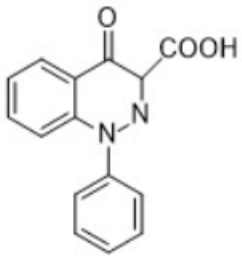


Figure 4: Structure of 1,4-dihydro-4-oxo-1-phenyl-cinnoline-3-carboxylic acid.

piperazin-1-yl)-6,6-bicinnoline. Newly synthesized bicinnolines were investigated for their cytotoxicity against cancer cells. To analyze the effectiveness of the prepared compounds, MDA-231 cells were used. There is a possibility of cytotoxic action (70%) in compounds 4k, 4n and 4o.[70]

Through intermolecular cyclization of the piperazinyl amidrazones, Eman *et al.* (2012) produced 3-piperazinyl cinnolines. For this reaction, a cyclizing agent known as (Polyphenyl acetylene) PPA was utilised. For this process, triethylamine was used to catalyse the coupling of N-substituted piperazine with the requisite quantity of hydrazonyl chloride. Reacting with the salts of 3-chloro-2,4-pentanedione and azenediazonium produces the needed for the japp-klingeman reaction, as illustrated in Figure 11.

Synthesized compounds were depictedas per the conducting cell viability assays by implementing tetrazolium dye against MCF-7 cells. Compound 8b showed potent activity and IC_{50} value was found to be 5.56 µM. Compounds 10b and 10d have IC_{50} values of 11.79, 8.57 respectively.[71]

Another cinnoline analog was prepared by Alexander and coworkers (2003) by the reaction of 6,7- methylenedioxy-4-cinnoline with PCl_5 and PCl_3.Compounds 2a-h were then synthesized by reacting the primary alkylamine with the appropriate substituent. The amides 3a-h may be synthesized from 2-iodo-4,5-dimethoxybenzoic acid chloride by reacting it with triethylamine and 4-amino-6,7-methlenedioxycinnoline in anhydrous methylene chloride. The desired compounds 4a-h was obtained through intramolecular cyclization of the iodobenzamides via the Heck reaction given in Figure 12.

Microtiter plate Tetrazolium cytotoxicity test was used to establish cell death (MTA). While testing human lymphoblast cell line RPM1840 for cytotoxicity, the synthesized compounds 4a, 4b and 4d revealed an IC_{50} value of 5 nm.[72]

Using a diazotization procedure carried out at 0°C, Parrino *et al.* (2014) produced compounds 2a-f via the scheme given in Figure 13. Using the stoichiometric combination of acetic acid and sodium nitrite. The 7-azaindole moiety was cyclized inside the molecule, yielding the end product. Antiproliferative activity was shown for compounds 1e, f produced upon a panel of human cell lines with a Mean Graph Midpoint (MG MID) in the 0.74-1.15 M range.[73]

Antifungal activity

By heating 2,3-dimethylbenzene-1,4-diol (1) with HNO3/HCl variation, Chung *et al.* (2006) produced 6 hydroxycinnolines, specifically 2,3-dichloro-5,6-dimethylcyclohexa-2,5-diene-1,4-dione 2.

Methyl-2-(2-chloro-4,5-dimethyl-3,6-dioxocyclohexa1,4-di enyl)-2-cyanoacetate 3 was prepared by nucleophilic replacement of compound 2 besides an equal quantity of methyl cyanoacetate in EtOH in the presence of ammonia. Compound 3 as well as hydrazine hydrate7 were dissolved in ethanol and allowed to reflux for an hour, yielding cinnoline 4a. Methyl -2- cyano-2-(2-arylthio-4,5-dimethyl-3,6-dioxocyclohexa1,4-dienyl) acetates 5a-e were composed by nucleophilic replacement of the chemical 3 along the appropriate aryl thiols in evaporating EtOH. By refluxing equal parts of amalgamated mixture of 5a-e and hydrazine hydrate in ethyl acetate for an hour, the cinnolines 4b-f could be made.

Compounds 4a-f as shown in Figure 14, which were produced, had strong antifungal activity against *Aspergillus niger, Cryptococcus neoformans* and *Candida krusei*. The outcome shows that the

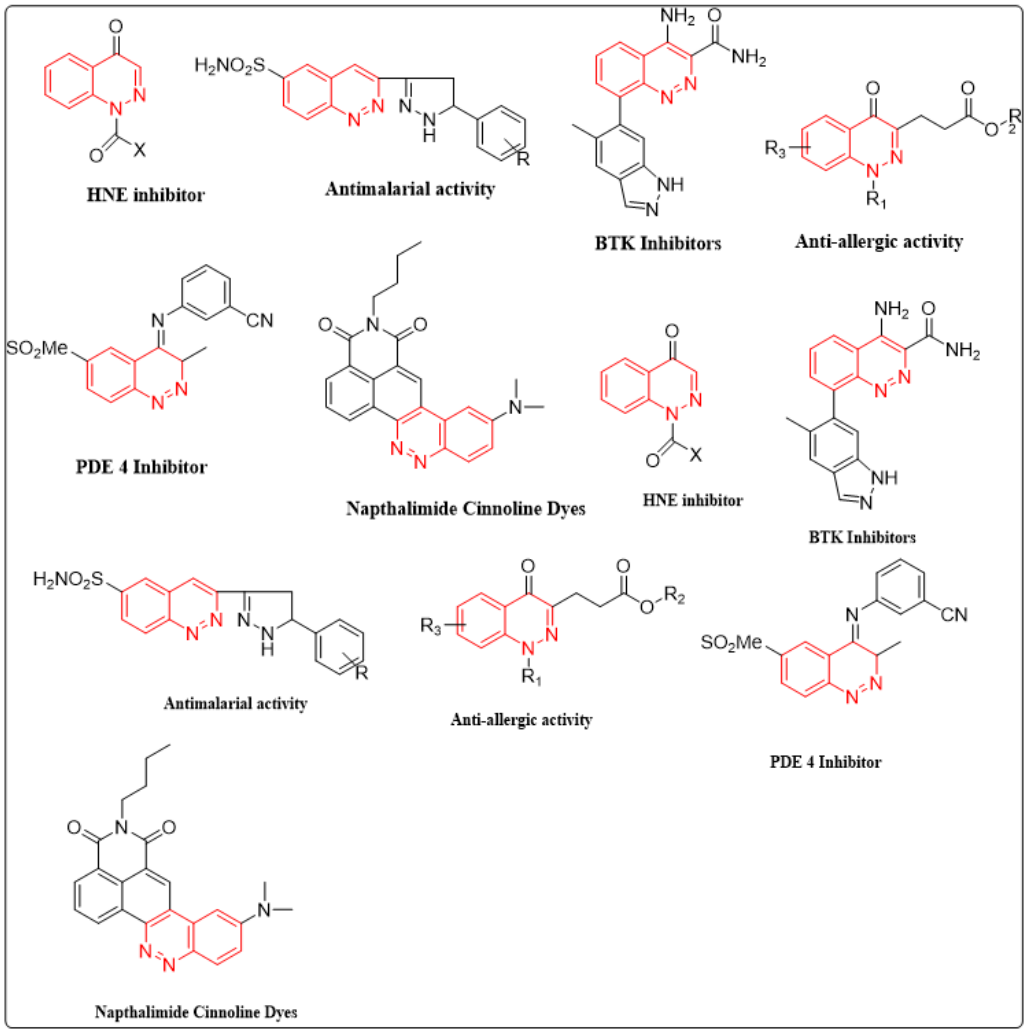


Figure 5: Pharmacologically active cinnoline nucleus compounds with varying activity.[43-61]

Minimum Inhibitory Concentration (MIC) was calculated and the range was found to be 0.2-100 g/mL, which is lower or higher than the MIC for the reference medication 5-florocytosine.[74]

Three different acetylcinnolines 2a-d given in Figure 15 were synthesized by Narayana *et al.* (2005) by interamolecular cyclization of substituted phenylhydrazono acetylacetones 1a-d. Using the serial plate dilution technique, the antifungal activity of the synthesized mixture was determined besides *Penicillium marneffei, Aspergillus fumigatus, Candida albicans, Aspergillus flavus* and in DMSO (Dimethyl sulfoxide). When compared to the gold standard medicine itraconazole, the range of the zone of inhibition was determined to be 5-20 mm.[75]

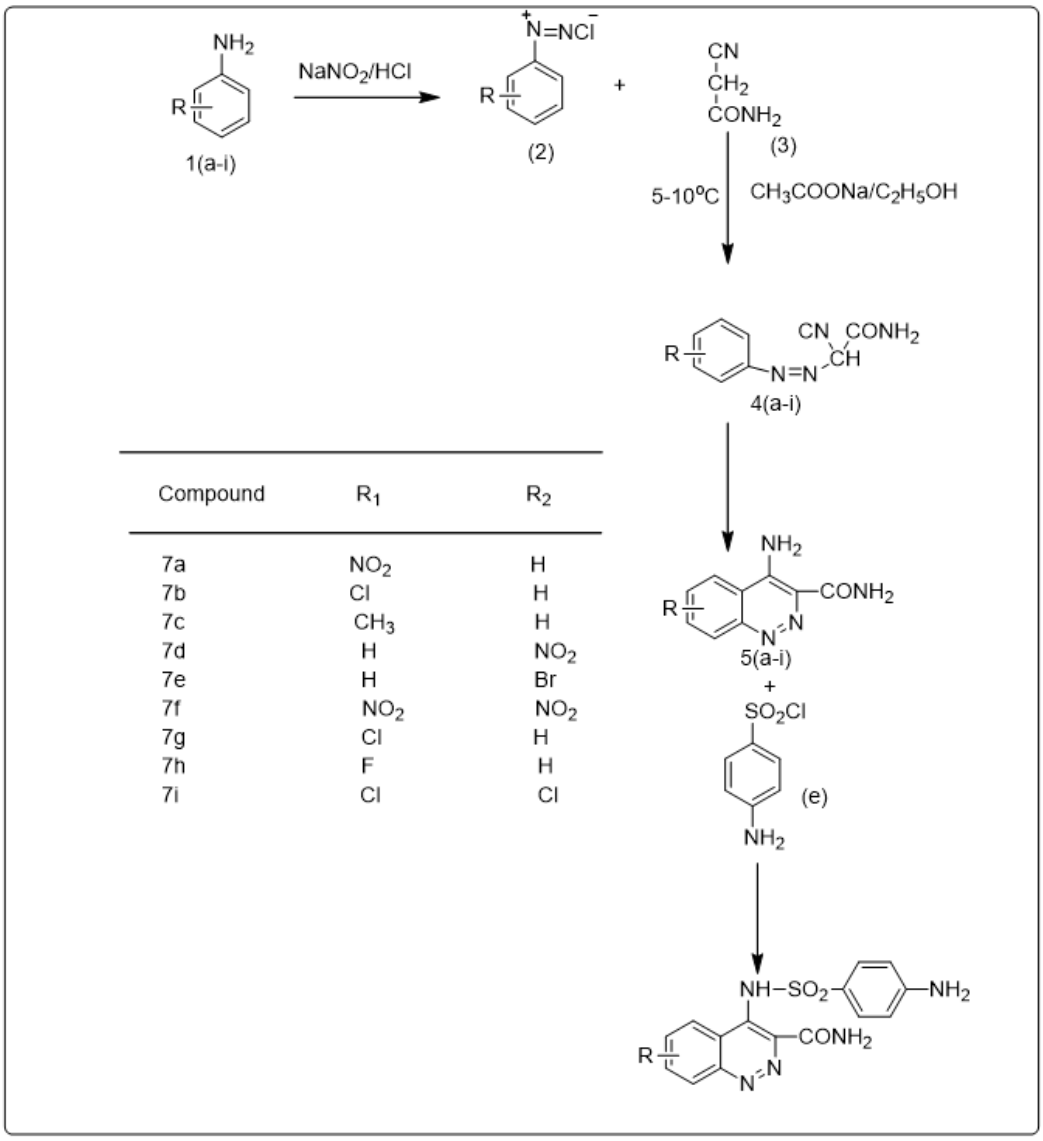
Anti-tubercular Activity

Tuberculosis (TB), caused by the Mycobacterium tuberculosis bacteria, is a very contagious disease. Because of the rise in treatment resistance among Mycobacterium species, there has been a heightened focus on tuberculosis with in the global health community.[76]

Cinnoline-substituted compounds were developed by Hurmath *et al.* (2015) by following the scheme given in Figure 16 and theiranti-tubercular effects were investigated. Using the Resazurin assay technique, the synthetic mixtures were evaluated for activity against Mycobacterium TB H37Rv at concentrations of 1 g/mL, 10 g/mL and 100 g/mL in DMSO. Being a standard, rifampicin 1 g/mL was used. In the result, it was found that Compound 4a was the most potent derivative to prevent Mycobacterium from growing at the concentration of 100 µg/mL.[77]

Anti-inflammatory Activity

Among the most often prescribed medications are Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). Clinical trials have shown that they are helpful in treating a wide range of conditions, including rheumatoid arthritis, osteoarthritis; tooth pain, gout dysmenorrhea, ankylosing spondylitis and migraine.[78] Novel



Compound	R_1	R_2
7a	NO_2	H
7b	Cl	H
7c	CH_3	H
7d	H	NO_2
7e	H	Br
7f	NO_2	NO_2
7g	Cl	H
7h	F	H
7i	Cl	Cl

Figure 6: Synthesis of cinnoline derivatives from p-amino benzene sulfonyl chloride.

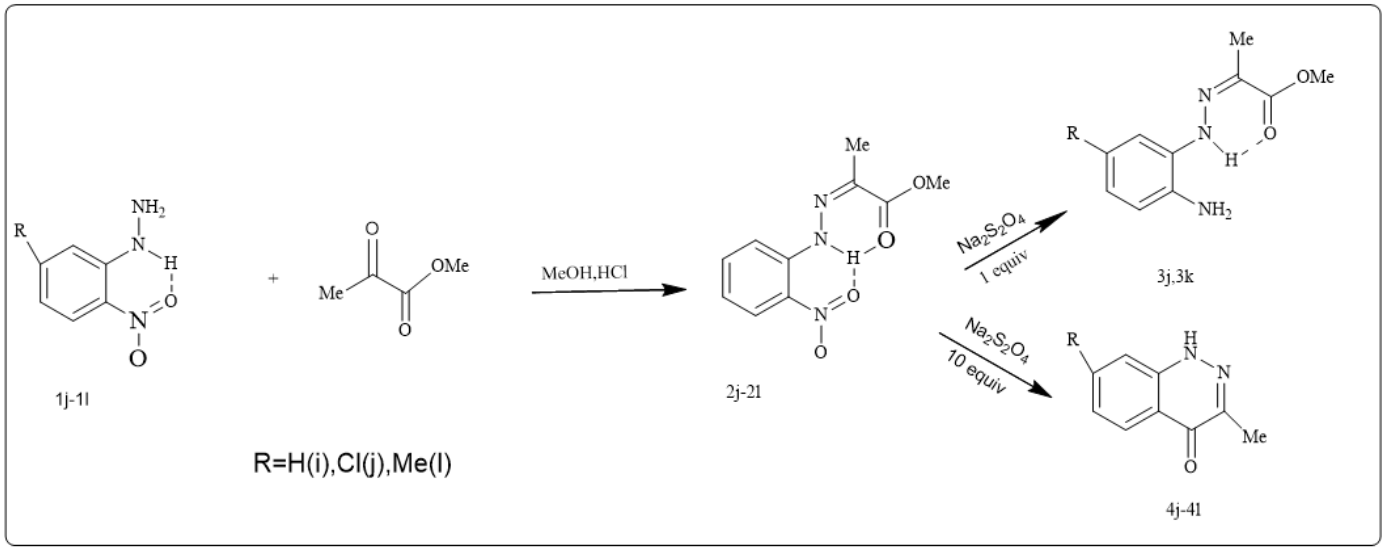


Figure 7: Synthesis of cinnoline derivatives from 2-nitrophenyl hydrazine.

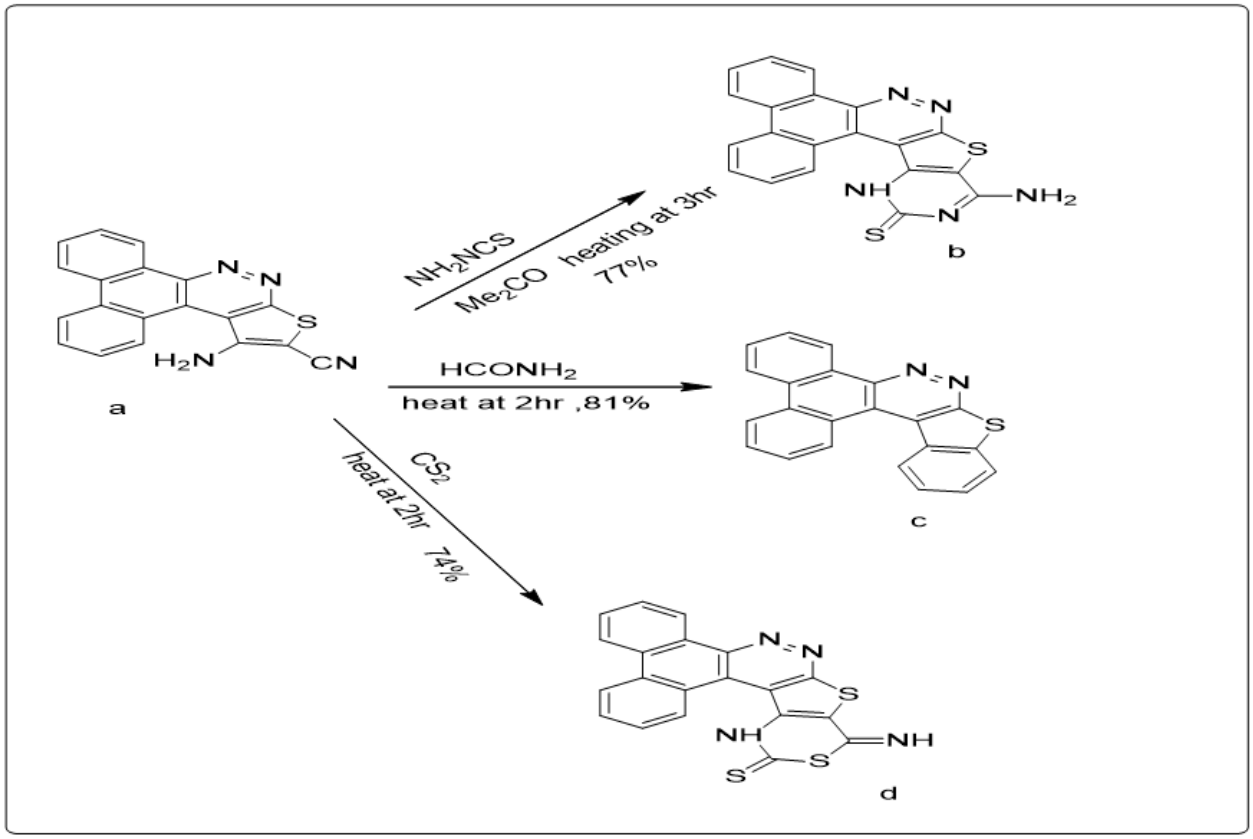


Figure 8: Synthesis of cinnoline derivative from 9-amino benzo{f,h}thienol, [2,3-c] cinnoline-8-Carbonitrile.

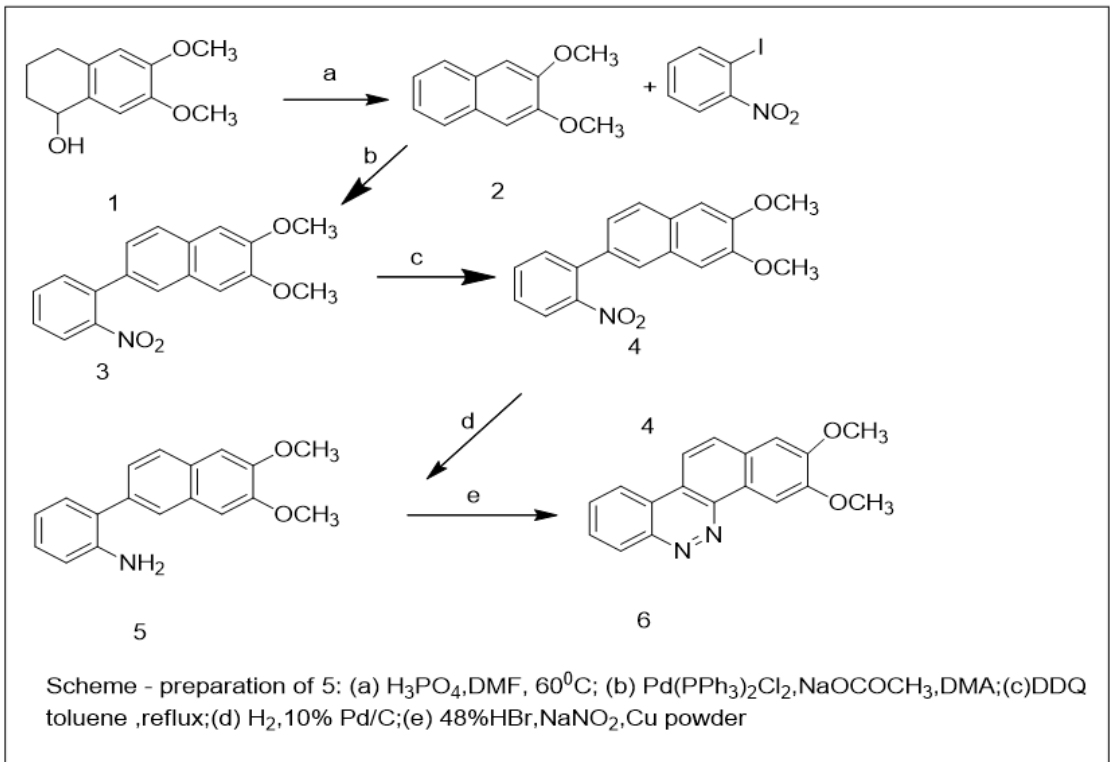


Figure 9: Synthesis of cinnoline derivative from 2,3 dimethoxy napthanol.

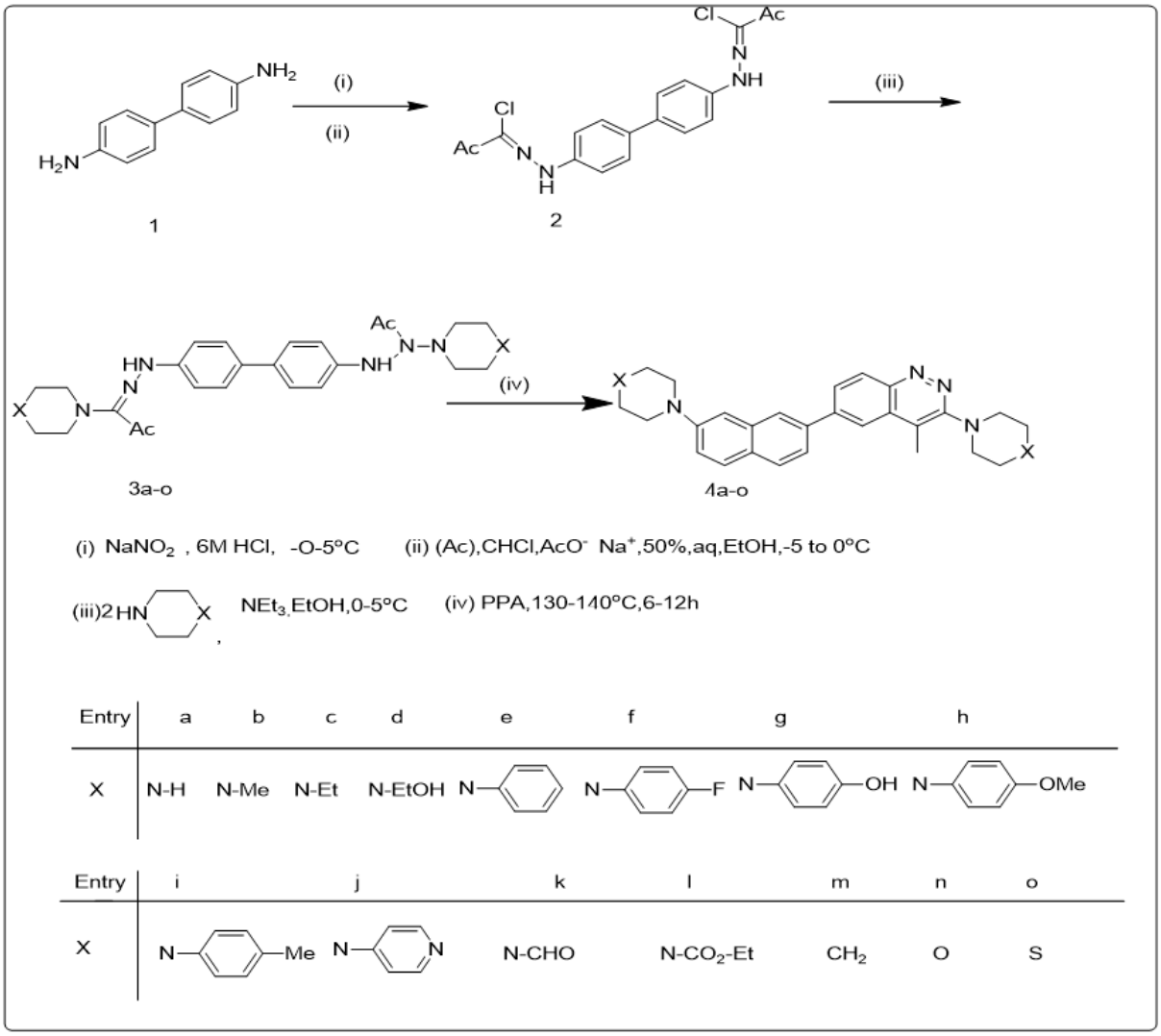


Figure 10: Synthesis of bicinnoline derivative from 1,1 biphenyl 4,4-diamine.

synthetic cinnoline derivatives were prepared by Tonk *et al.* in 2012. Compound 2 was made by reacting 3-chloro 4-floroaniline with ethyl acetoacetate or sodium acetate to produce a diazotized product. In existence of chlorobenzene and anhydrous AlCl3, acetyl -7-chloro-6-fluorocinnolin-4(1H)-one was produced in abundance by cyclization of ethyl-2- [2-(3-chloro-4-flurophenyl) hydrazinylidene]-3-oxobutanoate. Under acidic conditions, aryl hydrazines coupled with 1,3-dicarbonyl molecules resulted in the production of a single regioisomer. 1,3-diketone was obtained from compound 3 and then condensed along with acid hydrazides in a polar aprotic solvent (1,4-dioxane) containing a catalytic quantity of concentrated HCl to produce the desired compounds (4a-m). Whole scheme of synthesis is shown in Figure 17. A bioassay in which paw edema is generated by carrageenan was used to test the synthetic compounds for anti-inflammatory efficacy. Mixtures 4d-4l showed strong anti-inflammatory action, whereas mixtures 4f, 4i and 4m displayed the least. Similar to the standard medication naproxen (81.23% inhibition), compounds 4a, 4b, 4h, 4j and 4k exhibited potent anti-inflammatory action (64.40% inhibition, 67.94% inhibition, 68.46% inhibition and 66.25% inhibition), respectively.[79]

Drugs that block Phosphodiesterase 10A Intracellular levels of cAMP and cGMP are supervised by Phosphodiesterases (PDEs). Some of the many physiological functions that these cyclic nucleotides regulate include immune response, heart rate, reproduction, blood pressure, inflammation, neuroplasticity, vision and intestinal motility. PDEs are crucial to health because of the wide variety of physiological processes they regulate (via cAMP and cGMP, respectively). PDE10A inhibition may be useful for treating neurological diseases including Huntington's and schizophrenia.[80]

An inhibitor of phosphodiasterases 10 A (PDE10A) has been produced by Essa Hu *et al.* (2012) using the cinnoline derivative. With a 71% yield, 6,7-dimethoxycinnolin-4-ol 2 is produced through cyclization of 1-(2 amino-4,5 dimethoxy Phenyl)-1

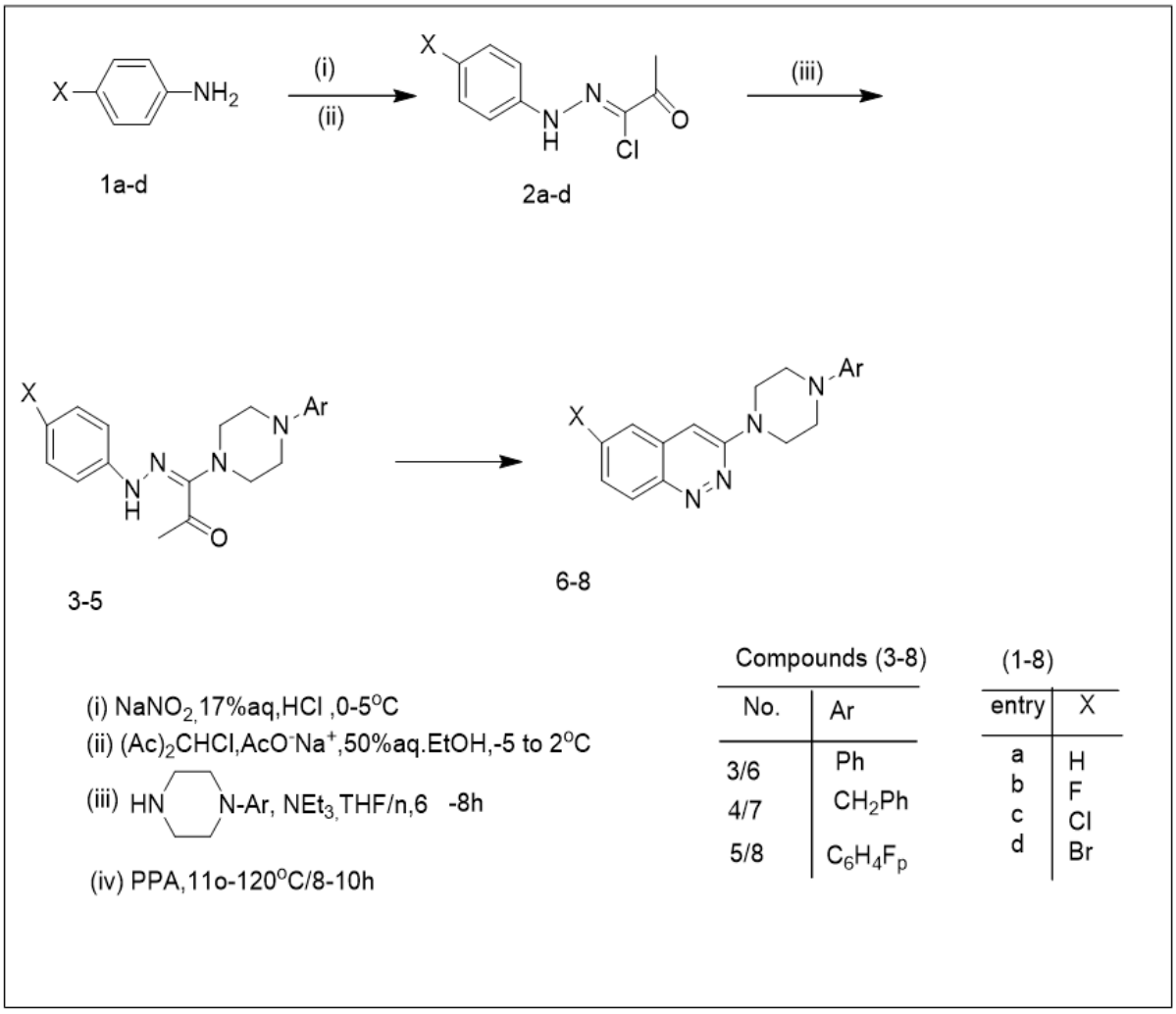


Figure 11: Synthesis of Cinnoline derivative from 4-substituted aniline.

ethanone with sodium nitrite. The 4-(6-fluoropyridin-3-yl)-6,7-dimethoxycinnoline scaffold 3 was made by brominating the starting chemical with phosphorus oxy bromide and coupling it along the proper substituted 6-fluoro-e-yl Boronic acid. The desired product 4 was made by warming the cinnoline pyridyl fluoride scaffold in DMSO besides the required amine.

Synthesized compounds as shown in Figure 18 were evaluated in a conditioned avoidance response behaviour paradigm in Sprague-Dawley rats at 3, 5, 6 and 10 mg/kg by oral gavage to assess their activity. Synthesized molecule exhibited potent inhibitory action, with an IC_{50} value of 7.6 nm.[81]

Parkinson's disease is the best-known medical illustration of the fallout from altering brain transmitter networks. As a result of the death of nigrostriatal dopaminergic neurons, striatal cholinergic neurons become functionally hyperactive in Parkinson's disease; this dysfunction may be partly corrected by increasing dopaminergic transmission or lowering anticholinergic transmission.[82]

Amer et al. (2011) synthesized three new classes of pyrimidino- and imidazolopyrazolopyridazine, triazine and polycyclic derivatives with the evaluation of all synthesized compounds for antiparkinsonian activities along with a comparison to Benzatropine. As shown in Figure 19 the Compound 2 was synthesized from phenanthraquinone 1. Compound 2 react with cinnamaldehyde and acrylonitrile to produce the final compounds. They were evaluated for their pharmacological action by measuring the % decrease of oxotremorine-induced effects by taking eight male mice (18-20 g). They were dosed orally through tested compounds (5 mg/kg) of oxetremorine. Then the rectal temperature was measured before administration of compounds and 1hr postoxetremorine dosage and the scores were recorded. Compound 3 showed moderate antiparkinsonian activity and the % decrease of oxotremorine-induced effect was calculated as 12% as compared to the standard drug benzatropine which has 26%.[83]

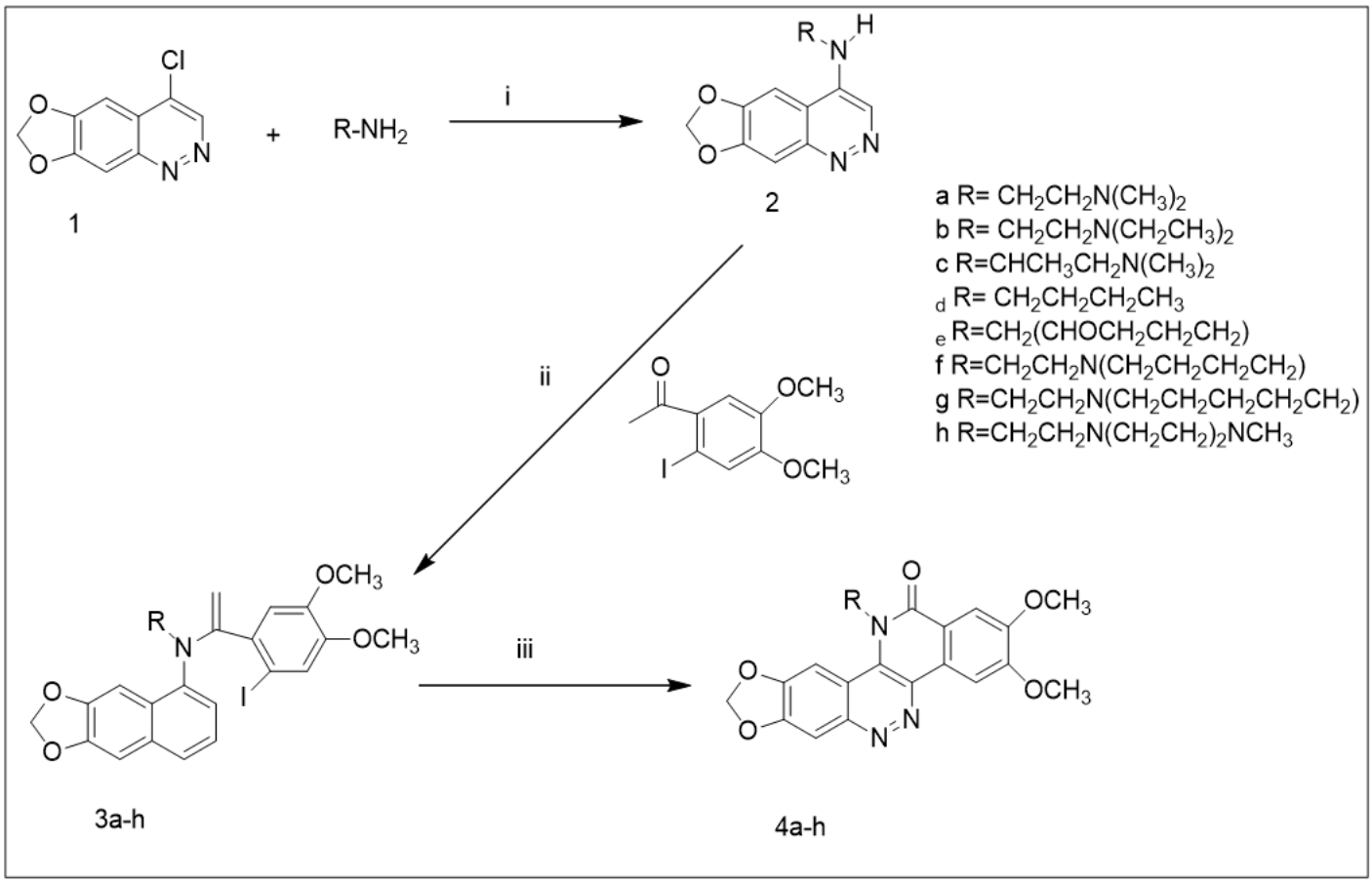


Figure 12: Synthesis of cinnoline derivative from 8-Chloro-1,3-dioxa-5,6-diaza-cyclopenta[b] naphthalene.

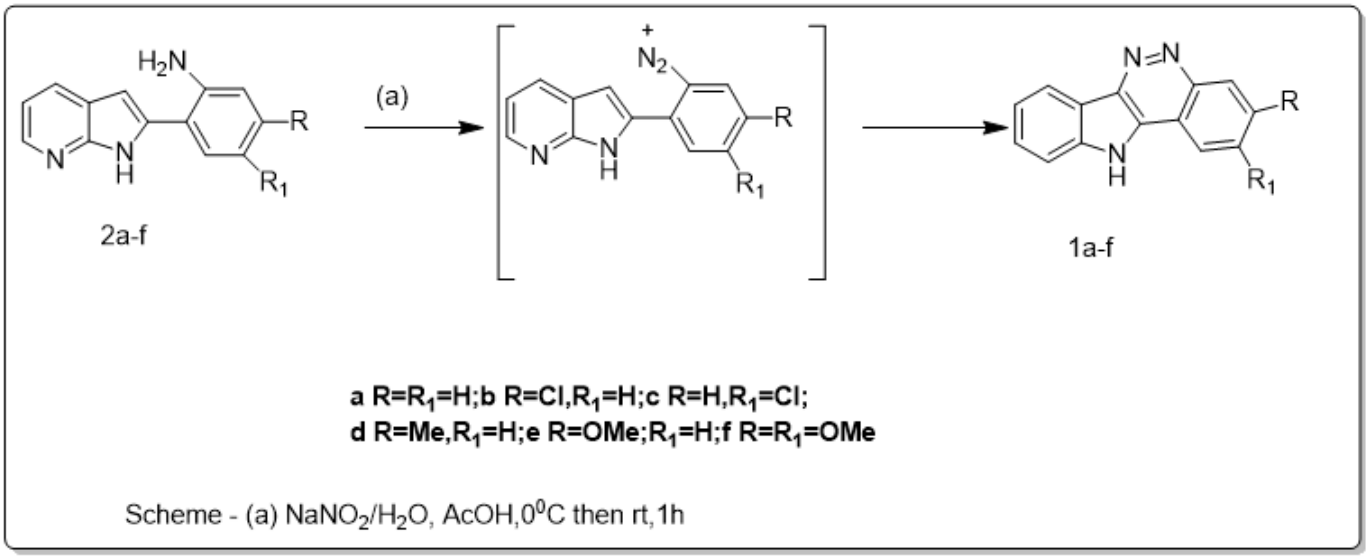
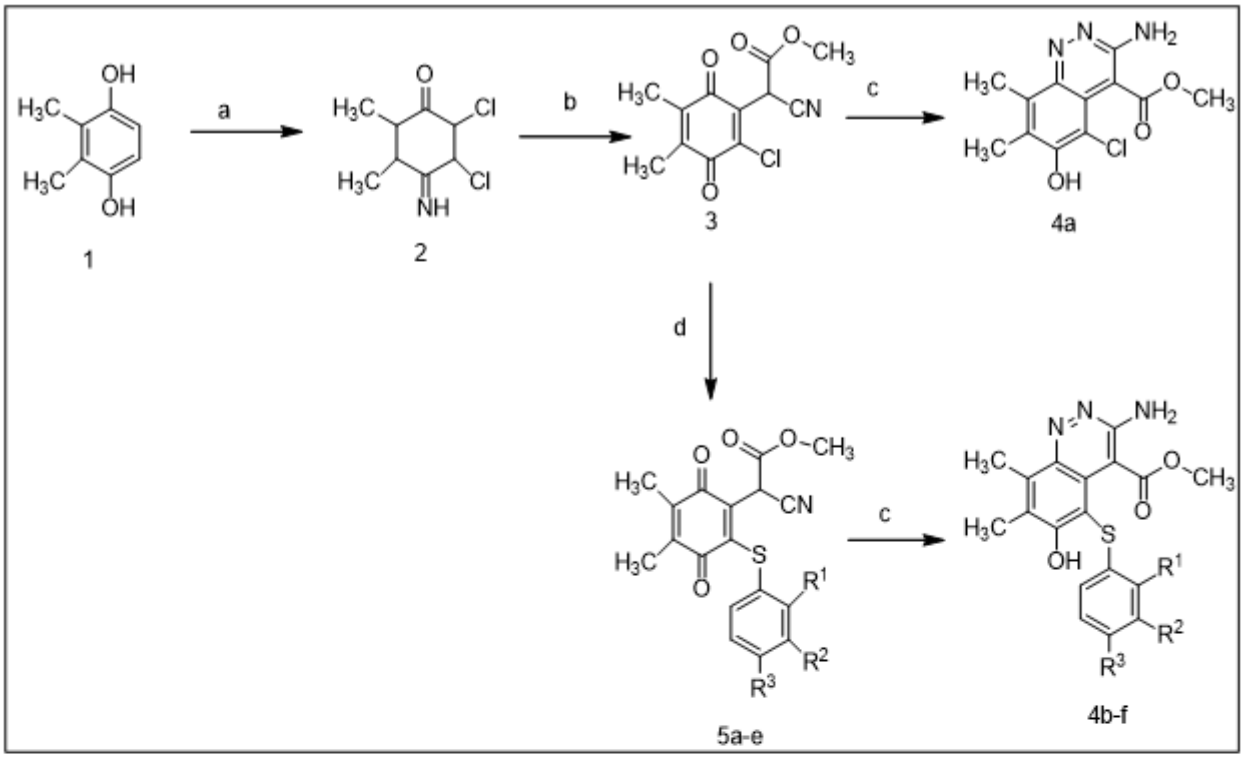


Figure 13: Synthesis of cinnoline derivatives from2(1 H -Pyrrolo[2,3b]pyridine-2-yl)phenylamine.



Scheme- Synthesis of 6-hydroxycinnolines .Reagent and conditions ;(a) HNO_3/HCl/190°C /10min(b) methyl cyanoacetate/EtOH/NH_4OH/rt/10 min ;(c) Hydrazine hydrate /EtOH/reflux/1h(d) arylthiol/EtOH/reflux/5h

Scheme -9

Compound	R^1	R^2	R^3
4a	-	-	-
4b	H	H	H
4c	H	H	CH_3
4d	H	CH_3	CH_3
4e	H	F	H
4f	H	CH_3	H
5a	H	H	H
5b	H	H	CH_3
5c	H	CH_3	CH_3
5d	H	F	H
5e	H	CH_3	H

Figure 14: Synthesis of cinnoline derivative from 2,3-Dimethyl-benzene-1,4-diol.

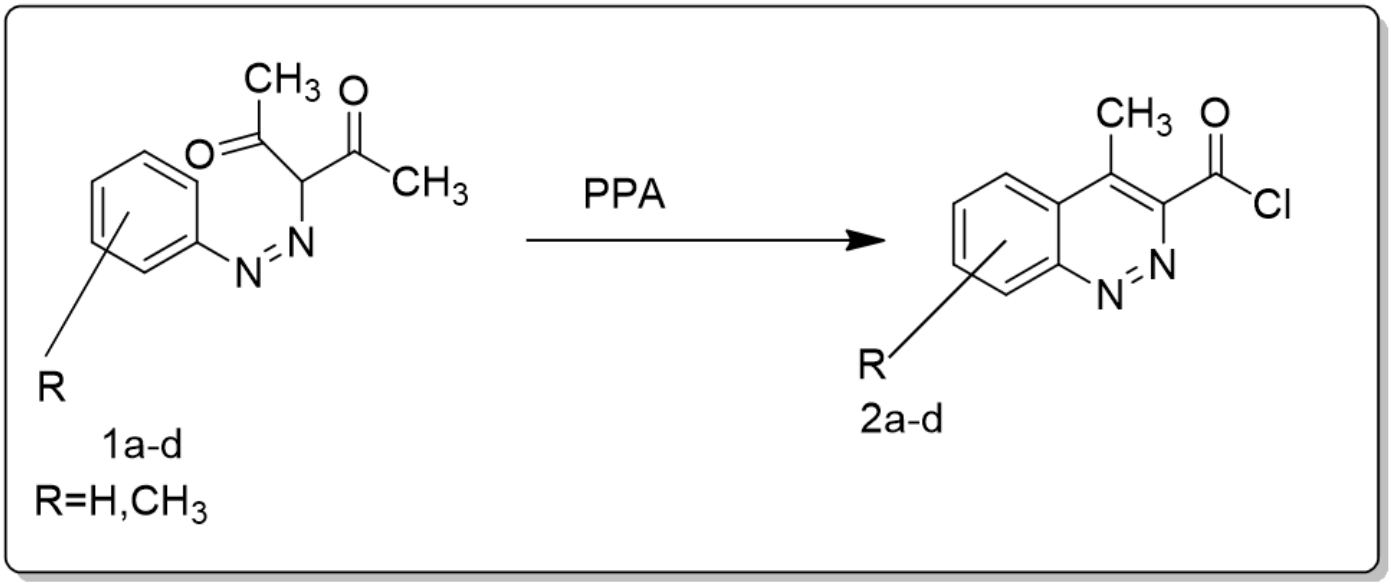


Figure 15: Synthesis of cinnoline derivative from Phenylhydrazonoacetylacetones.

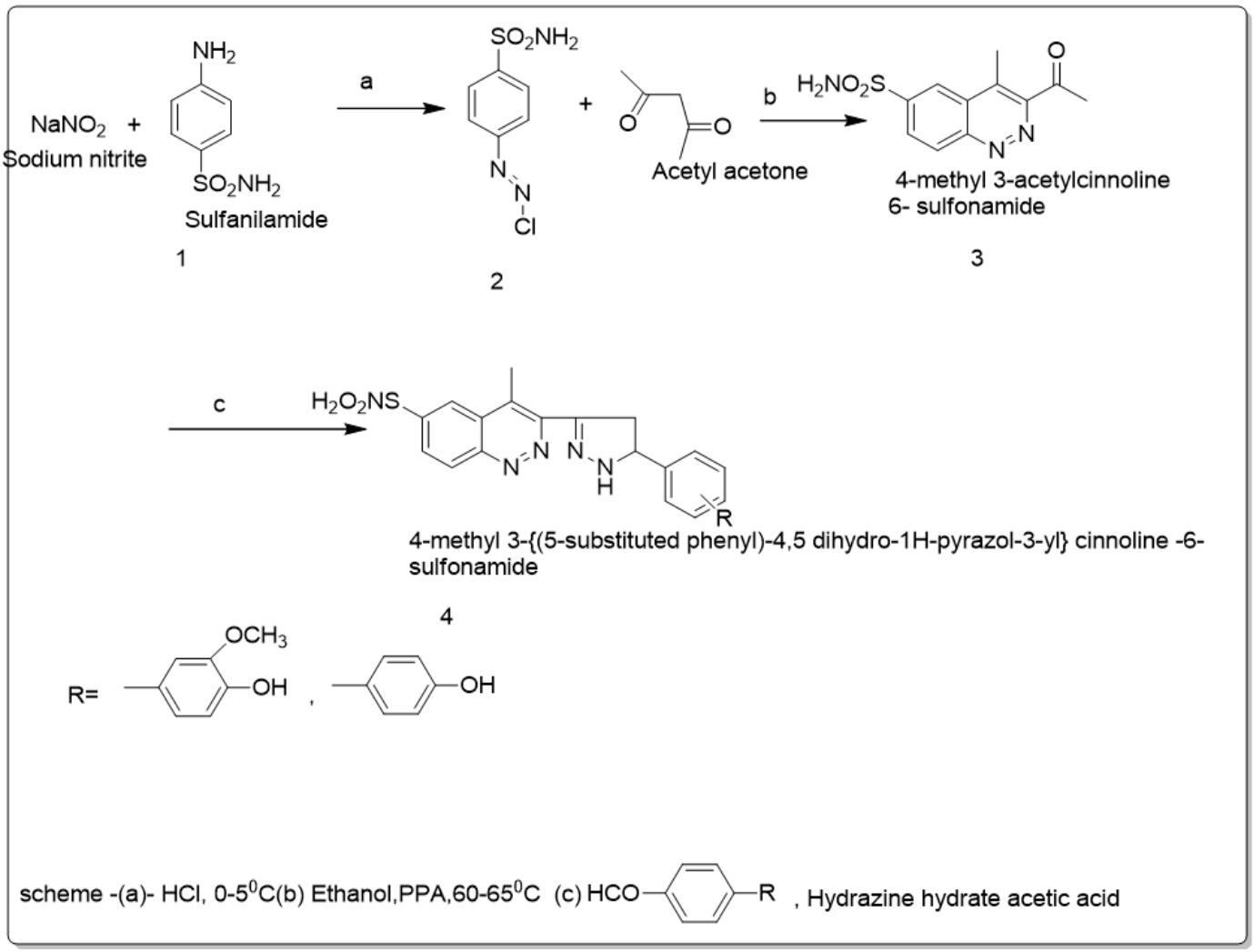
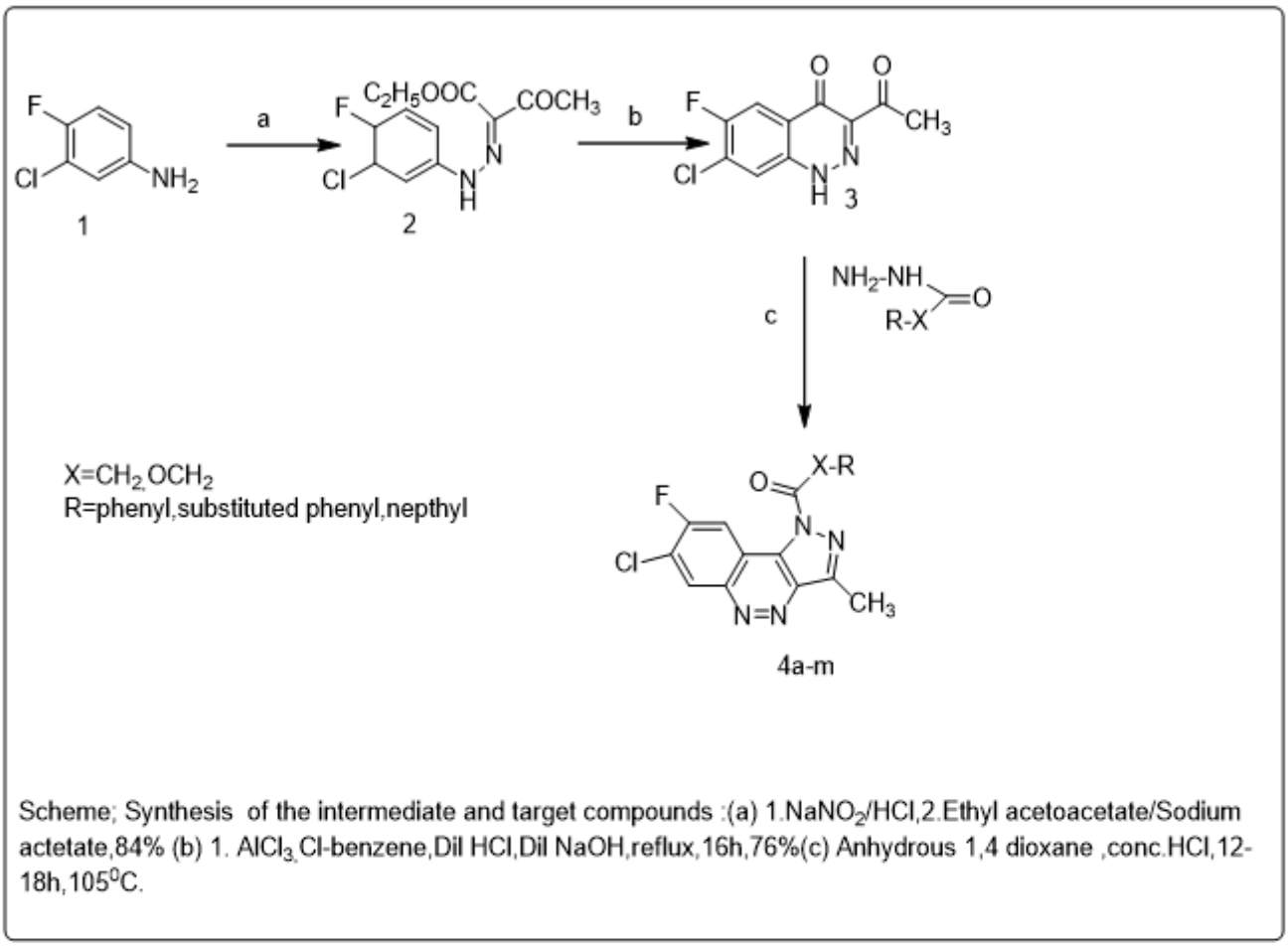


Figure 16: Synthesis of cinnoline derivative from Sulfanilamide.



Scheme; Synthesis of the intermediate and target compounds :(a) 1.$NaNO_2$/HCl,2.Ethyl acetoacetate/Sodium actetate,84% (b) 1. $AlCl_3$,Cl-benzene,Dil HCl,Dil NaOH,reflux,16h,76%(c) Anhydrous 1,4 dioxane ,conc.HCl,12-18h,105^{0}C.

Compound no.	R	X
4a	Phenyl-	-
4b	Phenyl-	CH_2
4c	Phenyl-	OCH_2
4d	p- methylphenyl-	-
4e	o,p-dichlorophenyl-	-
4f	o,p-dichlorophenyl-	OCH_2
4g	p-chlorophenyl-	-
4h	p-florophenyl-	-
4i	p-nitophenyl-	-
4j	p-aminophenyl-	-
4k	m,p-dimethoxyphenyl-	-
4l	p-methoxyphenyl-	-
4m	l-napthalyl-	CH_2

Figure 17: Synthesis of cinnoline derivative from 3-Chloro-4-Fluoro-Phenylamine.

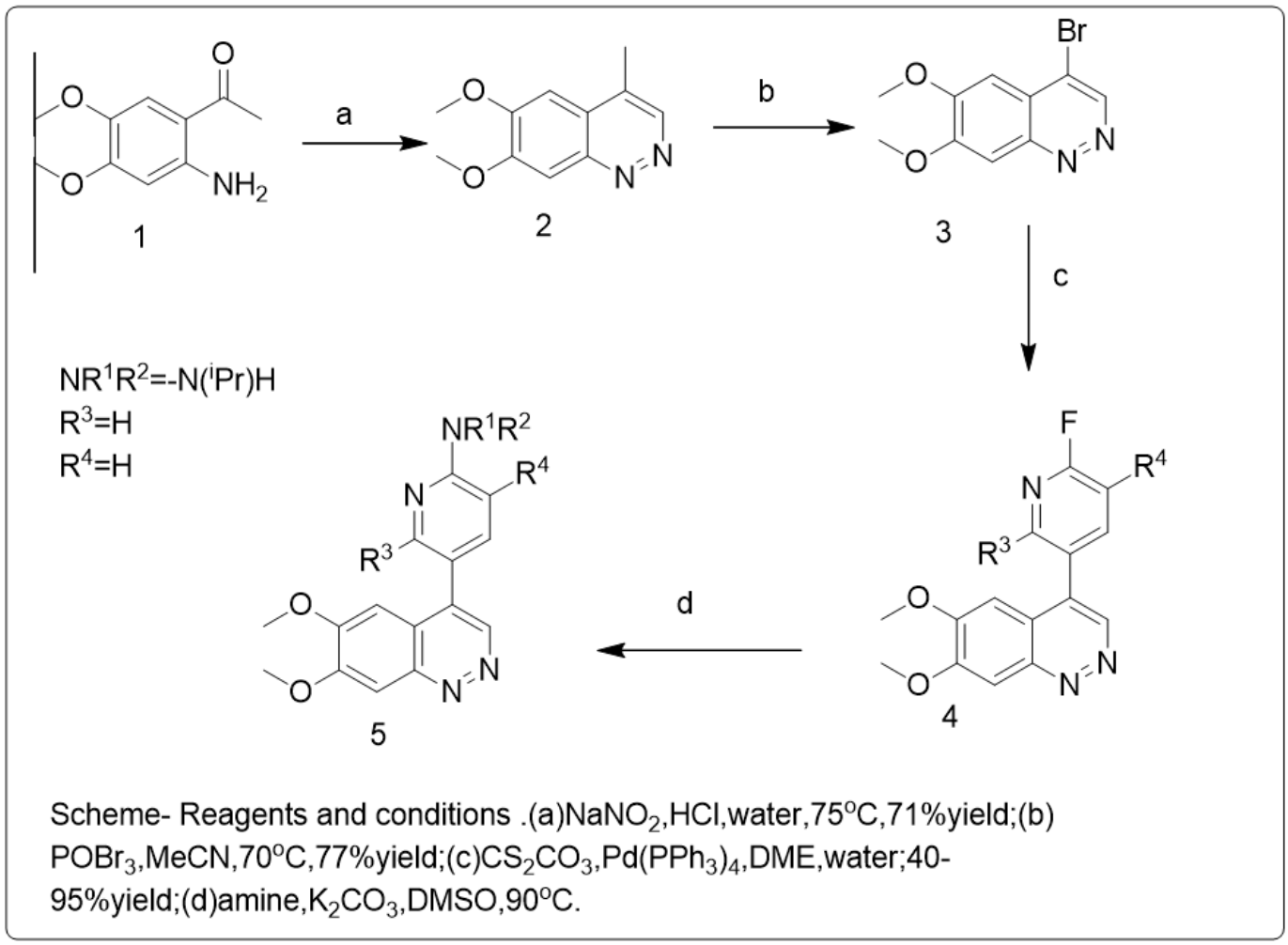


Figure 18: Synthesis of cinnoline derivative from 1-(2-amino-4,5-dimethoxy-Phenyl)-ethanone.

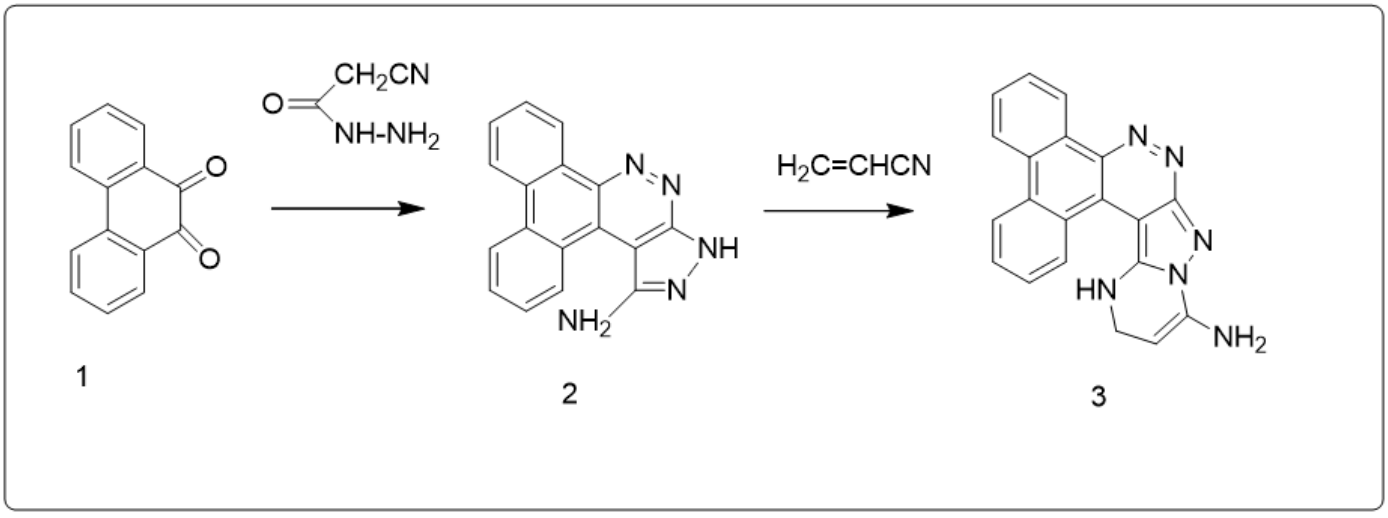


Figure 19: Synthesis of cinnoline derivative from Phenanthrene 9,10-dione.

CONCLUSION

In this review, cinnoline derivatives with varied pharmacological properties may be produced by several techniques. Cinnoline is a heterocyclic molecule with antibacterial, antifungal, anticancer, anti-malarial and anti-molluscidal properties. Cinnoline and its derivatives have condensed bicyclic aromatic heterocycles with two nitrogen atoms in their ring structure. To find novel antibacterial and auxiliary effects, cinnolines are the topic of rigorous and logical biological research experiments. Scientists might consider novel cinnoline derivatives as medications due to the rising quantity of publications. Recent breakthroughs in diverse biological activities and the creation of cinnoline scaffolds or derivatives are covered in the review. This study encourages greater research on the synthesis of cinnoline derivatives, which will be important in medication discovery and development.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CSF-1R: Colony Stimulating Factor -1 Receptor; **PDE 4:** Phosphodiesterase 4; **$GABA_A$:** Gamma-aminobutyric acid; **DMF:** N, N-Dimethylformamide; **MIC:** Minimum inhibitory concentration; **MTT:** Microtiter plate Tetrazolium; **PPA:** Polyphenyl acetylene; **TEA:** Triethanolamine; **MG_MID:** Mean graph midpoint; **DMSO:** Dimethyl sulfoxide; **NSAIDS:** Non-Steroidal anti-inflammatory; **cAMP:** Cyclic adenosine monophosphate; **cGMP:** Cyclic guanosine monophosphate.

SUMMARY

Many molecules with noteworthy pharmacological effects employ the cinnoline nucleus as a structural constituent. Absolute and resourceful information shows that the creation of cinnoline-based molecules contributes to the exploration of lead compounds with optimal pharmacological and pharmacokinetic characteristics.

These privileged structures have few synthetic techniques that are accessible and efficient. Traditional methods for making cinnolines have restricted substrate scope and multistep reactions. This article covers multiple synthesis approaches for cinnoline analogs with different pharmacological effects. These findings will help the researchers to build cinnoline derivatives with higher pharmacological activity.

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