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TARGETS AND BIOLOGICAL ACTIVITIES OF CINNOLINE DERIVATIVES: A REVIEW

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Abstract

Cinnoline is an innovative heterocyclic compound containing a six-membered ring fused with two nitrogen atoms. Cinnoline derivatives exhibited diverse pharmacological properties like anti-bacterial, anti-fungal,anti-parasitic, anti-inflammatory,anti-tubercular, and anti-cancer activity. In the current study, we have concentrated on the numerous biological functions and targets of cinnoline derivatives that have been studied by researchers over the last 15 years. This literature review will surely serve as the beginning point for further research and the creation of new cinnoline-based compounds with optimized properties.

Keywords: Cinnoline, Heterocyclic, Anti- Fungal, Anti- Bacterial, Biological.

INTRODUCTION

Organic molecules that are cyclic and include at least one heteroatom are known as heterocyclic compounds. An organic cyclic molecule with all its carbon atoms organized is called a carbocyclic compound as shown in Figure. 1 [1-6]. According to years of research, heterocycles are attractive molecules to develop possible physiologically active products [7-9]. Nitrogen, oxygen, and sulfur are the most common heteroatoms, however heterocyclic rings with other hetero atoms are also widely known [10-13]. Cinnolines are potentially useful building blocks in organic synthesis and drug discovery programs [14-17]. Cinnolines and heterocycle-fused cinnolines serve as particularly desirable chemical targets because they are prevalent in luminous chemicals, photoelectric materials, and bioactive compounds [18]. Synthetic and medicinal chemists have a keen interest in cinnolines fused with other heterocycles because of their useful structural properties [19-24]

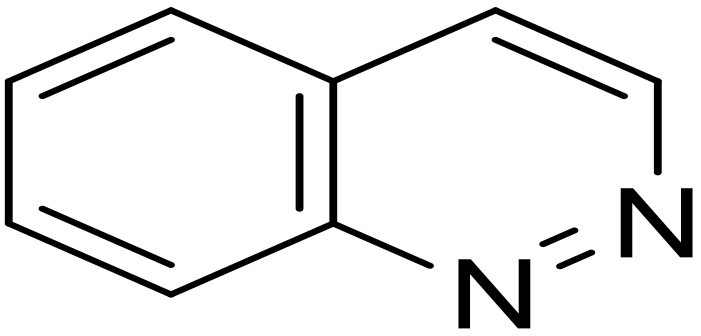


Figure 1: Structure of the Cinnoline Ring System [25,26]

Many natural compounds, alkaloids, receptors, inhibitors, and pharmacologically active salts use substituted cinnolinium salts as versatile building blocks [27]. Cinnolines

are generally thought of as the isosteric scaffold of quinolines and isoquinolines and have drawn a lot of interest because of their potential photoelectric use and various pharmacological activities like anti-inflammatory [28-32],anti-tumor [33-40],anti-proliferative [41-49],anti-fungal [50-57] antibacterial [58-66], molluscicidal [67-73], anti-depressant 74-78, anti-malarial [79], analgesic [80, 81], anti-psychotic [82],anti-parasitic 83,anti-thrombotic [84, 85], anti-tubercular activity [86], antihypertensive [87,88], insecticidal properties [89]. Cinnoline is also reported as a bactericide and fungicide [90, 91]. The derivatives of 5-nitro furfural were documented as anti-parasitic [92, 93]. There are several methods for the synthesis of cinnoline derivatives such as intramolecular cyclization, catalytic oxidative cyclization, catalytic reduction, condensation, azo coupling, and catalytic annulation [94-98]. Furthermore, research has been focused on the synthesis of heterocyclic compounds containing a cinnoline moiety published by many kinds of literature [99]. Some reported cinnoline analogs are shown in Figure. 2 and given in Table 1

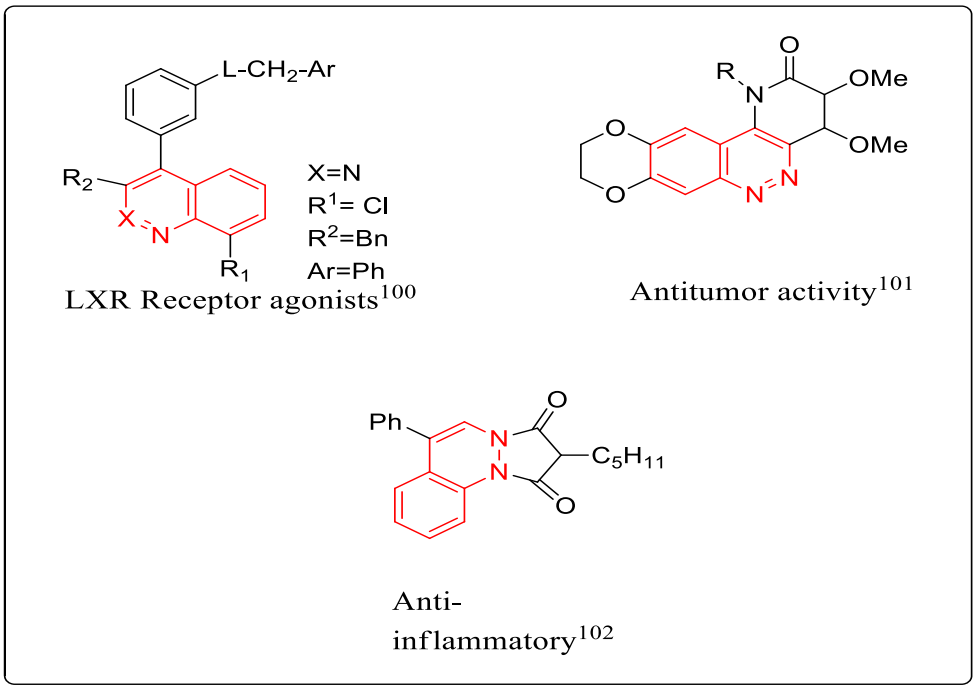
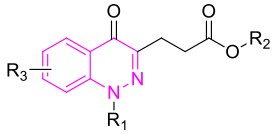
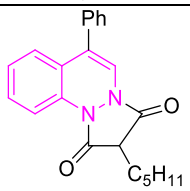
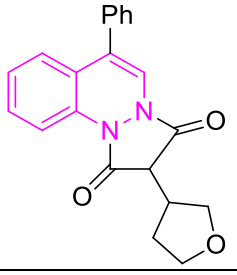
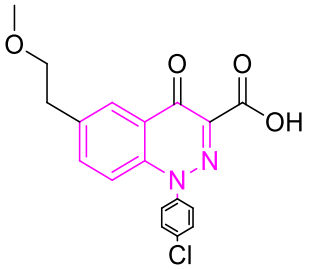
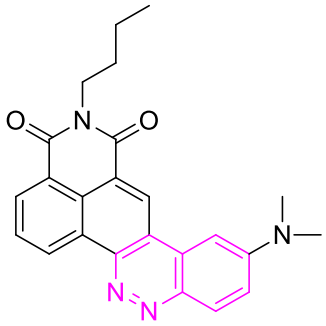
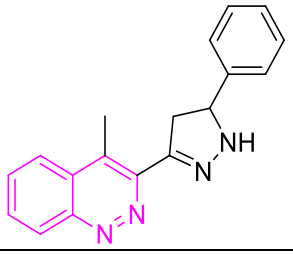
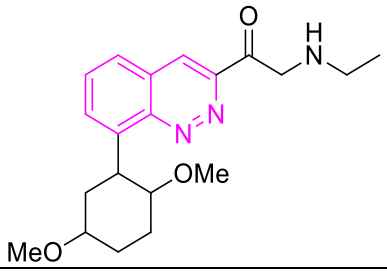


Figure 2: Examples of Biologically Active Cinnoline Analogs

Table 1: Shows Pharmacologically Active Compounds with Cinnoline Nucleus and having Different Pharmacological Activities [103-108]

Sr.No.	Structure	Activity
1.		Anti-malarial
2.		Anti-inflammatory

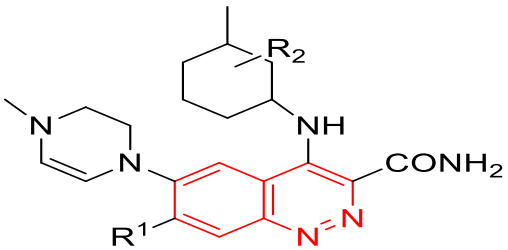
3.		Analgesic
4.		Pesticide
5.		Napthalimide cinnoline dyes
6.		Anti-microbial and insecticidal activity
7.		$GABA_A$ Modulator

Many cinnoline derivatives are reported to have different activities by targeting different receptors, proteins, enzymes etc. Such examples of cinnoline analogs acting on different targets are discussed in table 1.

Colony-Stimulating Factor 1 (CSF-1R) as Target for Cancer Treatment

Cinnoline is also reported to act on CSF-1R.[109] shown in figure 3. It is a class III receptor tyrosine kinase known as c-FMS that governs monocytes and macrophages' development, differentiation, and survival [110]. Colony-stimulating factor 1 (CSF1) and interleukin-34 (IL-34) are the natural ligands for the CSF1R, which is expressed by macrophages, microglia, and osteoclasts [111-114]. **El Gamal *et.al* 2018** state that CSF-1R is present in oocytes (immature egg cells), preimplantation embryos, epithelial

cells, and colonic epithelial cells. CSF was first identified by Stanley and Heard in 1997 [115]. **Stanley. *et.al* 2014** reported and confirmed in their study that Since CSF-1R is overexpressed in many tumors and in sites of inflammation, blocking it could be an effective treatment for cancer as well as autoimmune and inflammatory conditions. Excellent characteristics were observed for the 3-amido-4-aniline cinnolines (compound 1). Their IC_{50} values in 3T3 cell-based assay (stimulated with CSF-1 and engineered to express CSF-1R kinase) were 13 and 25 nM, respectively [117]. CSF-1R is implicated in the development of angiogenesis, invasion, and metastasis by tumor-associated macrophages, suggesting that they may be a promising oncology target. The 6-position of N-methyl piperazine produces compounds with good physicochemical characteristics, and the PK profile of 1b in many species was outstanding. Additionally, the kinase selectivity profile of cinnoline 1a was excellent [118].



Compound 1

Sr No.	R^1	R^2
1a	EtOH	2,4-F
1b	EtOH	2-F,4-Me
1c	EtOH	2-F,5-Me
1d	EtOH	2-F,3-Cl
1e	EtOh	2,3-Cl

Figure 3: Structure of Cinnoline Analogs Exhibiting CSF-1R (Colony Stimulating Factor) Inhibition

EPI (Efflux Proton Inhibitor) as Target for Resistant Developing Bacteria

Asif *et. al* 2011 reported cinnoline compounds can act as active agents to kill resistant developing bacteria is shown in figure 4. The resistance problem requires a renewed effort to find modified antimicrobial drugs that are effective against resistant pathogenic microorganisms [119]. New opportunities to reduce the spread of antibiotic resistance across the spectrum of medications by preventing drug efflux [120]. ***Atinet. Et. al 2019*** stated that efflux pumps are bacterial transport proteins that expel substrate from the cell to the outside. These substrates are often antibiotics, which causes efflux pump antibiotic resistance. Since the 1990s discovery of the first drug-resistant efflux pump, molecular microbiology has identified numerous efflux pumps in Gram-positive bacteria like methicillin-resistant Staphylococcus aureus (MRSA), Streptococcus pneumoniae, Clostridium difficile, and Gram-negative bacteria like Escherichia coli and Klebsiella pneumoniae [121].According to **Lomovskaya *et. al* 2006**, the pharmacokinetics of an EPI should be precisely matched with the pharmacokinetics of the antibiotic component of the combing device to achieve the most pharmacodynamic benefits [122]

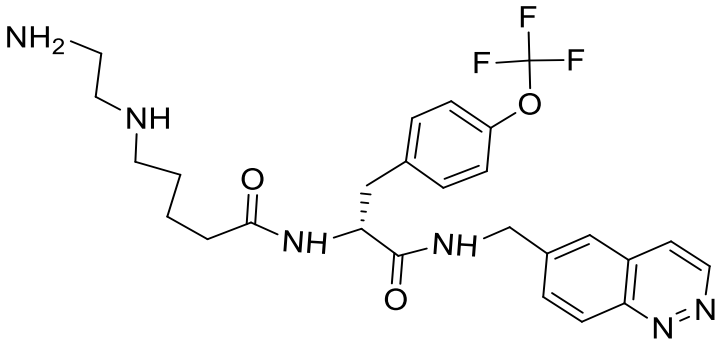
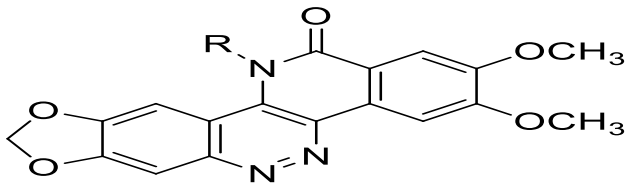


Figure 4: Cinnoline Derivative Shows Resistant Developing Antibacterial Activity

Topoisomerases I and Topoisomerase II as Target for Antitumor Activity

Cinnoline is also reported to have antitumor activity [123] shown in figure 5. ***Wang et.al* 2016** states that DNA Enzymes called topoisomerases to regulate and alter DNA's topological states by either passing another DNA strand through a transient break in the strand (type I topoisomerases) or breaking a pair of complementary strands and passing another double-stranded segment (type II topoisomerases) [124]. **Younong *et.al* 2003** demonstrated that these enzymes play a role in regulating the supercoiling of the template during RNA transcription on the basic variations in their initial processes, Topoisomerases can be divided into two main categories among which the mechanism connected to Topoisomerase II (TOP2) works by causing a double-strand DNA break, whereas topoisomerase I (TOP1) creates a single-strand DNA break [125]. Compounds 2a-d demonstrated several 11-substituted derivatives of 2,3-dimethoxy-8,9-methylenedioxy-11H-isoquino[4,3-c]cinnolin-12-one,(Figure 5) as reported by ***Ruchelman et al*. (2004)**. These analogs have IC50 values in the sub-5-nm range. TOP1-targeting activity and cytotoxicity are both reduced when the b- methyl substituent is added to the 11-(2-aminoethyl) side chain. Substituting hydrogen atoms for methylene deoxygen in position 2a reduces the cytotoxic and TOP1-targeting activities. These compounds also showed significant cross-resistance in the CPT-K5 camptothecin-resistant mutant cell line [126].



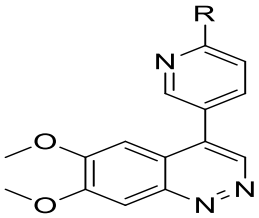
Compound 2

Sr No.	R
2a	$CH_2CH_2N(CH_3)$
2b	$CH_2CH_2N(CH_2CH_3)_2$
2c	$CHCH_3CH_2N(CH_3)_2$
2d	$CH_2CH_2CH_2CH_3$

Figure 5: Structure of Cinnoline Analogs as Topoisomerase Inhibitors

Phosphodiasterase10A (PDE10A) as Target for Schizopherenia

Chappie*et.al*2022 states that the striatum is a part of the basal ganglia system that has been hypothesised to have a role in controlling the response to extracellular production of cyclic nucleotides, and PDE10A, a single phosphodiesterase family member, is highly expressed there [127]. Phosphodiesterase 10A (PDE10A) inhibition has sparked considerable interest as a potential innovative strategy for treating the positive symptoms of schizophrenia [128]. The discovery of a class of enzymes capable of degrading cyclic AMP to its ineffective 5′-monophosphate form rapidly followed the initial description of cAMP as a second messenger1 [129]. PDE10A inhibitors have the potential to address an unmet medical need in the treatment of CNS diseases such as schizophrenia and Huntington's disease [130]. In a research study, **Essa hu *et. al* 2012** stated that compound 3a-f (Figure 6) acts as phosphodiesterase 10 A inhibitor and observed that the substitution of a chlorine atom to 3a with methyl group improved potency andIC_{50} of compound 3a-f was found to be 590nm. Removal of the chlorine from the 3a atom resulted in the loss of activity [131].



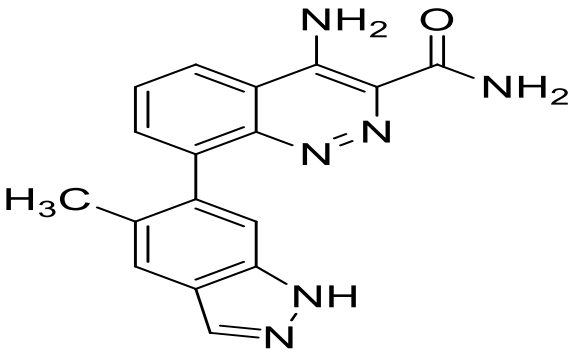
Compound 3

Sr.No.	compound	R
	3a	Cl
	3b	H
	3c	CH_3
	3d	CF_3
	3e	CN
	3f	NH_2

Figure 6: General Structure of Cinnoline Derivative for Phosphodiasterases 10A Inhibition

Bruton’s Tyrosine Kinase (Btk) as Target for Rheumatoid Arthritis

Although Bruton's tyrosine kinase (Btk) is a drug target for RA, the cellular and molecular mechanisms by which Btk triggers inflammation remain elusive [132, 133]. BTK belongs to the Tec family of non-receptor tyrosine kinase [130]. BTK was first determined as a primary immunodeficiency disease X-linked agammaglobulinemia in humans, which is caused by a BTK gene mutation 134. Btk was initially identified in human and mouse B cells as a crucial signaling protein in B cell antigen receptor (BCR) signaling and activity. ITAMs (immunoreceptor tyrosine-based activation motifs) bind to phospholipase C, gamma 2 (PLC2), which mobilizes Ca2+ and activates nuclear factor (NF)-B [135]. BTK inhibitors may also be effective in the treatment of disorders like rheumatoid arthritis, lupus, and glomerulonephritis [136, 137]. **Xia *et.al* 2019** synthesized cinnoline derivatives among which compound 4 (figure 7) was reported to be a strong reversible BTK inhibitor with poor aqueous solubility (at pH 7.4 0.05 g/mL), limiting its in vivo research [138]

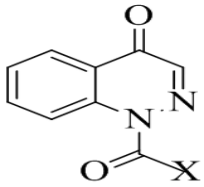


compound 4

Figure 7: Structure of BTK (Bruton's tyrosine kinase) Inhibitor With Cinnoline Nucleus

Human Neutrophil Elastase (HNE) As Target for Anti-Inflammatory Activity

Human neutrophil elastase (HNE) is a chymotrypsin-like serine protease found in neutrophil azurophilic granules, where it, along with other serine proteases, participates in the oxygen-independent process of internal and extracellular pathogen destruction [139-142]. HNE is essential for innate immune responses to microorganisms that are both intracellular and extracellular. HNE works by breaking down the membranes of Gram-negative bacteria that are being swallowed by neutrophil phagolysosomes [143] **Vergille *et. al* 2017**in their research emphasize that Compound 5a (Figure 8) is extremely strong and Ki values were found to be 75nm. The stability of the HNE inhibitor collectively was also tested by treating it with the most powerful cinnoline derivative 5b at a relatively high concentration (25 mM) [144].



Compound 5a-d

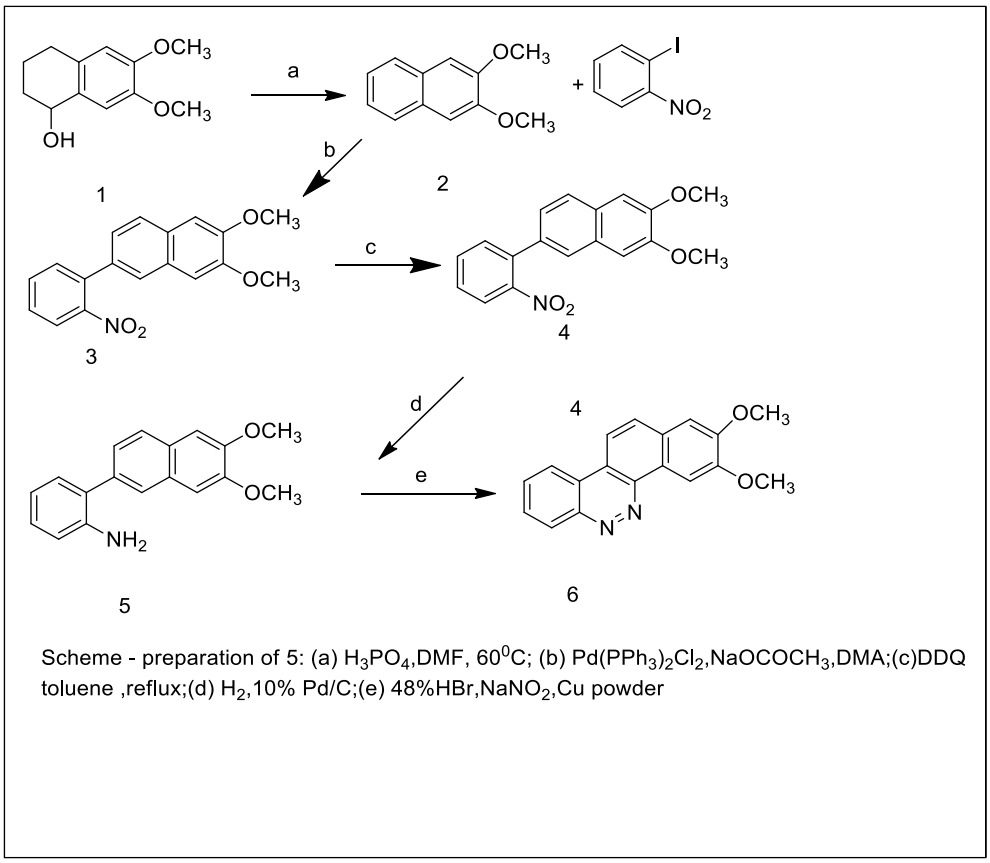
Sr No.	x
5a	m-CH_3-Ph
5b	CH_3
5c	C_2H_5
5d	C_3H_7

Figure 8: Potent Cinnoline Analog shows HNE (Human Neutrophil Elastase) Inhibition

Other Cinnoline Compounds with Anti- Cancer Activity

Cancer treatment is a major challenge for contemporary medicine [145]. **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 treated 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 IC50 value was determined to be 0.001 M, the synthesized molecule exhibited the strongest action against HeLa [146].



Scheme - preparation of 5: (a) H_3PO_4,DMF, 60^0C; (b) $Pd(PPh_3)_2Cl_2$,$NaOCOCH_3$,DMA;(c)DDQ toluene ,reflux;(d) H_2,10% Pd/C;(e) 48%HBr,$NaNO_2$,Cu powder

Figure 9: Synthesis of Cinnoline Derivative from 2,3 Dimethoxy Napthanol

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 degrees Celsius for 6-12 hours in order to generate 4,4'-dimethyl-3,3'-bis (4-substituted piperazin-1-yl)-6,6-bicinnoline. Newly synthesized bicinnolines were investigated for their cytotoxicity against cancer cells. To evaluate the effectiveness of the synthesized compounds, MDA-231 cells were used. There is a possibility of cytotoxic action (70%) in compounds 4k, 4n, and 4o [147].

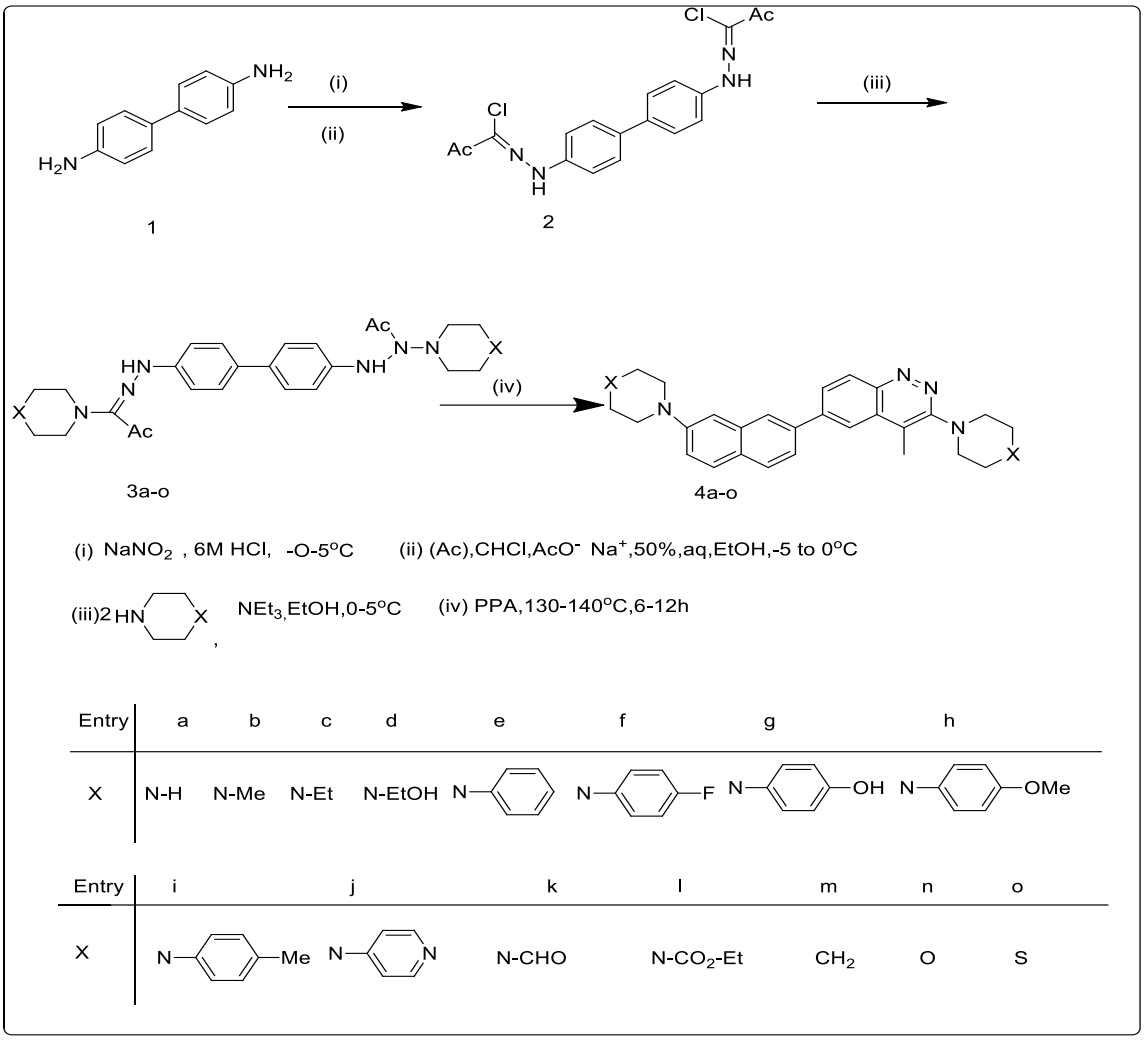


Figure 10: Synthesis of Bicinnoline Derivative from 1,1 biphenyl 4,4-diamine

Through intermolecular cyclization of the piperazinyl amidrazones, ***Eman et al***. **2012** produced 3-piperazinyl cinnolines. For this reaction, a cyclizing agent known as (Polyphenylacetylene)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 characterized by conducting cell viability assays using tetrazolium dye against MCF-7 cells. Compound 8b showed potent activity and IC_{50} value was found to be 5.56μM. compounds 10b and 10d have IC_{50} values of 11.79 and 8.57respectively [148].

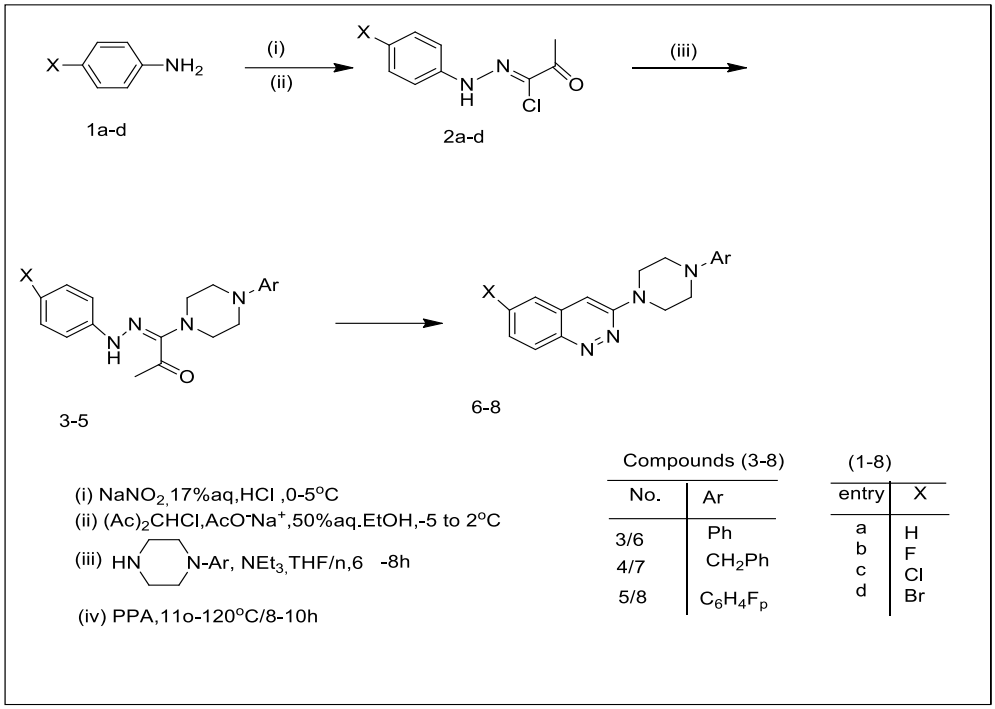


Figure 11: Synthesis of Cinnoline Derivative from 4-substituted Aniline

Another cinnoline analog was prepared by **Alexander *et. al.* 2003** by the reaction of 6,7- methylenedioxy-4- cinnoline with PCl5 and PCl3.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 were obtained through intramolecular cyclization of the iodobenzamides via the Heck reaction given in figure 12.

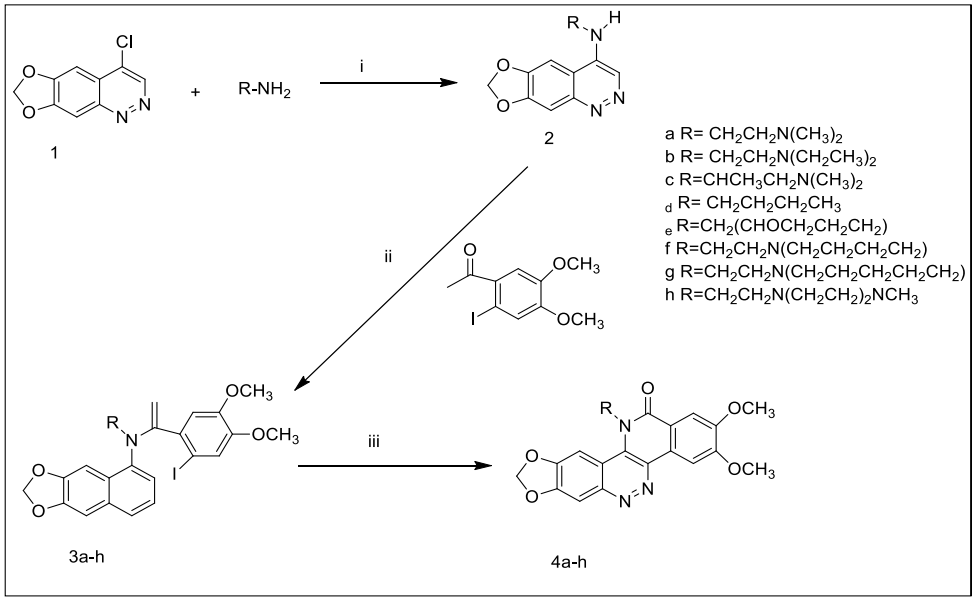


Figure 12: Synthesis of Cinnoline Derivative from 8-Chloro-1,3-dioxa-5,6-diaza-cyclopenta[b] napthalene

Microtiter plate tetrazolium cytotoxicity test was used to establish cell death (MTA). When tested for cytotoxicity in the human lymphoblast cell line RPM18402, the synthesized compounds 4a, 4b, and 4d revealed an IC50 value of 5Nm [149].

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 product. Antiproliferative activity was shown for compounds 1e, f produced against a panel of human cell lines with a mean graph midpoint (MG MID) in the 0.74-1.15M range [150].

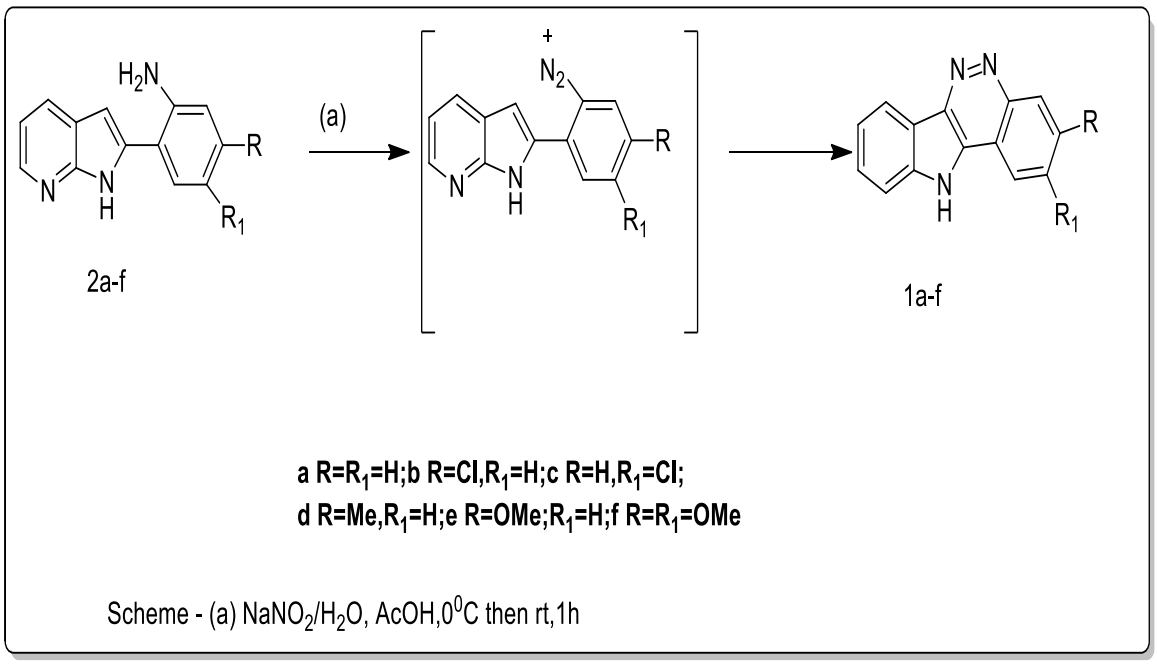


Figure 13: Synthesis of Cinnoline Derivatives from2(1 H -Pyrrolo [2,3b] pyridine-2-yl) phenylamine

Some other cinnoline nucleus containing derivatives targeting different receptors or targets are shown in Figure 14 [151-160]

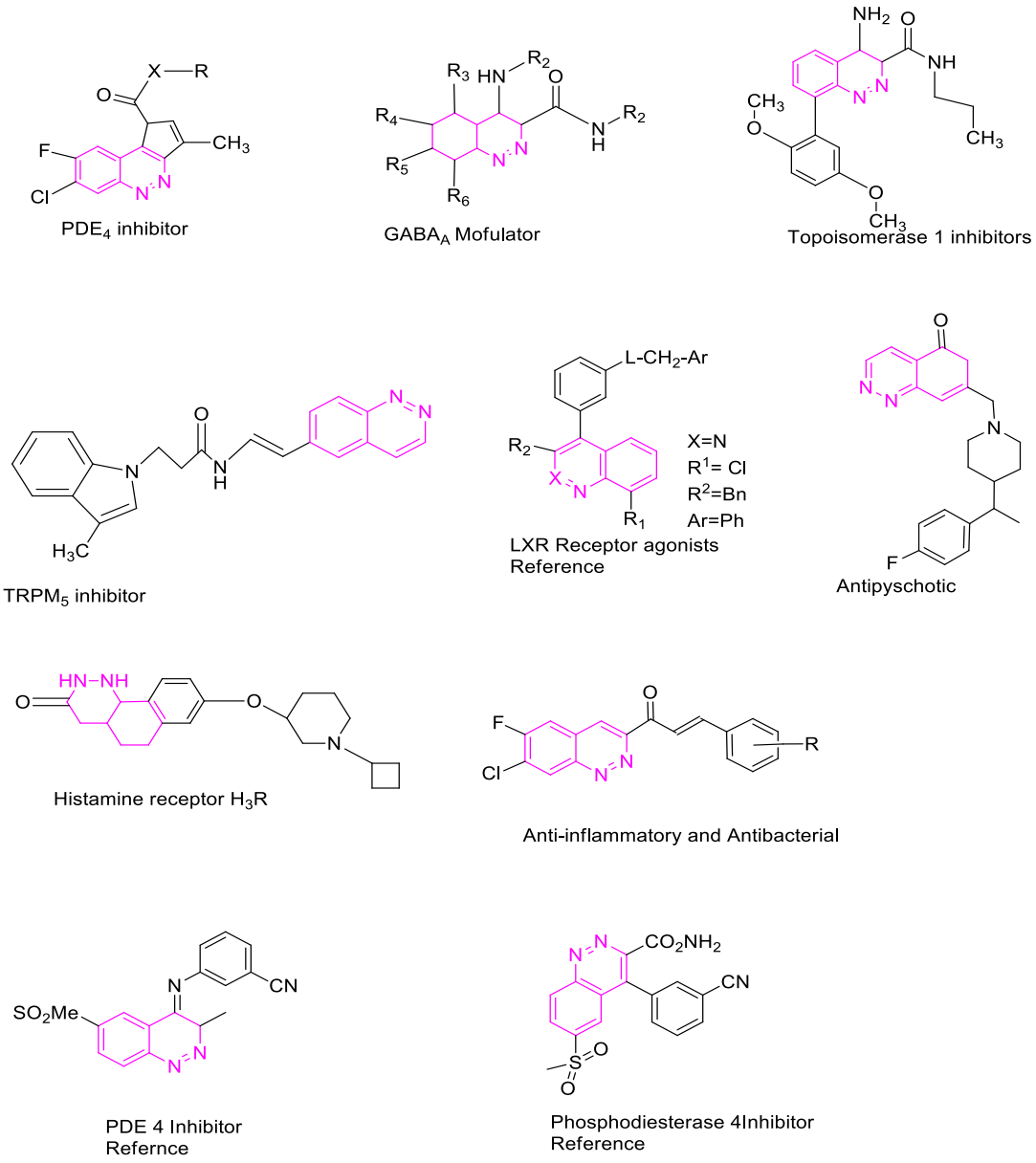


Figure 14: Cinnoline Compounds with Different Targets

CONCLUSION

Cinnoline is a heterocyclic molecule with antibacterial, antifungal, anticancer, anti-malarial, and anti-molluscidal properties. To find novel antibacterial and other effects, cinnolines are the topic of rigorous and logical biological research experiments. Compounds based on the cinnoline scaffold may form interactions with several biological targets, including topoisomerases, phosphodiesterases, and human neutrophil esterase in addition to receptors like CSF-1R. The importance of cinnoline derivatives in future drug development warrants more investigation into their synthesis, as shown by this work.

The new approaches to the treatment of various diseases will undoubtedly find this review paper useful. The leads or analogs discussed in this article may be utilized for the discovery of new medications by employing various forms of advanced technology and procedures.

Acknowledgement

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Conflict Of Interest

The authors declare no conflict of interest.

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