Original Article

A Comprehensive Review On Cinnoline Derivatives

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Abstract

Before the earliest living forms on our planet, heterocyclic mixtures were present. Several different types of natural particles and information were activated by these synthetics. Nature had selected heterocycles as the most significant organic building blocks. Cinnoline has a heterocyclic system with a fused six-member ring that comprises two nitrogen atoms and has garnered considerable attention in the field of chemical or synthetic research due to its distinctive structural activity. Cinnoline was a different heterocyclic aromatic atom with a number of special capabilities, including reducing, antifungal, antimalarial, anti-tubercular, anti-cancer activities, and so forth. Cinnoline's heterocyclic structure, which was interlaced into six ring components with two nitrogen molecules and had drawn considerable interest in a natural product or engineered investigations in a particular underlying function. This was the heterocyclic core that had the least amount of solidification, and research on it had garnered a lot of interest. Cinnoline is a member of a family of rather well-known heterocycles, yet research on its derivatives is still popular. Numerous studies have examined the biological property, structure-activity relationship, and applications in the field of medicine of cinnoline compounds, which exhibit intriguing bioactivity. Because of the interest in the wide range of pharmacological effects that these heterocyclic compounds with a cinnoline moiety exhibit, attention has been dedicated to their production. The synthesis, wide variety of functions, and applications of the aromatic molecule cinnoline are critically discussed in this study. In addition, this study has included various reported literature on the sophisticated synthesis and use of cinnoline in a variety of biological processes. The main focus of this review was on the antimicrobial, anti-inflammatory, and anthelmintic properties of cinnoline, a sweet-smelling chemical. It was also necessary to consider the numerous literary works on the further amalgamation and exploitation of cinnoline for this assessment.

Keywords: heterocyclic compounds, cinnoline, anthelminthic activity, anti-inflammatory activity, antimicrobial activity.

INTRODUCTION

The discovery of a new component of medicine has an impact on therapeutic science. One of the most important concepts in restorative science is an innovative drug dynamic part with an exercise component. Cinnoline is a separate class of synthetic chemicals that is used in a variety of organic and pharmacological processes in many everyday things. The history of heterocyclic chemistry is rich in new, useful molecules (Katrizky 1985). Nucleic acids, starches, macrocyclic hues, co-proteins, and alkaloids would all be able to be found in groups. Heterocycles are inextricably linked to natural cycles. Heterocycles are mostly based on pharmaceutical and agrochemical operations, which are crucial concerns. A heterocyclic structure known as cornucopy was created through tailored chemistry (Sammes 1979). Studies on heterocyclic builds and polycyclic accumulates are two particularly fascinating areas in this field. The first is the ongoing disclosure of novel heterocyclic materials that are necessary for all living cells, as well as the accessibility and digestion of a wide range of manufacturing products (Patterson et al., 1959; Chan, 1961). A lot of work was done to combine innovative therapeutic heterocycles and contemporary usage (Dupayrat 1970 and Mc Graw-Hill 2002). The identification, fusion, and production of new substance constituents suitable for therapeutic or pharmacological applications are all parts of restorative science, that is where science and pharmacology converge. Restorative science, which combines science and pharmacology, involves identifying, combining, and creating new material ingredients that are suitable for clinical or pharmaceutical purposes. It is concerned with the creation and blending of new particles, the assessment of the relationship between their design and natural behaviors, their assimilation and distribution throughout the body, their modification through metabolic processes, and their interactions with organic macromolecules (Nogrady and Weaver 2005). The most well-known hetero-particles include nitrogen, oxygen, and sulphur, as well as heterocyclic rings with additional hetero-iotas. Heterocyclic mixes are cyclic organs with about one hetero-iota. Due to their usage in diverse challenges, heterocyclic combinations have become one of the important families of natural synthetic chemicals used in many organic sectors (Alagarsamy 2010). Many heterocyclic combinations are used as antibacterial, urinary disinfectant, and mitigating medications in a variety of common illnesses. Heterocycles have been acknowledged as a

crucial primary component in clinical synthetic science, and they are frequently present in biomolecules as antifungal, antimicrobial, mitigating, antibacterial, cell reinforcements, hostile to allergics, herbicide-hindering, hostile to cancer action, and other biologically dynamic mixtures (Al-Mulla 2017).

Cinnoline

Cinnoline is a nitrogen-based natural premise comprised of diazo compounds, for example, 1,2-diazine (Hantsch-Widmann framework). In the isosteric framework, they are associated with quinoline or isoquinoline. V. Richter was quick to orchestrate his core in 1883, and he gave it the name heterocyclic framework. The immense scope of pharmacological properties of cinnoline and its subsidiaries, like antibacterial, anticancer, antifungal, and mitigating impacts has provoked consideration. Some of the mixtures in the cinnoline class are used as agrochemicals and have antithrombic and anti-warmth effects, as well as sedative and narcotic properties (Awad et al., 2011). Cinnoline is a strong, light yellow, 6-membered heterocyclic molecule (Fig.1) that dissolves at 39 °C and has a pKa of 2.64 and two Nitrogen heteroatoms. They respond as a result of the benzene ring and the electrophilic attack (Mishra et al., 2015).

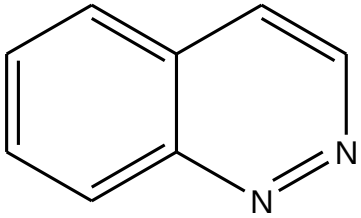
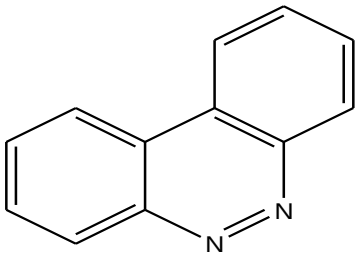


Fig: 1. Cinnoline structure

Cinnoline has bioactivity in a number of domains, including antithrombotic, antihypertensive, anticancer, antisecretory, and bactericidal activities, as do its benzo (Fig.2) and heterocyclic simple subordinates. The 4-amino cinnoline's antimicrobial, antihistamine, and bug spray properties have recently gained significance. Amino dimethyl ethyl cinnoline Dimethyl amine 4-carboxylate has been effective as an antifungal specialist and in the biosynthesis of cholesterol and tryptamine in animals. (Castle et al., 1961; Cignarella et al., 1989; Lown et al., 1990; Mujamoto et al., 1990; Patel et al., 1973).



Benzo(c) Cinnoline

Fig: 2. Benzo (e) Cinnoline

Cinnoline (1,2-benzodiazine) is included in a number of substances with important pharmacological and chemical significance (Artis et al., 2015). The ring structure has six members and two nitrogen atoms. It is isomeric to phthalazine and isosteric to quinoline or isoquinoline (Lewgowd et al., 2007 and Castle 1973).

Numerous distributions have been expounded on the blend of cinnoline and its subsidiaries (Vinogradova and Balova 2008; Kumari et al., 2016; Muralirajan et al., 2013; Kiriazis et al., 2007; Mathew et al., 2017; and Haddadin 2010). Until 2011, no mixtures with the cinnoline ring framework were found in nature. 2-furanmethanol-(5′11)-1,3-cyclopentadiene-[5,4-c] was the principal regular cinnoline subordinate found. While concentrating on the *in vitro* and in vivo hepatoprotective impacts of Cichorium endivia L. extricate, - 1H-cinnoline was distinguished (CEE) Because of their assorted natural activities relying upon the sort and area of their substituents, engineered compounds with a cinnoline structure have gotten a lot of consideration. Besides, they are oftentimes made as analogs of recently obtained quinoline or isoquinoline compounds (Satyanarayana et al., 2008; Devine et al., 2015; Alhambra et al., 2011; and Barlaam et al., 2018).

Anti-inflammatory activity

Jain et al., 2021 synthesized a series of piperazine derivatives of cinnoline to possess anti-inflammatory activity as evaluated using the rat paw edema method. They examined the piperazine-based heterocyclic (Fig.3) corrosive and discovered that its distinctive design has acquired an amazing role in the field of therapeutic science, luring researchers to grow innovative piperazine-based particles with a variety of organic exercises.

The existence of diverse synthetic compounds with different pharmacological characteristics may strengthen the evidence in the writing. Current analgesics and painkillers have been linked to damaging side effects, which has led to a decline in their use.

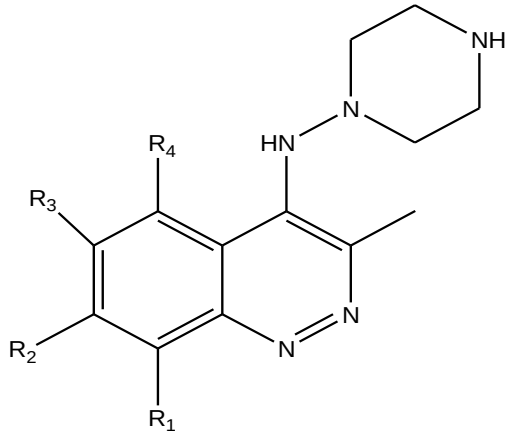


Fig: 3. Piperazine substituted derivatives of cinnoline

Singh et al., 2015 successfully synthesized, purified and characterized 6-sulphonamido-cinnolines (Fig. 4). All compounds were screened for anti-inflammatory activity using bovine serum albumin denaturation model. 6-sulphonamido cinnolines was obtained in good yield by Friedel-Craft reaction involving cyclisation. Sulphanilamide (1) with sodium nitrite in presence of Conc. HCl at 0-5°C form diazonium salt (2), which on treatment with cyanoacetamide gives aryl hydrazine (cyano) acetamide (3). This was reacted with anhydrous $AlCl_3$ in the presence of chlorobenzene to form 4-amino-6-sulphonamido-3-cinnolino carboxamides (4) which was further refluxed with formamide to give sulphonamido cinnolino- pyramidine (5). 4-amino-6-sulphonamido-3- cinnolino carboxamides in THF was stirred with various anilines(a-g) which gave different urea derivatives G-6(a- g). Sulphonamido cinnoline (4) in the presence of alcohol with 2-3 drops of glacial acetic acid was refluxed with various aldehydes (a-d) to give different schiff's base G-4 (a- d). 4-Hydrazino-6-sulfamoyl-cinnoline-3-carboxylic acid amide (5) was synthesized by sulphonamido cinnoline (63) with hydrazine hydrate in presence of ethylene glycol as a solvent.

All synthesized compounds were identified and characterized by physical methods like M.P., TLC, and spectral method UV, IR, and NMR data. The compounds were also subjected for bovine serum albumin denaturation which was considered as *in vitro* anti-inflammatory model. The newly synthesized compounds were tested for their microbial susceptibility using an *in vitro* model against Bacillus subtillis (gram +ve) and Escherichia coli (gram -ve). The compounds were also subjected to denaturation of bovine serum albumin, which was thought to be an *in vitro* anti-inflammatory model. The newly synthesized substances 4, 5, 9, 15 and 17 demonstrated strong antibacterial activity. Weak action was shown by other substances. The anti-inflammatory activity of compounds 5, 6, 7, and 13 was good. Others that were synthesized (4, 12, and 16) showed only moderate activity.

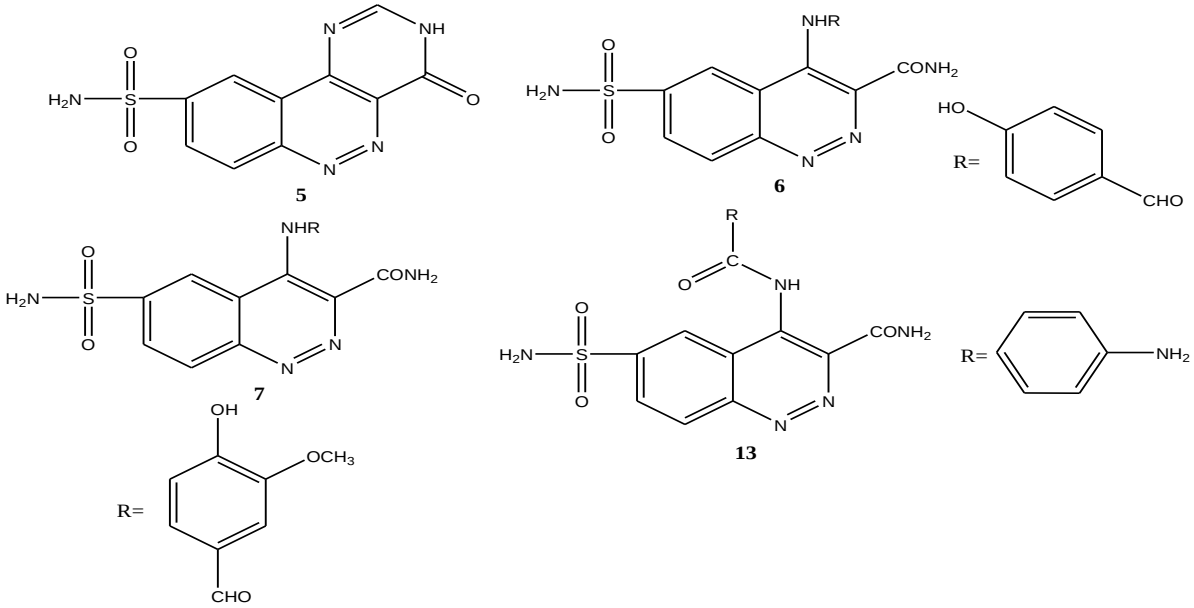


Fig. 4. Sulphonamido-cinnolines as anti-inflammatory compounds

Chaudhary et al., 2014 promising anti-bacterial efficacy, a novel series of condensed Cinnoline derivatives with or without Pyrazoline was developed. Combining the cyclic condensation reaction with the compound 3-chloro-4-fluoro aniline (1) results in 3-acetyl-7-chloro-6-fluoro cinnoline-4(1H)-one (3). Compound undergoes Claisen-Schmidt condensation with aromatic benzaldehyde to produce in good yields the equivalent 7-chloro-6-fluoro-3-[-3-substituted phenylprop-2-enoyl] cinnoline-4(3H)-one ($4_{a\text{-}f}$). In the process of cyclocondensing various substances with phenyl hydrazine, the product is 7-chloro-6-fluoro-3- [5-(substituted phenyl)1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]cinnoline-

4(3H)-one (5_{a-f}), (Fig.5). The newly synthesized chemicals have been identified by IR, ^{1}HNMR, and mass spectral investigations. Anti-inflammatory activity was determined by carrageenan induced rat paw edema method. The results of the investigation showed that compounds of cinnoline without pyrazoline and those of cinnoline with pyrazoline were active in reducing inflammation (% inhibition 3.49 to 58.20). Cinnoline with pyrazoline compound 5a and 5d showed good anti-inflammatory activity with % of inhibition 58.50 and 55.22 respectively. Compounds 5b and 5f shown less potent than standard drug. Cinnoline without pyrazoline compound 4a, 4b, 4d and 4f was found to be least potent.

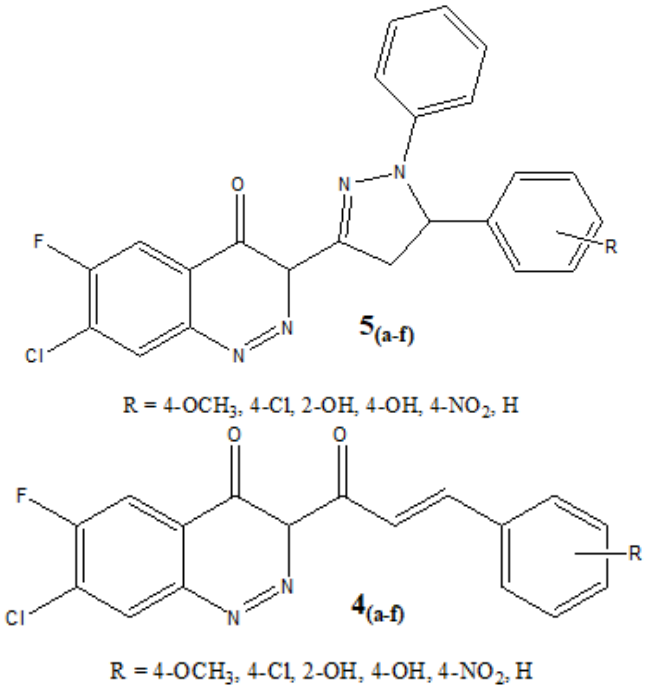


Fig: 5. Cinnoline derivatives with dual anti-inflammatory and antibacterial activity

Tonk et al., 2012 synthesized a series of pyrazolo [4,3-c]cinnoline derivatives (Fig.6), characterized, and tested for their anti-inflammatory and antibacterial properties. Test substances with strong anti-inflammatory properties were further examined for their ulcerogenic and lipid peroxidation potential. Comparing compounds 4d and 4l to naproxen, they demonstrated potential anti-inflammatory action with decreased ulcerogenic and lipid peroxidation activity. Docking results of these two compounds with COX-2 (PDB ID: 1CX2) also exhibited a strong binding profile. Compound 4i, one of the test derivatives, demonstrated notable antibacterial activity against gram-negative (Escherichia coli and Pseudomonas aeruginosa) and gram-positive (Staphylococcus aureus) pathogens. But in this investigation, compound 4b was found to be the best combined anti-inflammatory and antibacterial substance.

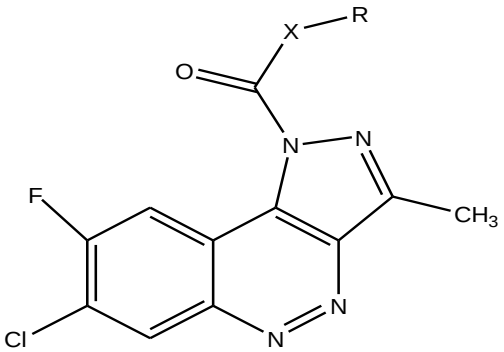


Fig: 6. Pyrazolo [4, 3-c] cinnoline derivatives as anti-inflammatory and antibacterial agents

Antimicrobial Activity

The quantity of MRS cases is continually expanding, just like the presentation of strains with less anti-microbial obstruction. Anti-microbials, immunosuppressive medications, intravenous catheters, relocate organ transfers, and continuous contamination episodes generally added to this ascent (Jain et al., 2021; Katrizky et al., 1985; and Kiriazis et al., 2007). Furthermore, manufactured prescriptions are not just costly and inadequate in non-industrial nations for treating illnesses, however they are additionally much of the time tainted and defiled. Subsequently, new disease control measures are important to stay away from microbial contamination (Gonzalez et al. 1996).

Culture conditions will be made utilizing microorganisms like microbes and organism. The impact of new heterocyclic orchestrated synthetic compounds on microscopic organisms will be tried *invitro* against a perceived reference

substance (Ruchelman et al., 2004; Hennequin et al., 1999; and Sato eint al., 2008)**.** The antimicrobial specialist's *in vitro* action was evaluated to decide the antimicrobial specialist's solidarity and affectability to a known portion of treatment by the provided miniature life form. Contamination protection from realized drug specialists is on the ascent all around the world, representing a developing remedial challenge (Grabill 1988; Sieradzki et al., 1999). Thus, new prescriptions with further developed movement against both medicine touchy and drug-safe ailments should be created as quickly as time permits. Cinnoline subordinates have been utilized to test a wide scope of antibacterial medications. Cinoxacin is a typical anti-toxin used to treat urinary lot diseases (Wiederhold 2017; Ventola 2015; Guay 1982).

Vargas et al., 2008 created two naphthyl ester quinolone derivatives (Fig.7) and tested their capacity to produce reactive oxygen species (ROS) like $^1O_2$, OH, and H_2O_2 upon photolysis with UV-A light. By using the histidine assay and luminol-enhanced chemiluminescence (LCL), respectively, it was possible to determine that the drugs cinoxacin (1), nalidixic acid (2), and their naphthyl ester derivatives (3), and (4), could produce a dose-dependent amount of singlet oxygen and ROS (O_2, OH) in cell-free systems. Escherichia coli were used to assess compounds 3 and 4 antibacterial activity in the dark and under radiation, and their results were compared to those of their parent compounds. By exposing the naphthyl esters of cinoxacin and nalidixic acid to radiation, an increase in antibacterial activity against E. coli was seen.

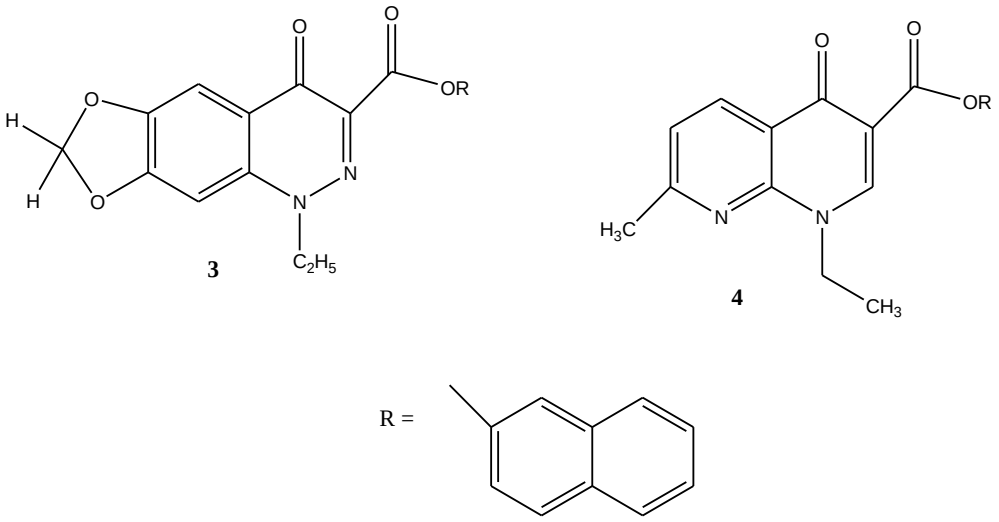
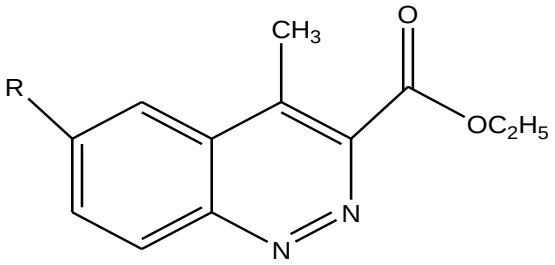


Fig: 7. Quinolones and their naphthyl ester derivatives

Jakhar 2018 synthesized 3-carbethoxy-6-substituted-4-methylcinnolines (Fig.8) by cyclization of phenylhydrazonocarbethoxyacetones under microwave irradiations used polyphosphoric acid as condensing agent. The phenylhydrazonocarbethoxyacetones were prepared from benzenediazonium chloride and ethylacetoacetate. The antibacterial potential of the synthesize compounds had been described against *S. aureus*, *E. coli*, *S. typhii*, *P. aeruginosa* and *K. pneumonia* used disk diffusion method. Antibacterial screening data indicate that all carbethoxycinnolines showed moderate to good activity against *E. coli*, *S. typhii*, *P. aeruginosa* and *K. pneumonia*. The compounds 2a, 2d and 2e showed moderate activity against *S. aureus*.

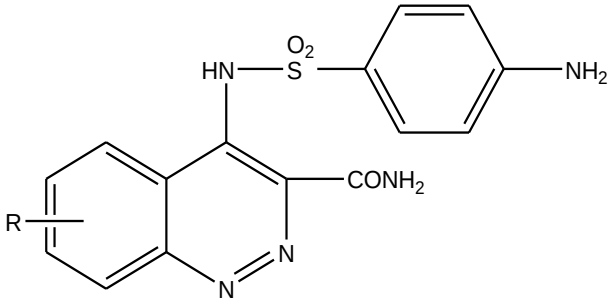


(2_{a-e})

R = H, CH_3, OCH_3, Cl, Br

Fig: 8. 3-carbethoxy-6-substituted-4-methylcinnolines

Vikas et al., 2009 synthesized substituted cinnoline sulphonamide derivatives (Fig.9) by condensation of p-amino-benzene sulphonyl chloride with different substituted 4-amino cinnoline 3-carboxamides. Hydrazone was produced by intramolecular cyclization, which was then coupled with cyanoacetamide in an aqueous ethanolic solution containing sodium acetate, followed by diazotization. Spectral data were used to describe them. The anti-microbial activity of each produced molecule was tested against *P. aeruginosa*, *E. coli*, *B. subtilis*, *S. aureus*, *C. albicans* and *A. niger*. Bromo and chloro substituted products among the chemicals studied had found strong antibacterial action.



$7_{a\text{-}i}$

Fig: 9. Substituted 4-(p-aminophenylsulphonamide) cinnoline-3-carboxamide

Yuvaraj et al., 2010 synthesized 3'-methyl-6-sulphamido-1'substituted-pyrazolo [4,3-c] cinnoline derivatives (Fig.10) by diazotizing sulphanilamide and coupling the resulting hydrazones to synthesize 3-acetyl-6-sulphamido-cinnolin-4-ones. Furthermore, treatments with hydrazine hydrate. TLC, UV, IR, and NMR spectral analysis were used to characterize the substances. The disc diffusion method was employed to screen for antibacterial activity against *C. albicans, E. coli, K. aurogeniosea, M. luteus, and B. cereus*.

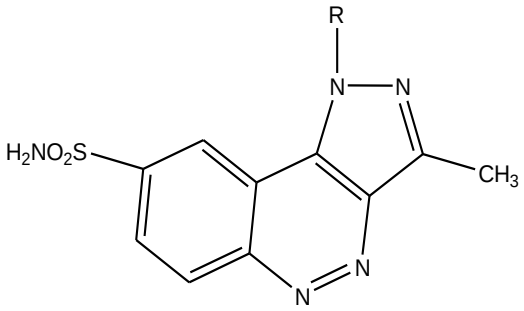
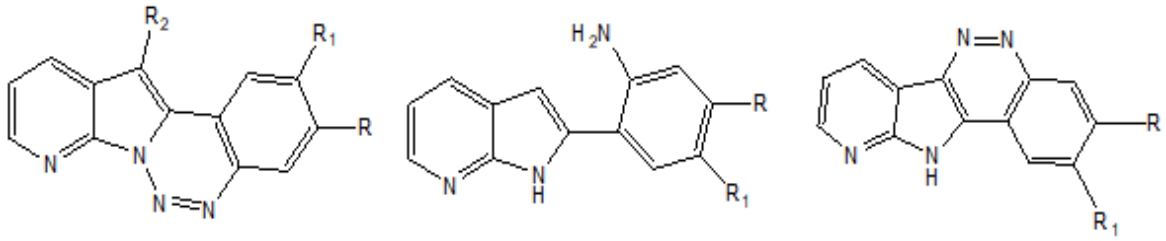


Fig: 10. 3-Methyl-6-sulphonamido-1'-substituted pyrazolo cinnolines

Parrino et al., 2014 portrayed the 11H-pyrido [3′,2′:4,5] pyrrolo [3,2-c] Cinnoline as a substance (Fig.11). The cinnoline derivative, pyrrolo [3,2-c], was tested on a board of 60 human growth cell lines by the National Cancer Institute and shown strong cytotoxicity (Bethesda, MD, USA). The drugs examined were unquestionably adequate in their ability to combat the leukaemia subpanel. It was also shown that MDR1 was active within cells. The compounds completely caused caspase-3, caspase-8, and caspase-9 activation as well as apoptosis, mitochondrial depolarization, responsive oxygen age, and other processes. They also function as topo-isomerase inhibitors.



R = H, Cl, Me, OMe; R_1 = H, Cl, OMe: R_2 = Br, NO

Fig: 11. 11H-pyrido [3′, 2′:4, 5] pyrrolo [3,2-c] Cinnoline as cytotoxics

Szumilak et al., 2019 His research examines the worldwide natural migration of cinnoline derivatives between 2005 and 2019 as directed by several exploration associations. The pathophysiology of different diseases is heavily influenced by GABA A, CSF-1R, and H3R receptors, as well as substances like cyclooxygenase-2, topoisomerases, phosphodiesterase, human neutrophil elastase, and Bruton tyrosine kinase. Platform conveyance for cinnoline increases Following that, medicines that are antibacterial, antifungal, soothing, pain-relieving, anxiolytic, and cancer-hostile should be used. Clinical preliminary trials are being conducted with a few cinnoline subordinates.

Fayed et al., 2019 synthesized number of new thienopyridazine derivatives (Fig.12) by using 9-aminodibenzo [f,h] thieno [2,3-c]cinnoline-8-carbonitrile as the starting material. Against the bacterial strains E. coli, S. aureus, B. subtilis, and K. pneumoniae as well as the fungal strains A. fumigatus and C. albicans, the target products demonstrate potential antibacterial and antifungal activities. Pyridothieno cinnoline derivatives exhibit the strongest antibacterial action against all examined microorganisms.

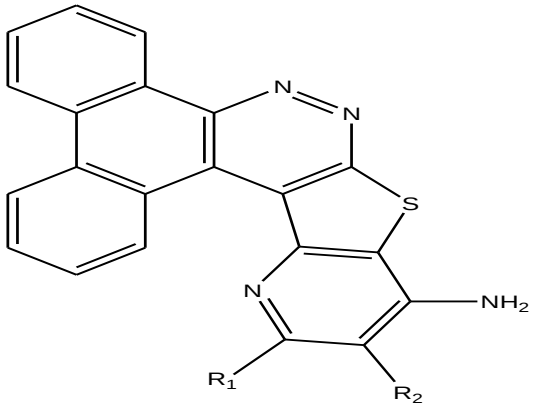


Fig: 12. Pyridothieno cinnoline derivatives as antibacterial agents

Anthelminthic activity of substituted cinnoline derivatives

One of the most common human illnesses, helminth contaminations affect a sizeable portion of the world's population. This general medical condition is a major contributor to ill health, sickness, eosinophilia, and pneumonia in impoverished nations. Antihelmintics are medications that eliminate or kill contaminated helminths, which are undoubtedly also present in the tissues through which their enormous hatchlings pass. Anthelmintic drugs are used to treat the digestive system (Choudhari 2006; Suzuki et al., 2019) By stealing food, producing blood misfortune, harming organs, causing internal or lymphatic blockage, and delivering poisons, they cause harm to the host. Even though it only seldom results in death, helminthiasis is a common cause of illness (Bundy 1994).

Novel amalgamation-based heterocyclic mixes are assessed *invitro* by comparing the creature's loss of motion and passing events to a recognised standardised substance. One of the most well-known signs of disease in humans, dairy cattle, and wild animals is helminthiasis. It continues to be the primary cause of human vulnerability, dependency, intellectual inability, and ageing, as well as of crucial financial setbacks in the domestic animal sector (Lo et al., 2017; Barraja et al. 1999). Flow gauge data suggests that just roundworms are believed to harm about 1.5 billion people worldwide (Vercuysse et al. 2018). The important helminth parasites of both animals and humans are rapidly becoming resistant to anthelmintics (Liu et al., 2020; Sangster et al. 2018).

Saxena et al., 2010 In order to study substitute cinnoline subsidiaries rich in imidazole (Fig 13) focus for anthelmint workouts, it was necessary to determine when worms stopped moving and when they died. Four cinnoline imidazole compounds demonstrated strong anthelmintic action as compared to mebendazole, with a worm passing in a much shorter amount of time and a somewhat longer immobility span.

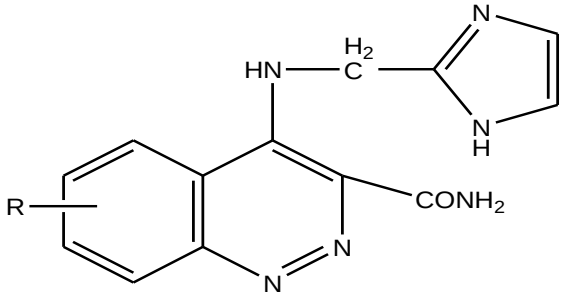


Fig: 13. Substitute cinnoline imidazole derivatives

Dahiya et al., 2008 synthesized novel 3,5-diiodo-4- (5-nitro-1H-2-imidazolyl) benzoyl amino acids and di/tri/tetrapeptides(Fig.14) employing coupling agents diisopropylcarbodiimide/dicyclohexylcarbodiimide (DIPC/DCC) and bases N-methylmorpholine/triethylamine (NMM/TEA). All of the newly synthesized compounds' structures were determined using elemental analysis, IR, 1H NMR, 13C NMR, and mass spectrum data. When synthesized imidazolopeptides were tested for anthelmintic activity, it was discovered that they had moderate to good bioactivity against the earthworms Megascoplex konkanensis, Pontoscotex corethruses, and Eudrilus eugeniea at dose levels of 2 mg mL^{-1}.

Dutta et al., 2010 developed a range of 1a-j 2-substituted 4.5-diphenyl imidazoles (Fig.14) in the presence of ammonium acetic acid derivatives and icy acidic corrosive by refluxing benzil in different aldehydes. IR, 1H NMR, and mass range data were used to approve the synthetic compound designs. Anthelmintic activity was evaluated for intensifies 1(a–j). The mixes exhibited death times ranging from 2.16 to 2.47 minutes at 1 percent (m/V), passing times ranging from 0.39 to 4.40 minutes, loss of motion periods ranging from 0.54 to 0.58 minutes, and common medications albendazole and piperazine citrates. The anthelmintic activity of five compounds, 2-[2-hydroxyphenyl]-4,5-Diphenylimidezole (1b), 2-[3-methoxyphenyl]-4,5-diphenyl imidazole (1c), 2-[2-phenylethenyl]-4,5-diphenyl imidazole (1e), 2-[4-fluorophenyl]-4,5-diphenyl imidazole (1g), and 2-[3-nitrophenyl]-4,5-diphenyl (1h) showed significant anthelmintic activity.

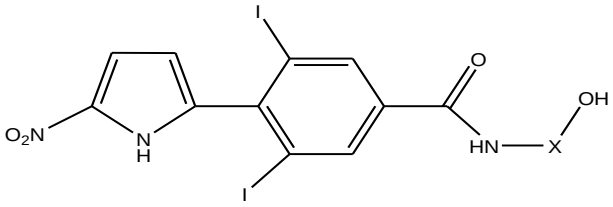
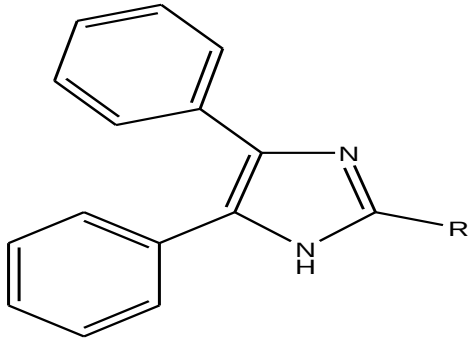


Fig: 14. Novel 3, 5-diiodo-4-(5-nitro-1H-2-imidazolyl) benzoyl amino acids and di/tri/tetra peptides



R – phenyl, 2-hydroxyphenyl, 3-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 2-phenylethenyl, 2-chlorophenyl, 4-fluorophenyl, 3-nitrophenyl, H, methyl

Fig. 14. 2-substituted 4.5-diphenyl imidazoles as anthelmintics

Varshney et al, 2014 synthesized Substituted Cinnoline benzimidazole derivatives (Fig.15) in four steps. First, substituted anilines were used to make diazonium salt, which was then used to make 3-chlorophenyl hydrazono (cyno) acetamide (2a-g), which was made by reacting cyano acetamide with 10 gm CH_3COONa and 15 ml alcohol. Step three produces 7-chloro substituted 4-aminocinnoline-3-carboxamide (3a-g) by treating 3-chlorophenylhydrazono (cyno) acetamide with anhydrous $AlCl_3$, chlorobenzene, and nitrogen gas for 30 minutes (p-amino benzimidazole) The reaction of substituted 4-amino cinnoline-3-carboxamide in DMF and o-chloro benzimidazole produced cinnoline -3-carboxamide. By using physical and analytical data, the produced substances were evaluated. The synthetic substances' anthelmintic potency was assessed. The anthelmintic activity of all the synthesized substituted cinnoline benzimidazoles ranged from moderate to good.

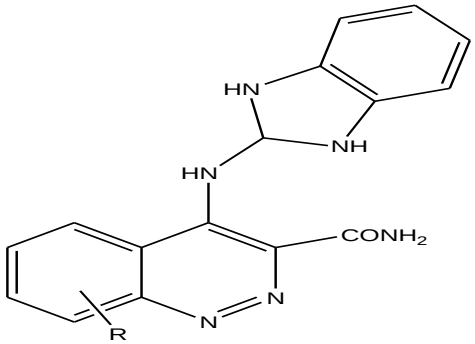


Fig. 15. substituted 4-(p-amino benzimidazole) cinnoline -3-carboxamide

Bhavsar et al., 2020 observed that anthelmintic specialists have been expanded lately, bringing about the advancement of medication obstruction. Subsequently, the improvement of novel anthelmintic prescriptions in the field of restorative science is irrefutably and quickly expanding. Ongoing exploration has shown countless amazingly successful and specific medications that can adequately eliminate helminthic parasites. This article audits the writing from the past nineteen years (2001–2019) on the assortment and anthelmintic movement of different heterocyclic compound creation processes.

CONCLUSION

In this paper, we have presented a review of studies focused on the biological activity of cinnoline derivatives carried out by numerous research groups across the globe between 1982 and 2022. The information provided makes it abundantly clear how important the cinnoline framework is as a building block of numerous valuable compounds. They are therefore designed for usage as anti-inflammatory, anti-microbial and anthelmintic medicines. In clinical trials, some cinnoline derivatives are being examined. It is undeniable that the creation of molecules based on cinnoline has significantly aided in the discovery of lead compounds with ideal pharmacodynamic and pharmacokinetic features. To find novel antimicrobial, anti-inflammatory & anthelmintics and other actions, cinnolines are therefore the focus of thorough and logical biological investigations. These results will serve as the foundation for developing new cinnoline

derivatives that could be employed as medicines or as molecules with additional biological functions. Subsequently, this heterocyclic center is available to additional investigation later.

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CONFLICT OF INTEREST

None conflict of interest has been declared by the authors.

REFERENCES

1. Alagarsamy V. Textbook of Medicinal Chemistry. 2013 Oct 9;3(1):43.
2. Alhambra C, Becker C, Blake T, Damewood Jr JR, Daniels T, Dembofsky BT, Gurley DA, Hall JE, Herzog KJ, Horchler CL, Ohnmacht CJ. Development and SAR of functionally selective allosteric modulators of GABAA receptors. Bioorganic & medicinal chemistry. 2011 May 1;19(9):2927-38.
3. Al-Mulla A. A review: biological importance of heterocyclic compounds. Der Pharma Chemica. 2017;9(13):141-7.
4. Artis D, Spits H. The biology of innate lymphoid cells. A review. Nature. 2015 January 15;517: 293–301.
5. Awad ED, El-Abadelah MM, Matar S, Zihlif MA, Naffa RG, Al-Momani EQ, Mubarak MS. Synthesis and Biological Activity of Some 3-(4-(Substituted)-piperazin-1-yl) cinnolines. Molecules. 2011 Dec 28;17(1):227-39.
6. Barlaam B, Cadogan E, Campbell A, Colclough N. Dishington A, Durant S, Goldberg K, Hassall L.A, Hughes G.D, MacFaul P.A. et al. Discovery of a series of 3-cinnoline carboxamides as orally bioavailable, highly potent, and selective ATM inhibitors. ACS Medicinal Chemistry Letters 2018 July 13;9: 809–814.
7. Barraja, P, Diana, P, Lauria, A, Passannanti A, Almerico A. M, Minnei C, Longu, S, Congiu D, Musiu, C, La Colla P. Indolo [3,2-c]cinnolines with antiproliferative, antifungal, and antibacterial activity. Bioorganic Medicinal Chemistry. 1999 August; 7(8): 1591-1596.
8. Bhavsar Zeel A, Acharya Prachi T, Divya J, Jethava, & Patel, Hitesh D. Recent advances in development of anthelmintic agents: Synthesis and Biological Screening. Synthetic Communications. 2020 March 9; 50(7): 917-946.
9. Bundy D.A. The global burden of intestinal nematode disease. Transactions of the society of Tropical Medicine & Hygiene. 1994 May 1;88(3):259–61.
10. Castle N.R; The Chemistry of Heterocyclic Compounds. John Wiley & Sons; New York, NY, USA: 1973; 27:1–231.
11. Castle Raymond N, & Onda M. for Cinnoline Chemistry. VI. Basic Esters Ethers & Amides. 1961 July 1; 26(7): 2374-2378.
12. Cahn R.S. An Introduction to Chemical Nomenclature. 1959; 63(8):716.
13. Chaudhary, J, Patel K, & Patel, C.N. Synthesis and biological screening of some cinnoline derivatives. International Journal of Universal Pharmacy and Bio Sciences. 2014; 3:128-140.
14. Chen C.J, Deng A.J, Liu C, Shi R. Qin H.L, Wang A.P. Hepatoprotective activity of Cichorium endivia L. extract and its chemical constituents: Molecules. 2011;16(11): 9049–9066.
15. Choudhari B.P, Mulwad V.V, Synthesis and antimicrobial screening of 3H,11H-9-methyl-3-oxopyrano [2,3-f]cinnolino [3,4-c]pyrrazole and its derivatives: Indian Journal of Chemistry-Section B. 2006;45B:309-313.
16. Cignarella G, Barlacco D, Pinna G.A, Curzu M.M, Tofanetti O, & Germini M. et al. Synthesis and biological evaluation of substituted benzo [H] cinnolinones and 3H-benzo [6, 7] cyclohepta [1, 2-c] pyridazinones: Higher homologs of the antihypertensive and antithrombotic 5H-indeno [1, 2-c] pyridazinones: Journal of Medicinal Chemistry. 1989 32(10): 2277-2282.
17. Dahiya R, Kumar A. Synthesis, spectral and anthelmintic activity studies on some novel imidazole derivatives. E-Journal of Chemistry. 2008 Nov 1;5(S2):1133-43.
18. Devine W, Woodring JL, Swaminathan U, Amata E, Patel G, Erath J, Roncal NE, Lee PJ, Leed SE, Rodriguez A, Mensa-Wilmot K. Protozoan parasite growth inhibitors discovered by cross-screening yield potent scaffolds for lead discovery. Journal of Medicinal Chemistry. 2015 Jul 23;58(14):5522-37.
19. Dutta S. Synthesis and anthelmintic activity of some novel 2-substituted-4, 5-diphenyl imidazoles. Acta Pharmaceutica. 2010 Jun 1;60(2):229-35.
20. Fayed AA, Yousif MN, Abdelgawad TT, Amr AE, Yousif NM, Gad FA. Synthesis and antimicrobial activity of novel polycyclic thienopyridazine derivatives. Chemistry of Heterocyclic Compounds. 2019 Aug;55(8):773-8.
21. Fernandes JV, Cobucci RN, Jatobá CA, de Medeiros Fernandes TA, de Azevedo JW, de Araújo JM. The role of the mediators of inflammation in cancer development. Pathology & Oncology Research. 2015 Jul;21(3):527-34.
22. Gonzalez CE, Venzon D, Lee S, Mueller BU, Pizzo PA, Walsh TJ. Risk factors for fungemia in children infected with human immunodeficiency virus: a case-control study. Clinical Infectious Diseases. 1996 Sep 1;23(3):515-21.
23. Graybill JR. Therapeutic agents. Infectious disease clinics of North America. 1988 Dec 1;2(4):805-25.
24. Guay DR. Cinoxacin (Cinobac, Eli Lilly & Co.). Drug Intelligence & Clinical Pharmacy. 1982 Dec;16(12):916-21.
25. Haddadin MJ, Zerdan RM, Kurth MJ, Fettinger JC. Efficient syntheses of the unknown quinolino [2, 3-c] cinnolines; synthesis of neocryptolepines. Organic Letters. 2010 Dec 3;12(23):5502-5.
26. Hennequin LF, Thomas AP, Johnstone C, Stokes ES, Plé PA, Lohmann JJ, Ogilvie DJ, Dukes M, Wedge SR, Curwen JO, Kendrew J. Design and structure activity relationship of a new class of potent VEGF receptor tyrosine kinase inhibitors. Journal of Medicinal Chemistry. 1999 Dec 30;42(26):5369-89.
27. Heppner F.L, Ransohoff R.M, Becher B. Immune attack: The role of inflammation in Alzheimer disease. Nature Reviews Neuroscience. 2015; 16:358–372.
28. Hu E, Kunz RK, Rumfelt S, Chen N, Bürli R, Li C, Andrews KL, Zhang J, Chmait S, Kogan J, Lindstrom M. Discovery of potent, selective, and metabolically stable 4-(pyridin-3-yl) cinnolines as novel phosphodiesterase 10A (PDE10A) inhibitors. Bioorganic & Medicinal Chemistry Letters. 2012 Mar 15;22(6):2262-5.
29. Isailovic N, Daigo K, Mantovani A, Selmi C. Interleukin-17 and innate immunity in infections and chronic inflammation. Journal of Autoimmunity. 2015 Jun 1;60:1-1.
30. J. Dupayrat. Structural nomenclature and Heterocycles. Technip, Paris. 1970.
31. Jain A, Chaudhary J, Khaira H, Chopra B, Dhingra A. Piperazine: a promising scaffold with analgesic and anti-inflammatory potential. Drug Research. 2021 Feb;71(02):62-72.
32. Katrizky A.R. Hand Book of Heterocyclic chemistry. Pergermon press. 1985:2-10.
33. Kiriazis A, Rüffer T, Jäntti S, Lang H, Yli-Kauhaluoma J. Stereoselective aza Diels− Alder reaction on solid phase: A facile synthesis of hexahydro cinnoline derivatives. Journal of Combinatorial Chemistry. 2007 Mar 12;9(2):263-6.
34. Kumari S, Kishore D, Paliwal S, Chauhan R, Dwivedi J, Mishra A. Transition metal-free one-pot synthesis of nitrogen-containing heterocycles. Molecular Diversity. 2016 Feb;20(1):185-232.

35. Lewgowd W, Stanczak A. Cinnoline derivatives with biological activity. Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry. 2007 Feb;340(2):65-80.
36. Lewgowd W, Stanczak A. Cinnoline derivatives with biological activity. Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry. 2007 Feb;340(2):65-80.
37. Liu M, Panda SK, Luyten W. Plant-based natural products for the discovery and development of novel anthelmintics against nematodes. Biomolecules. 2020 Mar 9;10(3):426.
38. Lo NC, Addiss DG, Hotez PJ, King CH, Stothard JR, Evans DS, Colley DG, Lin W, Coulibaly JT, Bustinduy AL, Raso G. A call to strengthen the global strategy against schistosomiasis and soil-transmitted helminthiasis: the time is now. The Lancet Infectious Diseases. 2017 Feb 1;17(2):e64-9.
39. Loane DJ, Kumar A. Microglia in the TBI brain: the good, the bad, and the dysregulated. Experimental Neurology. 2016 Jan 1;275:316-27.
40. Lown J.W, Morgan A.R, Yen S.F, Wang Y.H, Wilson Y.H, & Wilson W.D. Biochemistry. 1990; 24:4028.
41. Lucas SM, Rothwell NJ, Gibson RM. The role of inflammation in CNS injury and disease. British Journal of Pharmacology. 2006 Jan;147(S1):S232-40.
42. Mathew T, Papp AÁ, Paknia F, Fustero S, Prakash GS. Benzodiazines: recent synthetic advances. Chemical Society Reviews. 2017;46(10):3060-94.
43. Mc Graw-Hill. Encyclopedia of Science and Technology. 2002; 9(8): 491- 492,
44. Mishra P, Middha A, Saxena V, Saxena A. Synthesis and evaluation of anti-inflammatory activity of some cinnoline derivatives-4 (-2-amino-thiophene) cinnoline-3-carboxamide. Pharmaceutical and Biosciences Journal. 2016 Jun 24:64-8.
45. Mishra P, Saxena V, Minu K, Abhishek S. Synthesis, characterization and anti-inflammatory activity of cinnolines (pyrazole) derivatives. Journal of Pharmaceutical and Biological Sciences. 2015;10(6):77-82.
46. Muralirajan K, Cheng CH. Rhodium (III)-Catalyzed Synthesis of Cinnolinium Salts from Azobenzenes and Alkynes: Application to the Synthesis of Indoles and Cinnolines. Chemistry–A European Journal. 2013 May 10;19(20):6198-202.
47. Nogrady T, Weaver DF. Medicinal chemistry: a molecular and biochemical approach. Oxford University Press; 2005 Aug 11;3:7-9.
48. Parasuraman P, Shanmugarajan RS, Aravazhi T, Nehru K, Mathiazhaga T, Rajakumari R. Synthesis, characterization and antimicrobial evaluation of some substituted 4-amino cinnoline-3-carboxamide derivatives. International Journal of Pharmacy & Life Sciences. 2012 Feb 1;3(2).
49. Parrino B, Carbone A, Muscarella M, Spanò V, Montalbano A, Barraja P, Salvador A, Vedaldi D, Cirrincione G, Diana P. 11 H-Pyrido [3′, 2′: 4, 5] pyrrolo [3, 2-c] cinnoline and pyrido [3′, 2′: 4, 5] pyrrolo [1, 2-c][1, 2, 3] benzotriazine: Two new ring systems with antitumor activity. Journal of Medicinal Chemistry. 2014 Nov 26;57(22):9495-511.
50. Patel N. R, Singerman G. M, Stanovnik B, Tidler M. Condensed Pyridazines Including Cinnolines and Phthalazines. The Chemistry of Heterocyclic Compounds. Weissberger, A., Ed.; Wiley: New York. 1973;27.
51. Patterson A.M, Capell L. T, & Walkar D.F. The Ring Index. A list of Ring systems used in organic chemistry. American Chemical Society Washington D. C. 1959;2.
52. Pedraza-Alva G, Pérez-Martínez L, Valdez-Hernández L, Meza-Sosa KF, Ando-Kuri M. Negative regulation of the inflammasome: keeping inflammation under control. Immunological Reviews. 2015 May;265(1):231-57.
53. Rock KL, Lai JJ, Kono H. Innate and adaptive immune responses to cell death. Immunological Reviews. 2011 Sep;243(1):191-205.
54. Ruchelman AL, Singh SK, Ray A, Wu X, Yang JM, Zhou N, Liu A, Liu LF, LaVoie EJ. 11H-Isoquino [4, 3-c] cinnolin-12-ones: novel anticancer agents with potent topoisomerase I-targeting activity and cytotoxicity. Bioorganic & Medicinal Chemistry. 2004 Feb 15;12(4):795-806.
55. Sammes P.G. Comprehensive Organic Chemistry. Pergermon Press Oxford; 1979;4.
56. Sangster NC, Cowling A, Woodgate RG. Ten events that defined anthelmintic resistance research. Trends in Parasitology. 2018 Jul 1;34(7):553-63.
57. Sato Y, Suzuki Y, Yamamoto K, Kuroiwa S, Maruyama S, inventors; Nippon Kayaku Co Ltd, assignee. Novel 3-phenyltetrahydrocinnolin-5-ol derivative and medicinal use thereof. United States Patent Application US 11/597,232. 2008 Feb 14.
58. Satyanarayana M, Feng W, Cheng L, Liu AA, Tsai YC, Liu LF, LaVoie EJ. Syntheses and biological evaluation of topoisomerase I-targeting agents related to 11-[2-(N, N-dimethylamino) ethyl]-2, 3-dimethoxy-8, 9-methylenedioxy-11H-isoquino [4, 3-c] cinnolin-12-one (ARC-31). Bioorganic & Medicinal Chemistry. 2008 Aug 15;16(16):7824-31.
59. Saxena V, Hoque M, Satyanarayana D, Saxena A, Kumar A. Anthelmintic activity of substituted cinnoline imidazole derivatives. Journal of Veterinary Parasitology. 2010;24(1):101-2.
60. Shankhdhar P, Saxena V. Synthesis and evaluation of anthelmintic activity of some substituted cinnolothiophene derivatives. World Journal of Pharmaceutical Research. 2016 July 4;5(8):737-743.
61. Shruti V, Vikas S, Rohit K. Synthesis, characterization and biological activity of substituted cinnoline benzimidazole derivatives. International Journal of Pharmaceutical Sciences Review and Research. 2014;27:69-73.
62. Sieradzki K, Wu S, Tomasz A. Inactivation of the methicillin resistance gene mecA in vancomycin-resistant Staphylococcus aureus. Microbial drug resistance. 1999;5(4):253-7.
63. Singh A, Nargund D. Synthesis and Pharmacological evaluation of 6-Sulphonamido cinnoline for Pharmacological and antibacterial activity. International Journal of Current Trends in Pharmaceutical Research. 2015;3(5): 1023-1029.
64. Suzuki I, Nakadate M, Nakashima T, Nagasawa N. Synthesis of cinnoline 1, 2-dioxide. Tetrahedron Letters. 1966 Jan 1;7(25):2899-903.
65. Szumilak M, Stanczak A. Cinnoline scaffold—a molecular heart of medicinal chemistry. Molecules. 2019 Jun 18;24(12):2271.
66. Tonk RK, Bawa S, Chawla G, Deora GS, Kumar S, Rathore V, Mulakayala N, Rajaram A, Kalle AM, Afzal O. Synthesis and pharmacological evaluation of pyrazolo [4, 3-c] cinnoline derivatives as potential anti-inflammatory and antibacterial agents. European Journal of Medicinal Chemistry. 2012 Nov 1;57:176-84.
67. Vargas F, Zoltan T, Rivas C, Ramirez A, Cordero T, Díaz Y, Izzo C, Cárdenas YM, López V, Gómez L, Ortega J. Synthesis, primary photophysical and antibacterial properties of naphthyl ester cinoxacin and nalidixic acid derivatives. Journal of Photochemistry and Photobiology B: Biology. 2008 Aug 21;92(2):83-90.
68. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. Pharmacy and Therapeutics. 2015 Apr;40(4):277.
69. Vercruysse J, Charlier J, Van Dijk J, Morgan ER, Geary T, von Samson-Himmelstjerna G, Claerebout E. Control of helminth ruminant infections by 2030. Parasitology. 2018 Nov;145(13):1655-64.
70. Vignali DA, Kuchroo VK. IL-12 family cytokines: immunological playmakers. Nature Immunology. 2012 Aug;13(8):722-8.
71. Vikas S, Darbhamulla S. Synthesis, characterization and biological activities of substituted cinnoline culphonamides. African Health Sciences. 2009;9(4).
72. Vinogradova OV, Balova IA. Methods for the synthesis of cinnolines. Chemistry of Heterocyclic Compounds. 2008 May;44(5):501-22.
73. Waisman A, Liblau R.S, Becher B. Innate and adaptive immune responses in the CNS. Lancet Neurology. 2015;14(9):945–955.
74. Wiederhold NP. Antifungal resistance: current trends and future strategies to combat. Infection and Drug Resistance. 2017;10:249.
75. Yu Y, Singh SK, Liu A, Li TK, Liu LF, LaVoie EJ. Substituted dibenzo [c, h] cinnolines: Topoisomerase I-targeting anticancer agents. Bioorganic & Medicinal Chemistry. 2003 Apr 1;11(7):1475-91.
76. Yuvaraj TV, Unnissa SH, Surendiran NS, Binumon V. Synthesis and antimicrobial screening of some novel cinnoline derivatives. Asian Journal of Research in Chemistry. 2010;3(4):853-8.
77. Zhao D, Wu Q, Huang X, Song F, Lv T, You J. A general method to diverse cinnolines and cinnolinium salts. Chemistry–A European Journal. 2013 May 10;19(20):6239-44.