World of Cinnolines: A Mini Review

Authors: Priya Kumar*, Dr. K. Saravanan[1], Dr. Vikas saxena[2]

**Research Scholar, Department of Pharmacy, Bhagwant University, Ajmer, Rajasthan, Email id:*

[1]Research Dean, Bhagwant University, Ajmer, Rajasthan

[2]Director, Rakshpal Bahadur College of Pharmacy, Bareilly, Uttar Pradesh

ABSTRACT

Cinnolines is one of the most interesting heterocyclic nucleus rings which have been used so far with its usage in magnificent biological activities. Its condensed bicyclic aromatic heterocyclic contains two nitrogen atoms. Cinnolines exhibit a wide range of biological activities such as anticancer, antimicrobial, antiviral properties and many more. Derivatives of cinnoline have shown promise as kinase inhibitors, which are important targets for anticancer therapy. Furthermore, cinnoline derivatives have also demonstrated activity against several viruses, including the hepatitis B virus and influenza virus. Cinnoline derivatives have also been investigated for their potential use in the treatment of infectious diseases. In addition to their potential as drugs, cinnolines have also been studied for their use in material science. One of the challenges in the synthesis of cinnolines is the low regioselectivity of many of the reactions used to prepare these compounds. This article provides an overview of recent developments and pharmacological advances of cinnolines that has been studied over a long period of time since it has been introduced to the world. Its pharmacological developments have also been studies from last ten years which has shown wide biological advancements. However, several new methods have been developed in recent years to address this. Overall, cinnolines represent an exciting area of research with promising applications in both chemistry and biology.

Keywords : *Cinnolines, Anticancer activity, pharmacological advancements*

INTRODUCTION

Cinnolines (1,2-benzodiazine) with the formula $C_8H_6N_2$ is considered as one of the most interesting aromatic heterocyclic compound (Figure 1) that posses wide range of pharmaceutical activities [1].

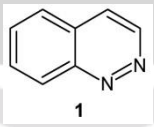

Figure 1

It contains two vicinal nitrogen atoms, an isosteric relative to either quinoline or isoquinoline and isomeric with phthalazine [2]. The numbering system has been done from one of the Nitrogen atom that present on the para position as depicted (Figure 2). Cinnolines are one of the two benzo subordinates of pyridazines, have been essentially pre-arranged through buildups of hydrazine subsidiaries with carbonyl mixtures followed by ring terminations of different sorts [3,4,5].

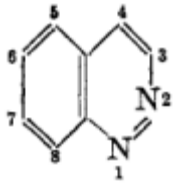

Figure 2

Cinnolines synthesis has been fairly discussed and published in several papers and its derivative preparation is still continues [1,6,7,8,9,10,11,12]. Over a period of long time no cinnoline derivative were prepared from any source but after 2011 2-furanmethanol-(5′→11)-1,3-cyclopentadiene-[5,4-c]-1H-cinnoline 2 (Figure 3) was secluded from *Cichorium endivia* when investigating the in vivo and in vitro hepatoprotective properties of *Cichorium endivia L.* extract (CEE) [13).

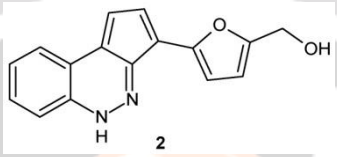

Figure 3

Several papers since Von Richert [7] has introduced Cinnoline to the world have been made and cinnoline got publicity in abundance and its derivatives too has very well described as pharmaceutically active. In this paper, we have reviewed the work that has been discussed in the past ten years where cinnoline and its derivatives have shown potential therapeutic usage.

PHARMACOLOGICAL ADVANCEMENTS OF CINNOLINE DERIVATIVES

1.1 Antimicrobial Activity

The entire world is suffering from one or other kind of infections and to get heals from infections different formulations and preparations have been done. Cinnoline derivatives as they have shown potential therapeutic use are now in trend and are giving potent results [14,15,16]. As cinnoline derivatives have shown potency in antimicrobial activity which results in the designing and synthesizing more novel derivatives of cinnolines [1,17].

Barraja P and his team have synthesized a series of novel indolo[3,2-c]cinnolines derivatives (Figure 4) that has shown great potency as antifungal activity particularly against *Cryptococcus neoformans* [18].

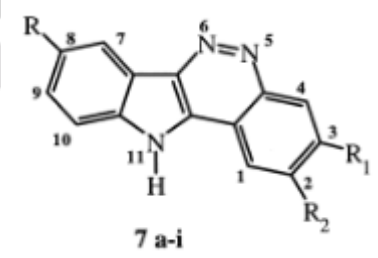

Figure 4

Moreover, 6-hydroxycinnolines (Figure 5) were combined and tried for in vitro antifungal movement against *Candida* and *Aspergillus* species. It was explained that the vast majority of the got intensifies shown strong antifungal movement against *C. krusei*, *C. neoformans*, and *A. niger*, with the most elevated action towards *C. neoformans* [19].

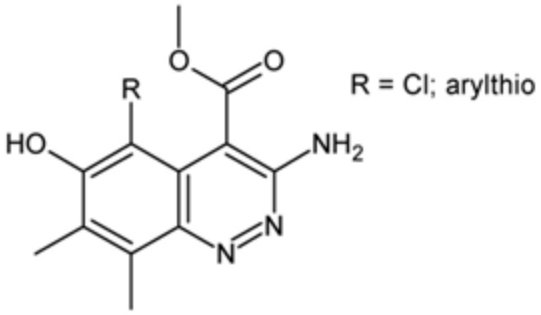

Figure 5

1.2 Anthelminthic activity

Helminth contamination is considered as one of the prevalent sicknesses which can be seen in today's era [20]. Antihelmintics condition can be noticed in both humans and animals. The sickness includes the infection of all types of flatworms i.e. flukes (trematodes) and tapeworms (cestodes) as well as round worms (nematodes) [21]. WHO estimated and recorded the world's population of nearly 1.5 billion or 24% suffering from harbour parasitic worm causing the increase in both mortality and morbidity rate [22]. The majority of anthelmintics and nematicides are limited in their action between trematodes, cestodes, and nematodes, for example, praziquantel, a drug used in the treatment of most humans infected with trematodes or cestodes (Table 1) and thought to act by disrupting calcium homeostasis, has no activity against nematodes. Only benzimidazoles have cross-phyla activity and even then are more active against nematodes than against cestodes or trematodes [23].

Schistosomiasis (blood fluke)	**Intestinal round worms**
Oxamnaquine	Piperazine
Praziquantel	Benzimidazoles
	Morantel
	Pyrantel
Cestodiasis (tape worm)	Levamisole
Albendazole	Avermectins and milbemycins
Niclosamide	Tribendimidine
Benzimidazoles	
Praziquantel	
Fasciolasis (liver fluke)	**Filariasis (tissue round worms)**
Triclabendazole	Diethylcarbamazine
	Albendazole
	Ivermectin

Table 1 (Anthelmintic drugs and nematicides: studies in *Caenorhabditis elegans*)

With the increase in helminth infection the Antihelmintic drugs are now in high demand in both humans and animals. Several cinnoline derivatives have been synthesized to work against Antihelmintic activity [24].

1.3 Analgesic and Anti-inflammatory Activities

Cinnoline derivatives have gained significant interest in recent years due to their diverse biological activities, including their analgesic and anti-inflammatory properties. A number of cinnoline derivatives have been reported to exhibit significant analgesic and anti-inflammatory activities in various preclinical and clinical studies.

One such compound is Flavopiridol, a cinnoline derivative originally identified as a cyclin-dependent kinase (CDK) inhibitor, which has also been reported to exhibit potent analgesic and anti-inflammatory activities. In a study conducted by Deng et al. [25], Flavopiridol was shown to significantly reduce inflammation and pain in a murine model of carrageenan-induced paw edema and mechanical hyperalgesia. The compound was found to inhibit the production of pro-inflammatory cytokines and promote the expression of anti-inflammatory cytokines, leading to a reduction in inflammation and pain. Flavopiridol has also been reported to exhibit analgesic effects in other preclinical studies, including a rat model of neuropathic pain (Ning et al., 2019).

Another cinnoline derivative with reported analgesic and anti-inflammatory activities is LQB-118. In a study conducted by Zhang et al. (2019), LQB-118 was shown to exhibit potent anti-inflammatory and analgesic effects in a mouse model of lipopolysaccharide-induced acute lung injury. The compound was found to reduce the levels of pro-inflammatory cytokines and increase the levels of anti-inflammatory cytokines, leading to a reduction in lung inflammation and pain. LQB-118 has also been reported to exhibit analgesic effects in a mouse model of chronic pain induced by spinal nerve ligation (Xu et al., 2021).

Ro-31-8220 is another cinnoline derivative that has been reported to exhibit analgesic and anti-inflammatory activities. In a study conducted by Hashimoto et al. in 2004, Ro-31-8220 was shown to significantly reduce mechanical allodynia and thermal hyperalgesia in a rat model of neuropathic pain induced by partial sciatic nerve ligation. The compound was found to inhibit the activity of protein kinase C (PKC), a key regulator of nociceptive signaling, leading to a reduction in pain [26]. Ro-31-8220 has also been reported to exhibit anti-inflammatory effects in other preclinical studies, including a mouse model of inflammatory bowel disease [27].

In summary, cinnoline derivatives have shown great promise as potential analgesic and anti-inflammatory agents. The diverse biological activities of cinnoline derivatives and their structural flexibility make them attractive targets for drug discovery and development. Further research is needed to fully elucidate the mechanisms of action of cinnoline derivatives and to evaluate their therapeutic potential in clinical settings.

CONCLUSION

This mini review has presented the studies based on the review focused on the synthesis of cinnolines and their pharmacological advantages that has happened all over the world. This review has reviewed only certain activities though cinnolines are capable of much more than that. The development of cinnolines novel molecules even in the upcoming era will give benefit to the scientific society every now and then.

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