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A CONCISE REVIEW ON CINNOLINE SCAFFOLD

Aswathy J.[1]*, Dr. Prasobh G. R.[1], Prof. Sheeja Rekha A. G.[1], Athira A. S.[1], Kavya Raveendran[1]

[1]Assistant Professor, Department of Pharmaceutical Chemistry, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala.

[2]Principal, Head of Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala.

[3]Professor, Head of Department of Pharmaceutical Chemistry, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala.

[4]Assistant Professor, Department of Pharmaceutical Chemistry, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala.

[5]Assistant Professor, Department of Pharmacology, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala.

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***Corresponding Author**
Aswathy J.
Assistant Professor, Department of Pharmaceutical Chemistry, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala.

ABSTRACT

Cinnoline has good attention in the field of research study due to its wide spectrum of biological activity and therapeutic applications. Cinnoline is a good lead compound for the synthesis of novel drugs. There is a growing interest in the synthesis of several cinnoline derivatives as better drug candidates for the treatment of various diseases. Cinnoline contain a strong pharmacophoric moiety and ring structure it attracts the researchers to this nucleus for the synthesis of novel drugs. Through this review, introduce a new way for a researcher by introducing this nucleus and develop a novel class of drugs who have a better therapeutic profile. In this review, mainly discuss the different pharmacological activity of cinnoline which has already discussed by the researchers. These reports have resulted in a great number of contributions in diverse areas of interest. This study may produce a new way for the researchers to design and develop the cinnoline derivatives with good pharmacological activities.

KEYWORDS: Cinnoline, Anticancer agent, antibacterial, anti-inflammatory and anti-fungal activity.

INTRODUCTION

Cinnoline or 1,2-diazanaphthalene or 1, 2- benzodiazine or benzopyridazine (Fig.1) are important class of heterocyclic compounds. Cinnoline is a fused six membered ring containing two nitrogen atoms with special structural activity have been showed special interest in chemical or synthetic research field.[1,2]

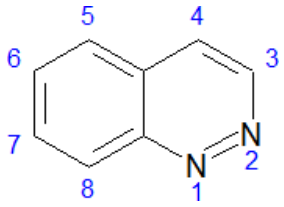

Fig.1: Structure of Cinnoline.

Several research studies are focused on the cinnoline nucleus due to their wide applicability. Cinnoline derivatives are promising drug candidate for the treatment of various diseases. The pharmacological activities exhibited by cinnoline are anti-inflammatory, antihypertensive, cytotoxic, antitumor, anticancer, anticonvulsant, antibacterial, antitubercular and antifungal activity.[3,4] There is a number of cinnoline based drugs are available.

Many researchers consider the cinnoline is a good therapeutic target for studying different pharmacological activities. Cinnoline forms a different derivative with interesting biological properties due to the presence of better pharmacophoric moiety.[5] It has a versatile pharmacophore with more medicinal significance. The medicinal chemist has more attention towards the cinnoline nucleus.[6] It is an attractive building block for the synthesis of many drugs. It is a versatile lead for the development of new drugs. Among a large variety of nitrogen- containing heterocyclic compounds, heterocyclic containing hydrazine has considerable attention because of their pharmacological properties and clinical applications.[7]

Mishra Pankaj et al synthesized substituted cinnoline thiophene derivatives (Fig.2), the compounds which are halogen mainly chloro, bromo and fluoro substituted were showed potent antibacterial, anti-inflammatory and anti-fungal activity than other compounds. Especially chloro substituted compounds showed more potent antimicrobial activity and anti-inflammatory activity among all the substituted cinnoline thiophene compounds.[8]

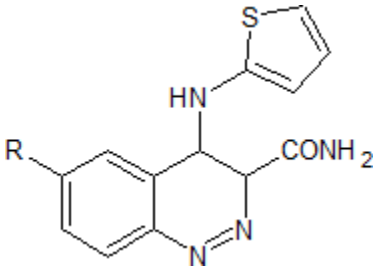

Fig.2: Substituted cinnoline thiophene derivatives.

Vikas et al synthesized substituted cinnoline sulphonamide derivatives (Fig.3) by the condensation of p-amino-benzene sulphonyl chloride with various substituted 4-amino cinnoline 3-carboxamides which was obtained by the intramolecular cyclization of the hydrazone which in turn obtained by coupling with cyanoacetamide in aqueous ethanolic solution containing sodium acetate followed by diazotisation. All the synthesized compounds were screened for their anti- microbial activity. Among the compounds tested bromo and chloro substituted products showed significant antimicrobial activity.[9]

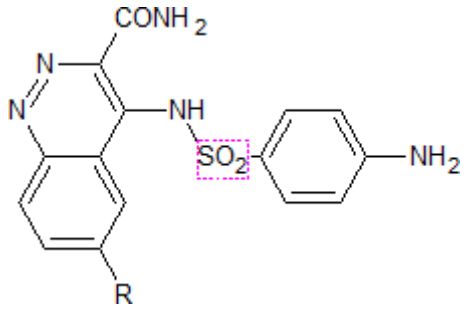

Fig. 3: Cinnoline sulphonamide derivatives.

Parrino et al synthesized 11H-pyrido, pyrrolo [3,2-c] cinnoline derivative (fig.4) which exhibited high cytotoxic activity against a panel of 60 human tumor cell lines. Particular efficacy of tested compounds was observed against the leukemia subpanel. They also found to move in cells over expressing MDR. The compounds caused apoptosis, mitochondrial depolarization, generation of reactive oxygen species, and therefore the activation of caspase-3, caspase-8, and caspase-9. They acted as topo isomerase I inhibitors.[10]

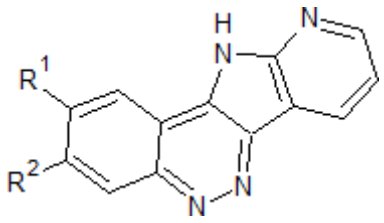

Fig. 4: Pyrido pyrrolo cinnoline derivatives.

Parasuraman et al synthesized 7-substituted 4- amino cinnoline-3-carboxamide derivatives (Figure.5) that were evaluated against a panel of Gram+ and Gram− bacteria. All the synthesized compounds exhibited moderate to good antibacterial activity. The MIC (Minimal inhibitory concentration) of tested compounds against V. cholera, E. coli, B. substills, B. linctus, M. luteus, S. aureus, K. pneumoniae, Corynebacterium and S. albus was found to be within the range of 6.25–25 µg/mL. They synthesized another compounds exhibited moderate to good antifungal activity against A. fumigatus, S. griseus, A. niger, A. parasitus, C. albicans and M. ruber, with the zone of inhibition between 8–27 mm. MIC values were found to be within the range of 6.25– 25 µg/Ml.[11]

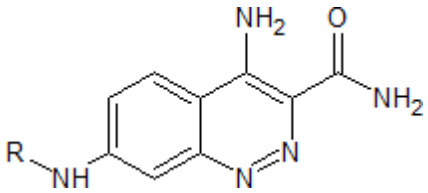

Fig.5: 7-substituted 4- amino cinnoline-3-carboxamide derivatives.

Kalyani et al designed and synthesized a series of novel cinnoline fused mannich bases by the condensation reaction of 4-methyl-3-acetyl cinnoline with different secondary aromatic and aliphatic amines. The biological potential of newly synthesized compounds (Figure 6) are evaluated for their antibacterial activity against Staphylococcus aureus (Gram positive), and Escherichia coli (Gram negative) bacteria. Compounds having larger hydrophobic substitutions such as diphenyl and dicyclohexane groups at amino group creating bulkier region resulted in relatively higher antibacterial against S. aureus and E. coli when compared to Streptomycin.[12]

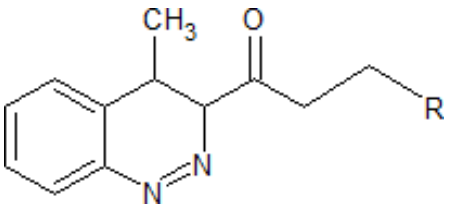

Fig. 6: Cinnoline fused Mannich Bases.

Hurmath Unnissa et al synthesized a series of pyridazine derivatives by diazotization of substituted anilines followed by Friedel-Crafts acylation and coupling to form corresponding hydrazones which on Intramolecular cyclization forms 3- acetyl-substituted benz pyridazine-4(1H)-one. Further condensation reaction by treatment with hydrazine hydrate yields the

expected 3'-methy-substituted –pyrazolo[4,3-C] cinnoline derivatives (Figure 7). All the synthesized compounds were checked for drug likeliness using Molinspiration software and toxicity prediction studies were conducted using Protox and Gusar software and found to be efficatious and sreening for antimicrobial activity studies. Evaluation of the results from anti-bacterial studies showed that synthesized pyridazine derivatives exhibit moderate to good antibacterial with a zone of inhibition were found to be in the range of (5-30mm) as compared to standard ciprofloxacin(10µg/disc).[13]

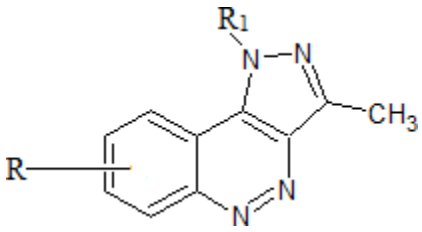

Fig. 7: Pyrazolo cinnoline derivatives.

Zoidis et al synthesized tetra- and pentacyclic cinnoline based compounds indeno[1,2-c]cinnoline (Figure 8) and benzo[h]indeno[1,2-c]cinnoline respectively, bearing protonable amino groups. All tested compounds inhibited proliferation of human cervical carcinoma (HeLa) and human breast adenocarcinoma (MCF-7) cell lines also as displayed intercalating properties on different macromolecule strands, with preference for G-quadruplex sequences. The aminobutylamide derivative exhibited the very best antiproliferative activity with IC50 values of 45 nM and 85 nM on HeLa and MCF-7, respectively, whereas the pentacyclic derivative with an equivalent protonable moiety (N,N-dimethylamine) caused the very best thermal stabilization in melting studies and exerted acceptable inhibitory activity on human topoisomerase Iiα.[14]

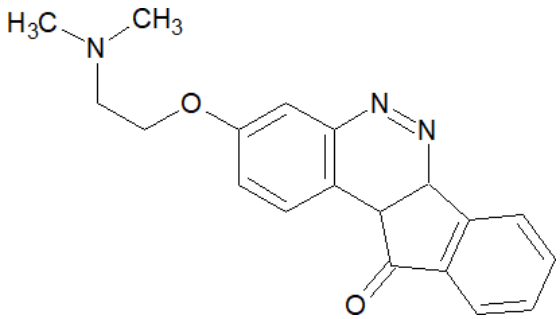

Fig. 8: Indeno cinnoline derivatives.

CONCLUSION

The data reported above clearly intimate that cinnolines are endowed with wide range of

biological activities such as anticonvulsant, cardiotonic, antimicrobial, antitumor, antihypertensive, analgesics, anti-inflammatory, antitubercular, vasorelaxant and other anticipated activities. It can be concluded that cinnoline have great potential for the synthesize of novel drugs. Because of the strong pharmacophoric group and ring position present in the cinnoline nucleus. The substitution of various functional groups in the cinnoline rings leads to various novel cinnoline derivatives with diverse biological activities. It is a promising lead molecule for the design and development of new drugs with potent biological activities.

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