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A concise literature review on synthesis and pharmacological actions of 1, 2 benzodiazine (cinnolines): Prashanthi Evangeline, Mulagani

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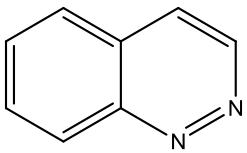
Abstract
Cinnoline (1, 2 benzodiazine or pyridine) is a novel aromatic bioactive heterocyclic compound which have wide range of pharmacological profiles like antimicrobial activity like antibacterial, antifungal, anti-inflammatory, antihelminthic activity, anti molluscicidal activity, antimalarial, anti-tuberculosis, anti tumor activity etc.
Cinnoline has a heterocyclic system, which is fused six member ring containing two nitrogen atoms with special structural activity have been showed special interest in chemical or synthetic research field. This review critically discusses about the synthesis, wide range of activities and applications of Cinnoline aromatic compound. Apart from that, this review is also enlisted the various reported literature based on advanced synthesis and application of Cinnoline in various biological activities.

Keywords: 1, 2 benzodiazine, cyclization reaction, cinn-tillating synthesis, biological activities

Introduction

Discovery of new world of medicine is attained through Medicinal chemistry. The main principle of medicinal chemistry is to establish new pharmacological active substance with mechanism of action. Cinnoline are important class of heterocyclic compounds which prevail in numerous natural products exhibiting a large range of biological and pharmaceutical activities. A rich tradition of research heterocyclic derivatives continues to achieve new medicinal agents [1]. The structure is optimized and new lead compound is evaluated for activity. Critical intention of this review is to focus on wide range of development of Cinnoline (Fig.1) (1, 2 benzodiazine) derivatives found to be wide spectrum of activities such as anti bacterial, antifungal, antihelminthic activity, antimalarial, anti molluscicidal activity, anti-tuberculosis anti inflammatory, antitumor, antioxidant. Heterocyclic rings having nitrogenous base are building blocks for activity. Most of the drugs are from natural origin result in discovery of the many synthetic drugs having the heterocyclic rings.



cinnoline

Fig 1

Cinnolines are discovered in the year 1883 its substituted derivatives play a critical role in dyes and medicinal compounds and manufacturing reagents in the field of analytical chemistry. The alternative name of Cinnoline is benzopyridazine, based on the position of function group they are named as followings, 3-methylcinnoline, 3-cinnolinol & 3-nitrocinnoline. The structures are given below (Fig.2).

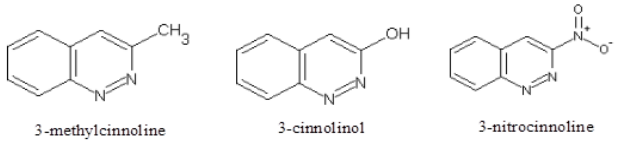


Fig 2

Cinnoline is an aromatic heterocyclic compound with the formula $C_8H_6N_2$. It is isomeric with phthalazine. Cinoxacin (Fig.3) is a Cinnoline analogue of the quinoline antibacterial which is used for urinary tract infection in these days [2].

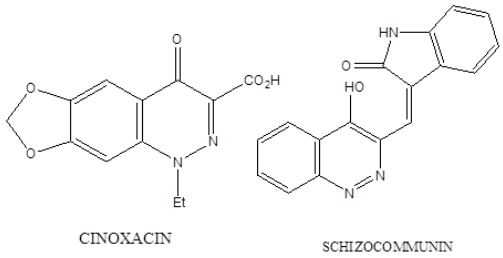
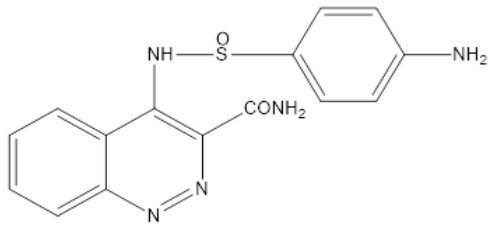


Fig 3

Heterocyclic compounds having nitrogenous base is attaining importance. Simple synthesis of Sulphonamide Cinnoline is obtained by treatment of substituted aniline with sodium nitrite in presence of hydrochloric acid at room temperature; obtained intermediate by coupling with cyanoacetamide in ethanol solution undergoes cyclization to give final compound which is screened for antimicrobial activity [3].



4-(4-aminophenylsulfinamido)cinnoline-3-carboxamide

Fig 4

Cinnoline is a free base can be obtained as oil by treatment of the hydrochloride with base. The free base melts at 39°C. It has a taste same that of chloral hydrate and leaves a sharp irritation for some time. A Von Richter-type first man who had described mechanism occurs in the thermal cyclization of N, N-dialkyl –N-(4-substituted -2-ethynylphenyl) triazenes. The reagent is o-Cl_2Ph, and a by-product of the reaction is 5-substituted isoindazoles. This is the first example of cyclization a triazene and inactivated alkyne compound undergoing cyclization under neutral conditions [4].

General method of Synthesis of Cinnoline

The diazonium chloride is obtained from diazotization of o-amino phenyl propiolic acid was heated in water at 70°C. Cyclization of intermediate compound leads to separation of 4-hydroxycinnoline-3-carboxylic acid (Fig.5) with good yield. When this 4-hydroxycinnoline-3-carboxylic acid was heated above its melting point, carbon di Oxide was liberated and 4-hydroxycinnoline was formed [5].

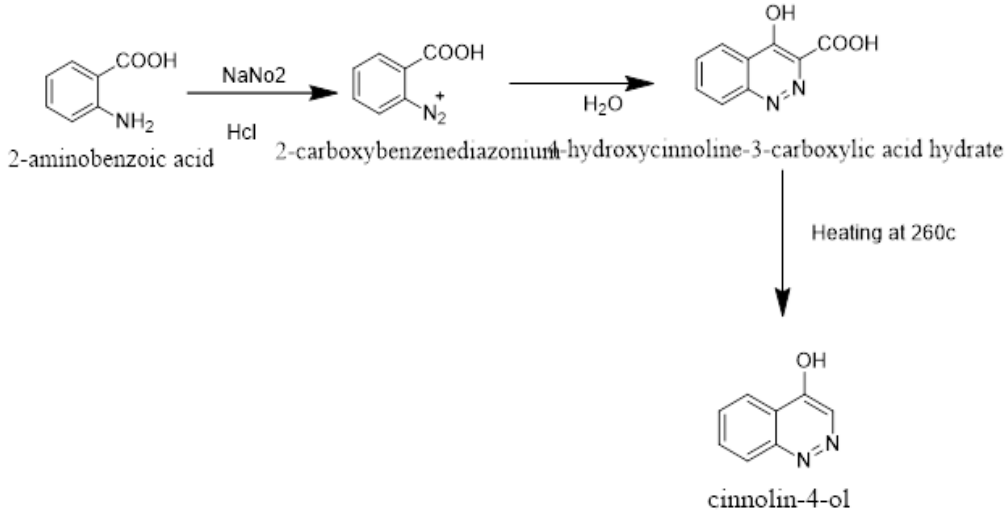


Fig 5

In solid state substituted cinnolines (Fig.6) are synthesized by attaching starting material polystyrene via bond to triazenes moiety. Acidic conditions are favorable activating alkynes to undergo cyclization. Yield formed varies from 47%-95% dependent upon nature of substitution of aromatic ring.

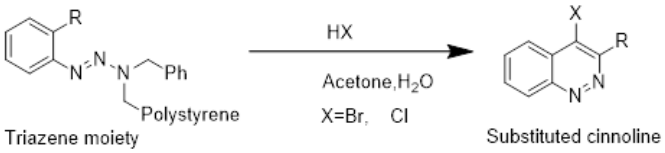


Fig 6

Alkalization reaction

Quinoxalino [2, 3-c] cinnoline (Fig.7) are easily formed from the series of 2-amino-3-(2-nitrophenyl) quinoxalines by cyclization in presence of metabolic KOH (heated). During the reaction 2-aminoquinoxalines underwent cyclization and alkoxylation at benzylic carbon by removal of water yields acetylated product [6].

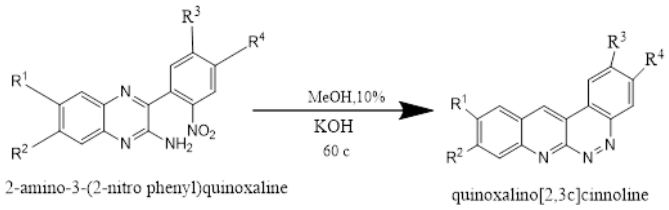


Fig 7

Cyclization reaction

Piperazinyl amidrazones in the presence of PPA at 110-120ºc for 8-10hr undergoes cyclization to give a intermediate N-substituted piperazine which Upton treatment with hydrazonoyl chloride in presence of triethylamine yield 3-piperazinyl cinnoline [7] (Fig.8).

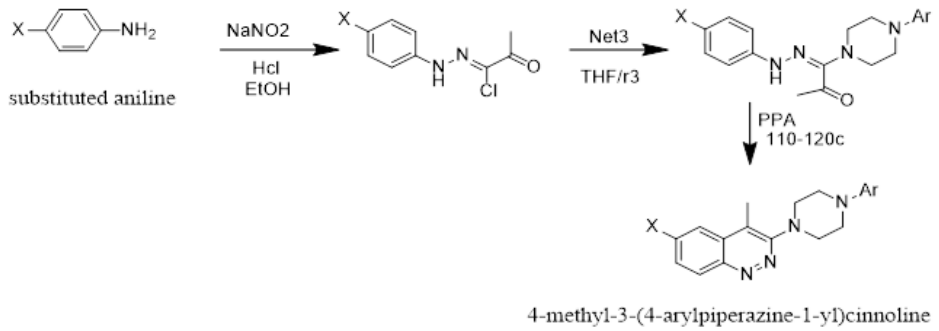


Fig 8

Retro synthetic route of cinnoline

Retro synthetic routes (cinn-tillating synthesis) of cinnoline were designed by tandem cupper catalyzed annulation to give simple hydrazine nucleophile [8] (Fig.9).

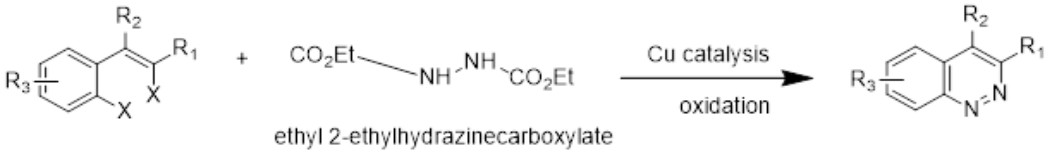


Fig 9

Synthesis of 3-acetyl cinnolines

Anshu Jakhar *et al.*, synthesized of 3-acetyl cinnolines (Fig.10) was done by inramolecular cyclization of substituted phenyl hydrazonoacetylacetones in presence of sulphuric acid with aluminium chloride in chlorobenzene in PPA at 60- 65c 75% of yield is obtained [9].

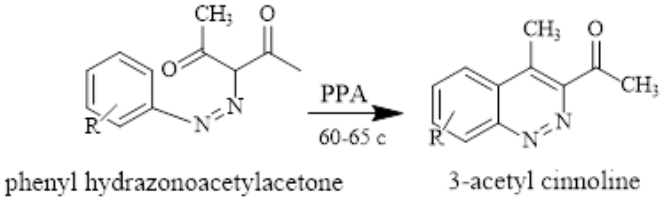


Fig 10

Anti-inflammatory activity

Synthesis of Pyrazolo [4, 3-c] cinnoline

Ton RK *et al.*, synthesized and pharmacological evaluation of pyrazolo [4, 3-*c*] cinnoline.This compound also reported anti-inflammatory activity, ulcerogenic and lipid per oxidation activity, anti-inflammatory activity. Ethyl hydrazinylidine oxobutanoate undergoes cyclization in presence of $Alcl_3$ and Chloro benzene by refluxing for 16hr yields 76% of product. Antibacterial property is determined against gram-negative *E.coli* and *Pseudomonas aeruginosa*, gram positive (*Staphylococcus aureus*). Newly synthesized compounds mainly 4e and 4i are potent antibacterial due to presence of 2,4-dichloro(4e) or 4-nitro(4i) substituent attached to benzoyl group of pyrazolo[4,3-c]cinnoline [10].

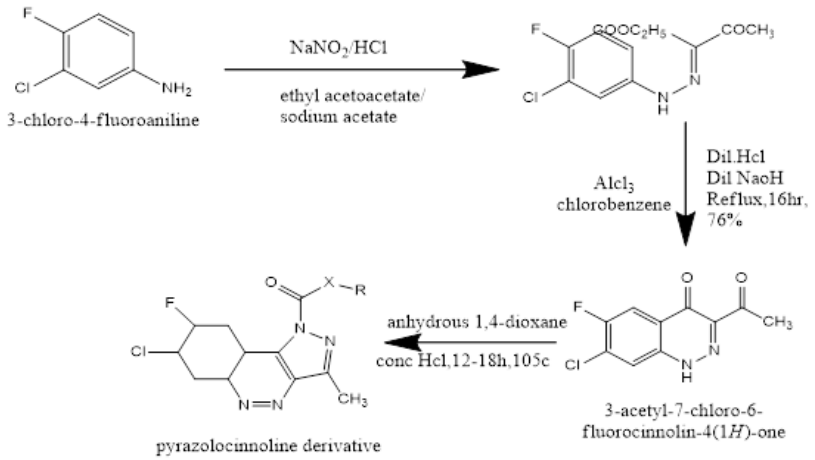


Fig 11

R=4a=phenyl, 4b=phenyl, 4c=phenyl-methyl phenyl, 4d=p-methyl phenyl, 4e=O, p-dichloro phenyl, 4f= O, p-dichlorophenyl, 4g= p-chlorophenyl, 4h= p-flurophenyl, 4i= p-nitrophenyl, 4j= p-aminophenyl, 4k= m, p-dimethoxyphenyl, 4i= p-methoxyphenyl, 4m=1-napthalyl

X=4b= CH_2, 4c= OCH_2, 4f= OCH_2, 4m= CH_2

Quinoxalino [2, 3-*c*] cinnolines

Haddadin MJ *et al.*, reported on Quinoxalino [2, 3-*c*] cinnolines and their 5-*N*-O methyl substituted Quinoxalino derivatives undergoes alkylation to give acetyls and ortho esters in high yield. Routes to the precursor of this alkylation reaction as well as other quinoxalino [2, 3,-c] cinnoline and their 5-oxide derivatives are reported. Most of these quinoxalino [2, 3-c] cinnoline were prepared by cyclization of corresponding 2-amino-3-(2- nitro phenyl) Quinoxalinoxide (Fig.12).

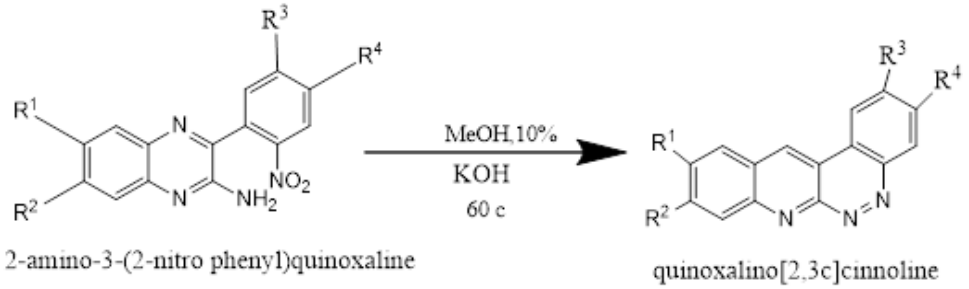


Fig 12

R^1=H, Cl, Br, Me, R2=H, MeO, R^3=H, Br, R4=H, Me

Quinoxalino [2, 3-c] cinnoline (Fig.3) are easily formed from the series of 2-amino-3-(2-nitrophenyl) quinoxalines by cyclization in presence of metabolic KOH (heated). During the reaction 2-aminoquinoxalines underwent cyclization and alkoxylaion at benzyl carbon by removal of water yields acetylated product

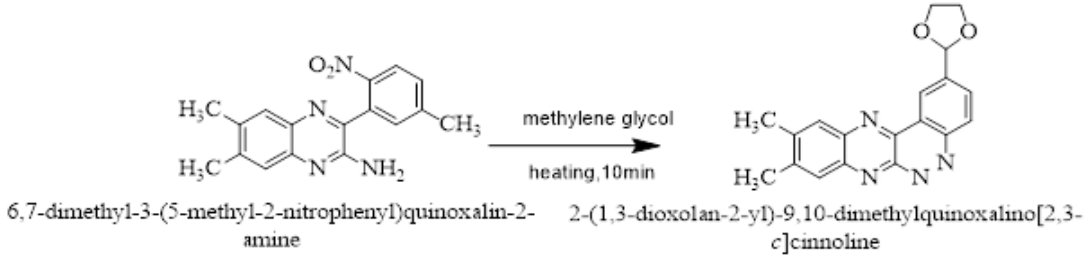


Fig 13

6, 7 dimethylquinoxalin is allowed to heat with ethylene glycol for 10 min, methyl carbon of 2-nitrophenyl group underwent alkoxylaion to give quinoxalino Cinnoline [11].

I Anti-tumor activity

3-(4-(Substituted)-piperazin-1-yl) cinnolines

Eman D.Awed *et al.*, reported on synthesis and biological activity of some 3-(4-(Substituted)-piperazin-1-yl) cinnolines (Fig.14). 1-(2-arylhydrazono)-1-(4-arylpiperazin-1-yl) propan-2-ones undergoes cyclization in presence of PPA to give 6-substituted-4-methyl-3-(4-arylpiperazin-1-yl). Derived compounds are tested for anti bacterial activity against *E.coli* and *Staphylococcus aureus* by Kirby Bauer method some of them shown potent activity against *C.albicans* with inhibition zone of 40%-55% when compared with nystain.The. The structures of the newly synthesized compounds were confirmed by elemental analyses, 1H-NMR, 13C-NMR, and ESI-HRMS spectral data. The antitumor, antibacterial, and antifungal activity of the newly synthesized compounds was reported [12].

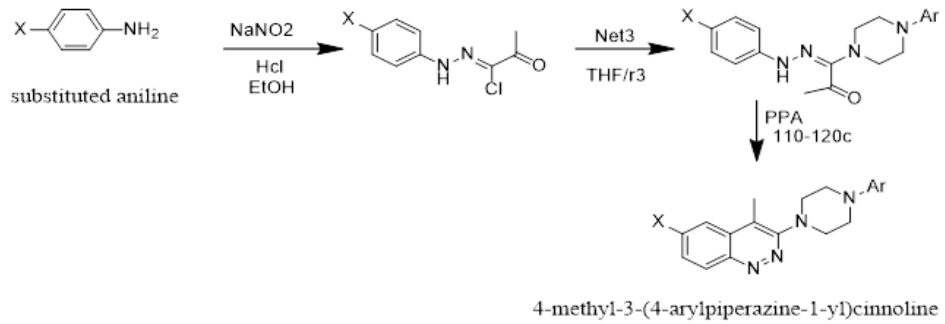


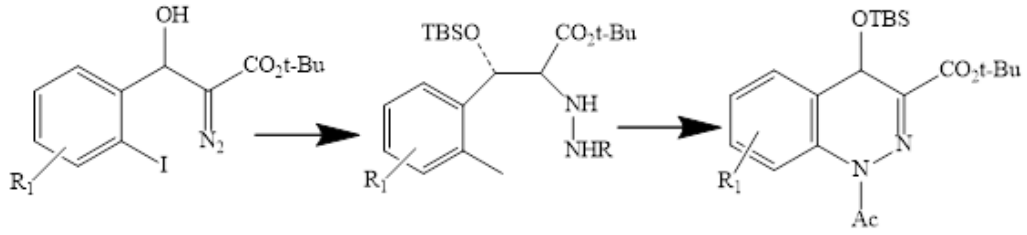
Fig 14

Compounds (3-10): Ar=Ph, CH_2Ph, and C_6H_4F Compounds (5-10): X=H, F, Cl, and Br The antitumor activity of compounds was screened by cell a viability assays with tetrazolium dye 3-(4, 5-dimethylthiazol-2-yl)-2, 5-

diphenyltetrazolium bromide (MTT).Cultures of MCF-7 breast cancer cells were treated first at a concentration of 50 go/Ml.

Cinnolines and 1-amino indole

Kazuya Hasegawa *et al.*, cinnolines are synthesised by Cu catalyzed intermolecular areolation of hydrazine using cyclization precursor by one pot procedure. Novel synthesis of cinnolines and 1-amino indole via Cu-catalyzed intra molecular n-areolation of hydrazine. The hydrazine and hydrazones are act as cyclization precursors derived from 3-haloaryl-3-hydroxy-2-diazopropanoates (Fig.15) by one pot procedure by phase transfer catalyst converts into corresponding nitrogen heterocyclic by Cu catalyst N-arylation [13].

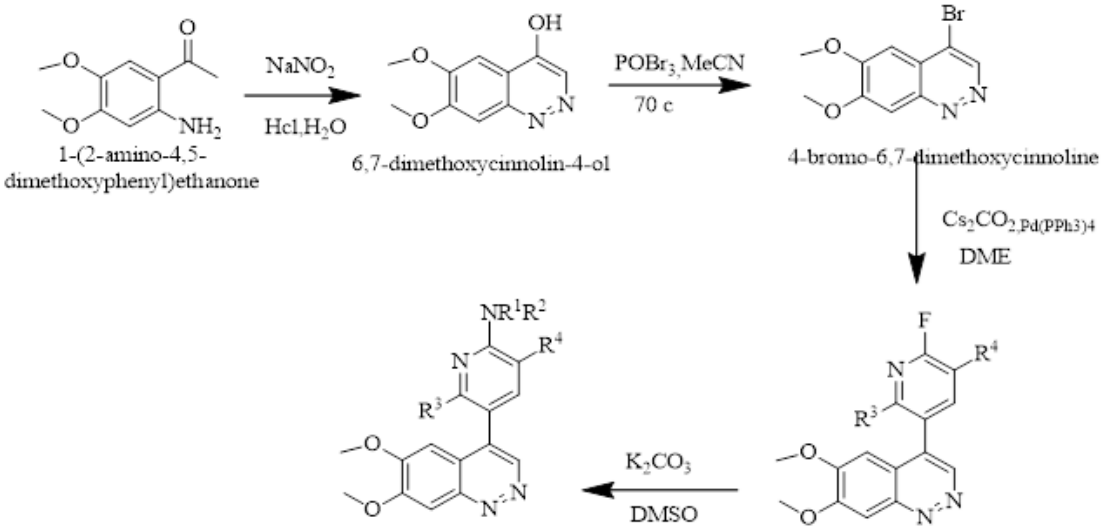


R^2=Cabs

Fig 15

Cinnolines as phosphodiesterase 10A (PDE10A) inhibitors

EssaHu *et al.* Reported for a potent, selective, and metabolically stable 4-(pyridin-3-yl) Cinnolines acts as important phosphodiesterase 10A (PDE10A) inhibitors. Substituent groups in pyridine ring of 4- (pyridin-3-yl) Cinnolines and potency were also reported. Introduction of same functional group which is ortho to aniline amine gives potent inhibitory activity of PD10A in Schizophrenia. Synthesised compounds are tested in conditioned avoidance response behavior model to predict the activity of compounds in Sprague-Dawley rats at 3, 5, 6 and 10mg/kg by oral gavage and one compound was reported for good inhibitory activity [14].



R=Cl, CH_3, CF_3, CN, NH_2

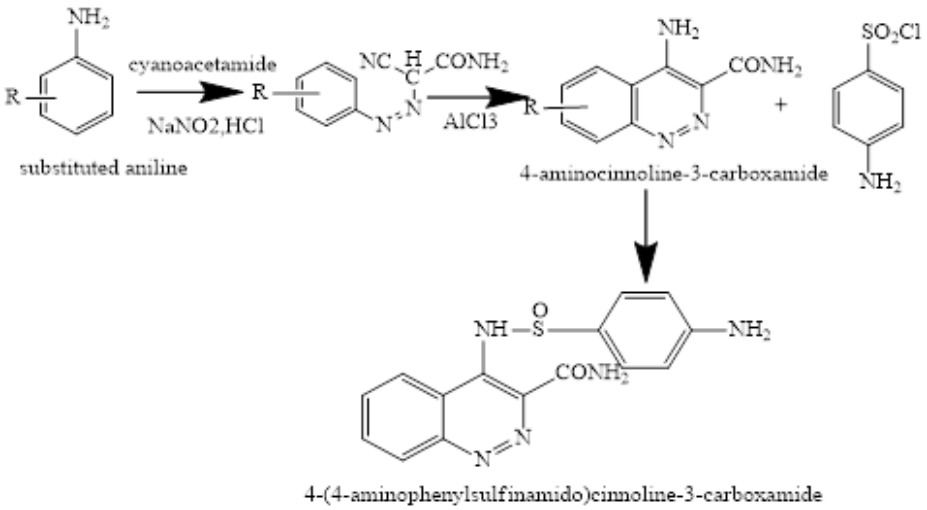
Fig 16

Cinnolines are novel inhibitor of phosphodiesterase 10A (PDE10A), SAR and mode of binding against PDE10A is analyzed by X-ray-co-crystal structure. Compound shown promising inhibitor of PDE10A in rats.

I. Anti bacterial and Anti-inflammatory Activity

4-(4-aminophenylsulfinamido) cinnoline-3-carboxamide

Vikas S *et al.*, reported on Synthesis, characterization and biological activities of substituted Cinnoline sulphonamides.



R^1=a=NO_2, Cl, CH_3, H, H, NO_2, Cl, F, Cl
R^2=H, H, H, NO_2, Br, NO_2, H, H, Cl

Fig 17

Substituted anilines are treated with cyanoacetamide in ethanol solution by coupling reaction which gives corresponding hydrazones upon cyclization in presence of AlCl3 in chlorobenzene results in formation substituted phenyl 4-amino cinnoline 3-carboxamide which further yields substituted 4-(p-amino phenyl sulphonamide) cinnoline 3-carboxamide the compounds has shown potent anti bacterial and antifungal activities by the disk diffusion method. Compounds had antibacterial activities and when compare to the standard drug norfloxacin. Compounds showed good antifungal activity and compared to the standard drug Griseofulvin [15].

Cinnoline in cell imaging

Sivakalai mayakrishna *et al.*, Synthesis of cinnolines *via* Rh (III)-catalyses dehydrogenative C–H/N–H functionalization aggregation induced emission and cell imaging.N-phenylphthalazine is treated with diphenyl acetylene in presence of diphenyl acetylene Rh catalyst, additive (10mol% $AgSbF_6$] and oxidant at 100 c under N_2 atm for 6hr and the product is isolated with 45% yield, structure elucidation was done by ^1H, ^{13}C, NMR

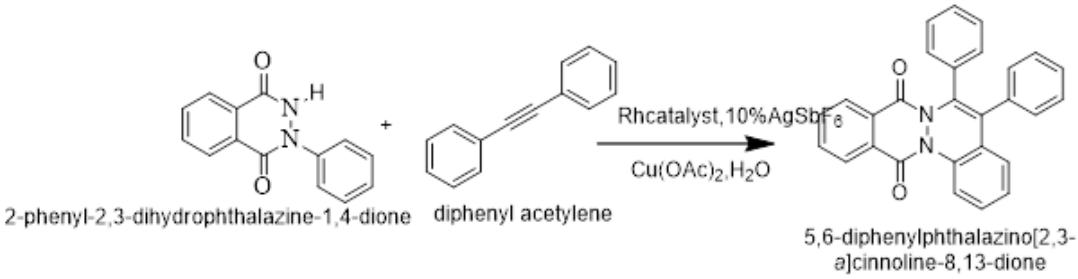


Fig 18

This method is advantageous for having tolerance to variety of functional groups and exhibited excellent regioselectively used in cell imaging [16].

4-((4H-imidazol-4-yl) amino) cinnoline-3-carboxamide derivatives

Mishra pankaj *et al.*, reported on cinnolines substituted by imadazole ring. All synthesized compounds are tested for anti bacterial, antifungal, and anti inflammatory, some of the compounds had evident with potent activity [17].

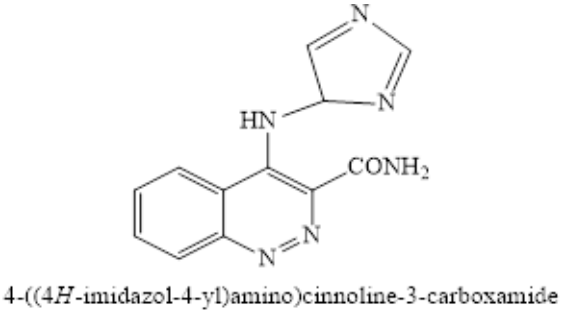


Fig 19

3-methyl-6, 7-dihydro-1H-indeno [6, 7, 1-def] cinnoline

N.I.Omelichkin *et al.*, reported on nitration of (3-methyl-6,7-dihydro-1H-indeno[6,7,1-def]cinnoline) (Fig.20) at different concentrations in glacial acetic acid,acetonitrile nitro methane and di- and tri nitro derivatives which needed harsh conditions and is accompanied by dehydrogenation to optain dimerization of the initial compound [18].

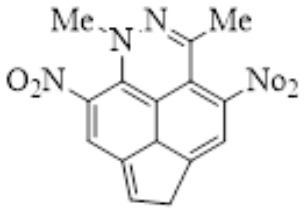
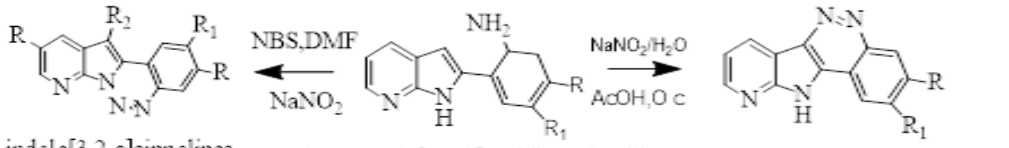


Fig 20

I.Anti-proliferative activity

11*H*-pyrido [3′, 2′:4, 5] pyrrolo [3, 2-*c*] cinnoline

Barbara parrino *et al.*, reported on new ring derivatives of 11*H*-pyrido [3′,2′:4,5] pyrrolo[3,2-*c*]cinnoline was synthesised by reaction between 3-methylpyridine and 2-aminobenzonitriles in presence of lithium diisopropylamide(LDA) undergoes dimerization to yield 45-62% and screened for anti tumour activity against all the human cell lines. Compounds 1e, f and 2c, e, f exhibited antiproliferative activity MG_MID values in the range of 0.74-1.15 μM [19].



a R=R_1=H; b R=Cl, R1=H;c R=H,R_1=Cl;
d R=Me, R1=H; e R=OMe; R1=H; f R=R_1=OMe

Fig 21

Halo substituted benzo [c] cinnoline

Ayunna K *et al.*, reported on electrophilic nitration of halo-substituted benzo[c]cinnolines and benzenoids has been achieved regioselectively. The nitro group entry was always ortho to the halo group or/and the aromatic ring. This regioselective electrophilic ortho-nitration was attained in mixed acid/mild temperature conditions. Chlorides and bromides perform equally well in directing these high-yielding ortho-selective reaction. Benzo[*c*]cinnoline (BC) and its derivatives have significant importance because of their biological activities, their potential as ligands for metals, and also for having highly stable molecular conformations with different [20].

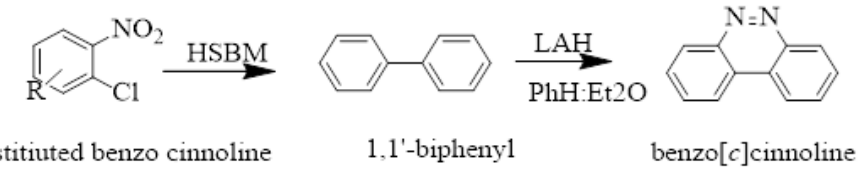


Fig 22

I.Anti- molluscicidal activity of new cinnoline dimedone

Fathy M.Abdelrazek *et al.*, reported synthesis and molluscicidal activity of new crinoline dimedone obtained from azo derivative were condensed with malononitrile which gives enol product. These compounds were diazotized with aromatic amine in presence of acetic acid yield obtained is high.compunds toxicity was evaluated towards biomphalaria (Ca.7mm shell diameter) Alexandria snail. Compunds mainly 7c, 9c are acting as potent molluscicidal agent [21].

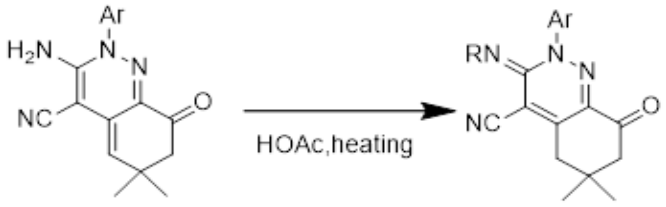


Fig 23

7a=Ar=Ph, 7b=Ar=4-Me- C_6H_4, 7C= Ar=4-Cl-C_6H_4 8a=R=H, 9a=R=Ac

Cinnolin-3(2H)-ones

Satyasheel Sharma *et al.*, reported on C-H functionalization of azobenzene with α-diazocompound in presence of rhodium (iii) as catalyst.cinnolin-3(2H)-ones (fig-24) are constructed by transformation and functionalization of C-H of azobenzene in presence of Meldrum's acid [22]

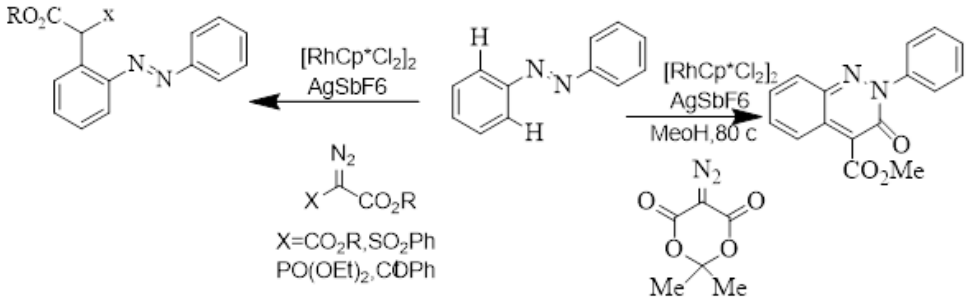


Fig 24

4-(Oxiran-2-ylmethoxy) cinnoline

Schofield K *et al.*, reported on the synthesis and reactivity of 4-(Oxiran-2-ylmethoxy) cinnoline (Fig.25) was prepared by treating 4-chlorocinnoline with glycidol/sodium hydride in presence of DMF. Derivatives are subjected for NMR studies [23].

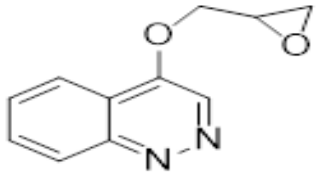


Fig 25

1, 2, 3, 6, 7, 8-Hexahydro cinnoline [5, 4, 3-cde]

Zhi-Qiang Gao *et al.*, reported on 1,2,3,6,7,8-Hexahydro cinnoline [5,4,3-cde] crinoline (Fig.26) synthesised by reaction of hydrazine hydrate80%(8mol) and 9-methyl-3,4,6,7-tetra hydro-2H-xanthene-1,8(5H,9H)-dione in presence of ethanol(8ml) by constant stirring crystals are separated on evaporation the obtained yield is 84%.X ray crystallographic studies are done for synthesised compounds [24].

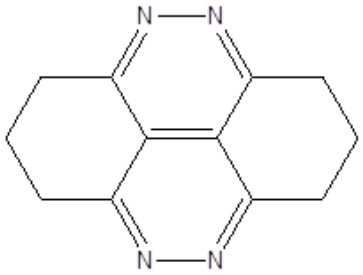


Fig 26

3-aroylcinnolines

Naouria *et al.*, Reported on an efficient synthesis of 3-aroylcinnolines (Fig.27) from aryl methyl ketenes. An efficient synthesis of 3-aroylcinnolines starting from the appropriate aryl methyl ketones is described. The latter were converted in two steps to the corresponding 3-oxo-3-aryl-2-arylhydrazonopropanals, which upon acid catalyzed cyclization in conc. sulfuric acid or polyphosphoric acid (PPA) led to the corresponding 3-aroylcinnolines [25].

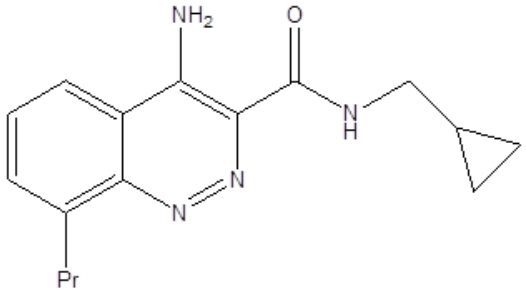


Fig 27

Benz[*h*]cinnoline derivatives

Moshe Abdel *et al.*, reported on an efficient and facile synthesis of substituted crinoline and Benz[*h*]crinoline derivatives [26].

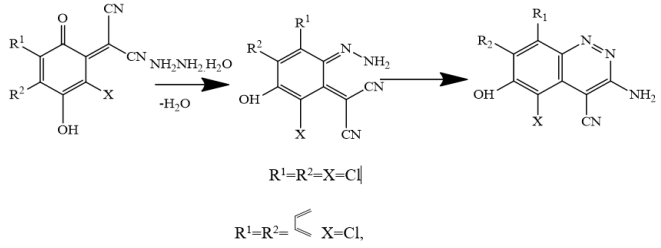


Fig 28

Conclusion

The data reported above clearly intimate that 1, 2 benzodiazine (cinnoline) are endowed with wide range of biological activities like antibacterial, antifungal, anti-inflammatory,anti-mullosicidal activity,anti-tuberculosis,anti tumor activity. The main intention of this review is to highlight cinnoline as a potent anti-microbial, are planned to synthesize and evaluate for anti microbial activities. The substituent groups at different position of Benzopyridine ring are responsible for spectrum and potency. Good antifungal activity of cinnolines over C.albicans was reported, presence of CH_3, Cl, F at the 6^{th} position of crinoline ring gives anti fungal activity. Replacement with Br decreases the activity.

Bactericidal activity against gram negative bacteria E.coli was documented, substitution at 4th postion of ring with sulphonamide moiety inhibits PABA activity it leads to antibacterial activity. Substitution of Br, Cl at 6th position of crinoline ring gives anti microbial activity. Halogen substituted derivatives increases the activity. Substitution of piperazine moiety substituted with phenyl group at 3rd position of cinnoline ring leads to antitumor activity. Replacement of phenyl group decreases the activity. The main intention of this review is to highlight cinnoline as a potent anti-microbial, are planned to synthesize and evaluate for anti microbial activities

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