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R E V I E W A R T I C L E

A Review: Synthesis and pharmacological evaluation of sulphonamido cinnoline

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A B S T R A C T

New drug synthesis not only done loping new chemical entities but also important for therapeutic need. They consist of the essential structural backbone of various pharmaceutical .Cinnoline molecules are very important aromatic heterocyclic compound that have been found to exhibit varied biological activity depending on the nature and position of diversity element .The antimicrobial agents available now have various drawbacks such as toxicity, drug resistance to microbes, and narrow spectrum of activity. Hence the design of new compounds to deal with the above problems has become one of the most challenging targets in antibacterial and antifungal research today. Hetero cyclic chemistry is the most challenging and a handsomely rewarding field of study, since it always attracts the attention of scientists working not only in the area of natural products but also in synthetic organic chemistry. Cinnoline is an aromatic heterocyclic compound with the formula C8H6N2 and can also be called as benzo derivative of pyridazine1. It is isomeric with phthalazine. Recent studies have shown that cinnoline and their derivatives exhibit various biological activity2 such as antihypertensive3, antithrombocytic4, antitumour5, anti-inflammatory6, anticancer 7 and bactericidal activity. Heterocycles play an important role in biology and are an important constituent of various biomolecules like DNA, RNA, vitamins and amino acids. The well known biological importance of sulphonamide derivatives as antibacterial, anticancer, anti-malarial, and anti-tubercular agents prompted us to introduce a sulphonamido group into the cinnoline ring hoping to get compound to enhance potency and synergistic effect8. Although sulphonamides have provided medicinal science with some of the most potent weapons for the effective conquest of many diseases of bacterial origin, there is still a long list of bacterial infections uninfluenced by the newer chemotherapeutic agents. Among them, leprosy and tuberculosis continue to constitute new challenges in chemotherapy. The present study focuses on an exploratory investigation in cinnolines by synthesizing novel sulphonamido cinnoline. This review analyses the principal approaches to the synthesis of the cinnoline nucleus, used as synthetic precursors of arenediazonium salts, The mechanisms of the transformations and the possibilities and limitations of the various methods are discussed. Special attention is paid to methods based on the cyclization of derivatives of arenediazonium salts, which have been developed substantially in recent years.

Keywords: Von Richter's synthesis, Busch and klett's synthesis, Antifungal, Antibacterial

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Drug synthesis not only done loping new chemical entities but also important for therapeutic need. They consist of the essential structural backbone of various pharmaceutical .Cinnoline molecules are very important aromatic heterocyclic compound that have been found to exhibit varied biological activity depending on the nature and position of diversity element. The antimicrobial agents available now have various drawbacks such as toxicity, drug resistance to microbes, and narrow spectrum of activity. Hence the design of new compounds to deal with the above problems has become one of the most challenging targets in antibacterial and antifungal research today.

Cinnoline is an aromatic heterocyclic compound with the formula C8H6N2 and can also be called as benzo derivative of pyridazine1. It is isomeric with phthalazine. Though it does not occur in nature, it is a vigorously developing branch of organic chemistry. Although cinnoline belong to a family of well known heteocycles, the interest in the study of its derivatives continues. Recent studies have shown that cinnoline and their derivatives exhibit various biological activity2 such as antihypertensive3, antithrombocytic4, antitumour5, anti-inflammatory6, anticancer7 and bactericidal activity.

Heterocycles play an important role in biology and are an important constituent of various biomolecules like DNA, RNA, vitamins and amino acids. The well known biological importance of sulphonamide derivatives as antibacterial, anticancer, anti-malarial, and anti-tubercular agents prompted us to introduce a sulphonamido group into the cinnoline ring hoping to get compound to enhance potency and synergistic effect8.

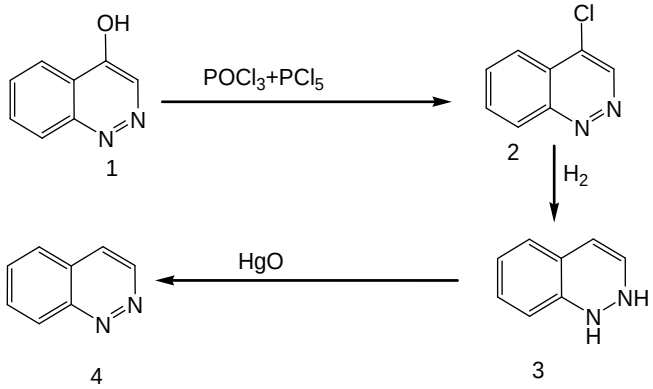
Although sulphonamides have provided medicinal science with some of the most potent weapons for the effective conquest of many diseases of bacterial origin, there is still a long list of bacterial infections uninfluenced by the newer chemotherapeutic agents. Among them, leprosy and tuberculosis continue to constitute new challenges in chemotherapy. The present study focuses on an exploratory investigation in cinnolines by synthesizing novel sulphonamido cinnoline. Cinnolines are class of compounds having potent anti-tumor, anti-malarial, anti-tubercular, anti-oxidant, anti-inflammatory and anti-microbial activity. Substituted cinnoline derivatives are known as topoisomerase-I targeting anticancer agents. A series of cinnoline derivative were synthesis and evaluated far good biological activity.

2. Synthesis of Cinnolines

1. Von Richter's synthesis
2. Busch and klett's synthesis
3. Borsche's synthesis
4. Baumgarten's synthesis
5. Widman-stoermer's synthesis

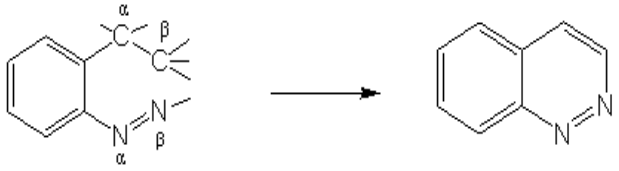
1. Busch and Klett's Synthesis:

The Pure cinnoline was obtained by converting 4-hydroxycinnoline obtained by Von Richter's method to 4-chlorocinnoline with a mixture of phosphorus oxychloride and phosphorus pentachloride, followed by the reduction of the latter with iron and sulphuric acid. The resulting 1, 2-dihydrocinnoline was finally oxidized to cinnoline with mercuric oxide.9



Scheme No: 1

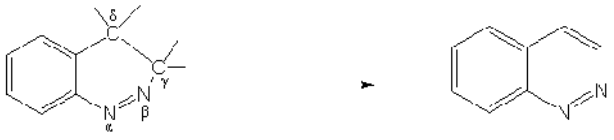
Three main approaches have been explored for the synthesis of cinnolines. The first approach makes use of the condensation between the β-nitrogen atom of a chain of two nitrogen atoms and the β-carbon atom of a chain of two more carbon atoms, these chains being oriented in the ortho-positions of a benzene ring.



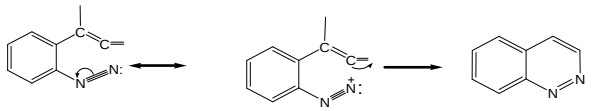
Scheme No: 2

In the second approach, the chain of two nitrogen atoms is increased by one carbon atom which condenses with the α-carbon atom of a second chain in the ortho position to build up the heterocyclic ring.

In the third approach, the α-carbon atom of a chain containing two nitrogen and two carbon atoms reacts with the hydrogen in the ortho position of the aromatic ring to yield the cinnoline derivative.



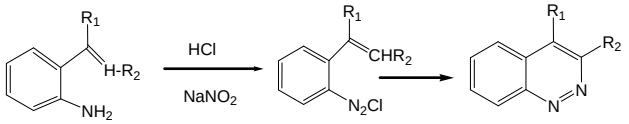
The mechanisms for these three synthetic approaches to the cinnoline structure, although not supported by experimental evidences. The first two approaches are believed to possess the common feature of electrophilic attack by the diazonium cation on the carbon-carbon centre of unsaturation.



Scheme No: 3

2. Widman-stoermer's synthesis:

On keeping a diazotized solution of 3-amino-4-isopropenylbenzoic acid at the room temperature, a product was formed which was identified as 4-methylcinnolin-7-carboxylic acid. Various cinnolines substituted in 3-and 4-positions were synthesized, starting from suitable o-amino phenylethylenes. In general, this method can be represented by the sequence of reactions.

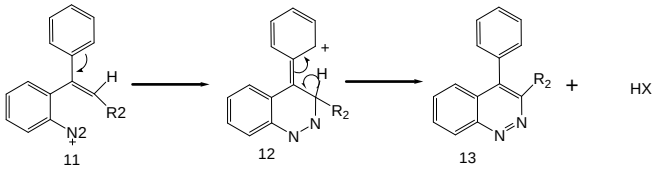


8 9 10

Scheme No: 4

Where, R1=Ph, R2=H

Mechanism of Widman-Stoermer's synthesis:

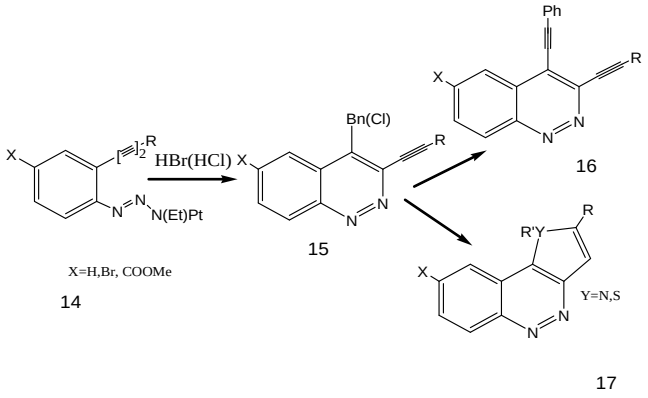


11 12 13

Scheme No: 5

The reaction is usually very rapid and seemingly independent of the geometrical configuration of the group around the ethylenic linkage

Olga V. et al**,** have reported in 2009. A short route to 3-alkynyl-4-bromo (chloro) cinnolines by Richter-type cyclization of ortho-(dodeca-1,3-diynyl)aryltriaz-1-enes.[10]

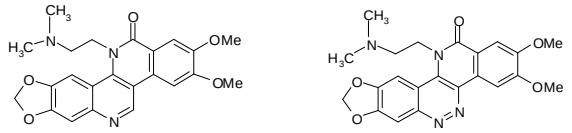


X=H,Br, COOMe

14 15 16 17

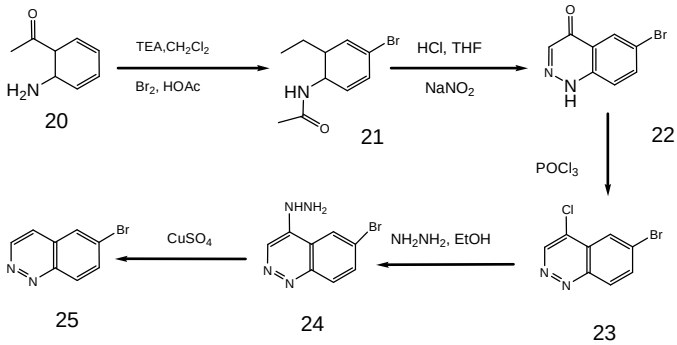
Scheme No: 6

Mavurapu S and co-workers have reported in 2008, the synthesis of several analogs of ARC-31 which exhibited very potent TOP1-targeting activity and were highly cytotoxic.[11]



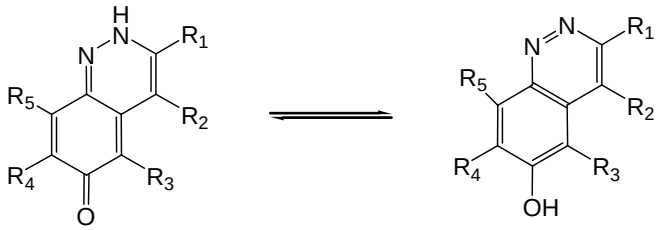
18 **ARC-111** **19** **ARC-31**

Keith WW et al**.** have reported in 2006, the synthesis of a series of hetero-aryl pyridine derivatives which showed cellular activity and significantly showed tumour growth**.**[12]



20 21 22 23 24 25

Scheme No: 7



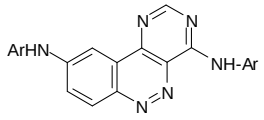
26 27

In 2006, Chung-Kyu Ryu and co-workers have reported, synthesis of 6-hydroxycinnolines 2 and cyclohexa-2, 5-

diene-1, 4-dione derivatives and tested for *in vitro* antifungal activity against Candida and *Aspergillus* species. 6-Hydroxycinnolines showed, in general, more potent antifungal activity against Candida species than the other cyclohexa-2, 5-diene-1, 4-diones**.**[13]

6- Hydroxy cinnolines cinnoline-6(2H)-ones

Hassan Mohammed et al, have reported in 2005, the preparation of cinnoline derivatives using hydrazones as starting materials via Friedel-Craft alkylation. Cyclization of the cinnoline derivatives gave pyrimido-cinnolines. These are thought to have certain biological activities.[14]



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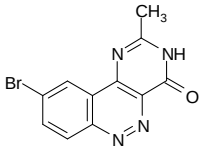
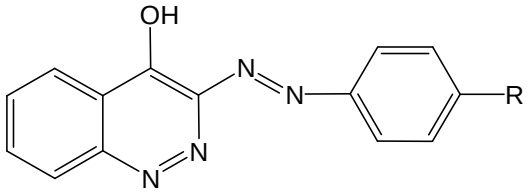


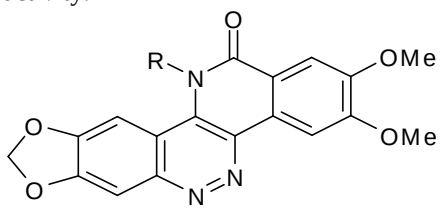
29

Nasr M et al, have reported in 2004 studied electronic spectra, solvate chromic behavior and acid–base properties of some azo cinnoline compounds.[15]



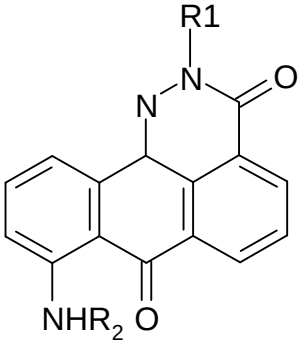
30

Alexander and co-workers**,** have reported in 2004, synthesis of 2, 3-dimethoxy-8, 9-methylenedioxy-11-[(2-dimethylamino) ethyl]-11H-isoquino [4, 3-c] cinnolin-12-one as a novel topoisomerase I-targeting agents with potent cytotoxic activity.[16]



31

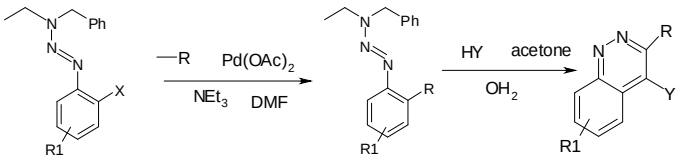
Barbara Stefan et al**,** have reported in 2003, the synthesis of2,7-Dihydro-3Hdibenzo[de,h]cinnoline-3,7-dione derivatives as anticancer agents. The activity was determined as Multidrug Resistant Cell Line.[17]



32

Where, R1= R_2= alkyl amino alkyl, H.

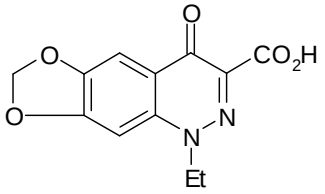
Stefan B S et al, have reported in 2002**,** the synthesis and biological activity of indolo [3,2-c]cinnolines with antiproliferative, antifungal and antibacterial activity. [18]



33 **34** **35**

Scheme No: 8

In 2001, Nouria A and co-workers have reported the synthesis of benzopyridazine derivatives and studied them for antibacterial activity.[19]



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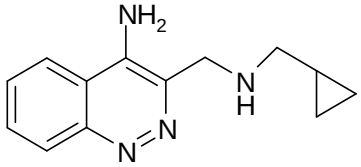

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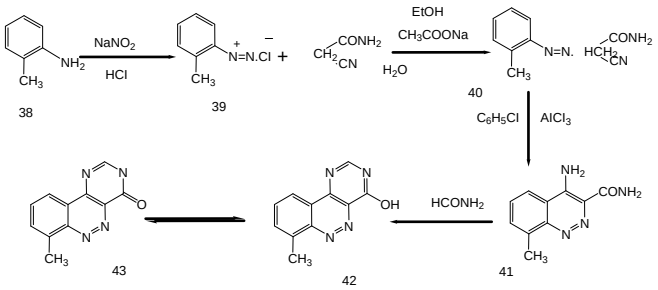
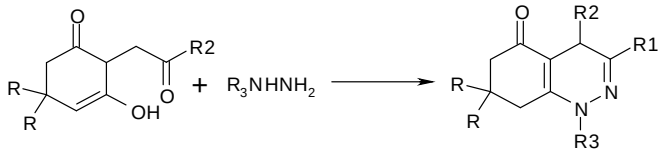
Nargund LVG et al, in 1994 synthesized and screened for antibacterial activity some substituted 4- aryloxy pyrimido (5, 4- c) cinnolines.[20]



Scheme No-9

Nagarajan and co-workers have reported in 1986, the synthesis of 4, 6, 7, and 8-tetrahydro-5-(1H) cinnolines by the reaction of substituted dime-dones with hydrazines.[21]



44 45

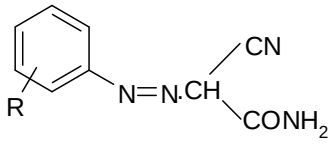
Scheme No-10

Where, A R =Me, R1 =Ph, R3 =H

B R=R1 =Me, R2=H, R3= (CH2) 2NMe2

C R= R2= H, R1= Ph, R3=Ph

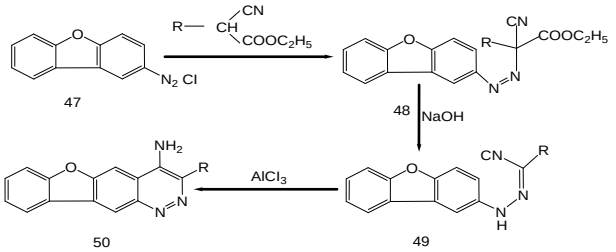
Gewald et al**,** have reported in 1984, described the present investigation which makes use of the elegant method. An useful intermediate for the synthetic sequence (phenylhydrazono) (cyano) acetamide was prepared by the interaction between diazonium salts of substituted anilines and active methylene compounds such as cyanoacetamide through the Japp-Klingemann reaction.[22]



46

Where, R = H, 7-Me, and 9-Me

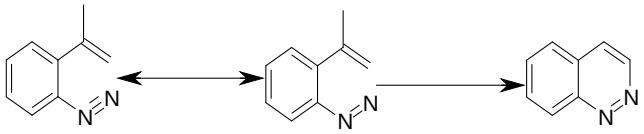
In 1980, Laduree and group have reported the synthesis of 4-amino-[1]–benzofuro [3, 2-g] cinnoline by cyclization of the Z-configuration of cyanoarylhydrazones. The latter compounds have been synthesized via interaction between the diazonium salt of 3-aminodibenzofuran and various active methylene compounds via the Japp-Klingeman reaction. [23]



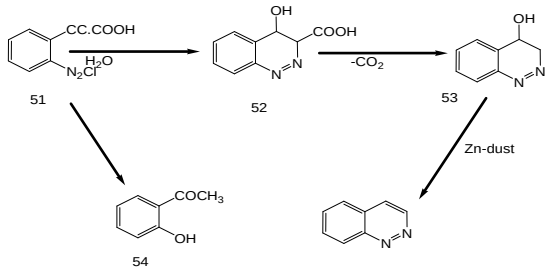
Scheme No: 11

Where, R=H, Me, Et,  , R=Ph.

Simpson et al**,** have reported in 1953, put forwarded the plausible mechanisms for these three synthetic approaches to the cinnoline structure, although not supported by experimental evidences. The first two approaches are believed to possess the common feature of electrophilic attack by the diazonium cation on the carbon-carbon centre of unsaturation as below.[24]



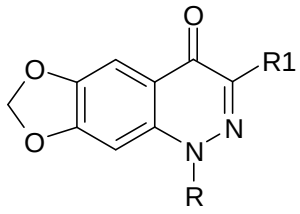
Richter and group have reported in 1883, the formation of the dinitrogen heterocyclic system in the course of his unsuccessful attempts to prepare o-hydroxy-acetophenone by heating the diazonium chloride of o-amino-phenylpropionic acid with water. The resulting hydroxyacid, on decarboxylation yielded the compound, which on subsequent heating with zinc dust gave the new heterocyclic compound.[25]



Scheme No: 12

Cinnolines of Pharmacological Interest:

Ansley et al**,** have reported in 1970, a number of 1-alkyl-6, 7-methylene-dioxy-4(1H)-oxocinnolin-3-carboxylic acids.



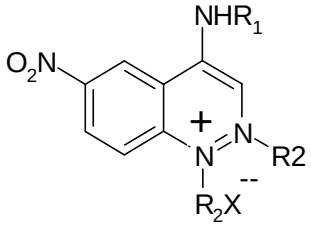
55

Where, R =Me, Pr, iso-Pr, CH_2CH_2OH; CH_2- $CH=CH_2$ and R1 = Et, CN or COOH

These compounds and their salts were found to be active against Mycoplasms gallicepticum, Escherichia coli, Salmonella Dublin, Vibricoli, Eruvina amylovora and Xanthomonas Phaseoli. [26]

Lunt and co-workers have reported in 1968, 4-substituted amino-cinnoline analogues of chloroquine together with several substituted α, w-di (cinnolin-4-ylamino) alkanes and their diquaternary salts and subjected them for antiprotozoal activity. [27]

In 1967, Barber and group have reported, prepared several 4-amino-and 4- (substituted aniline)-6-nitro cinnoline quaternary salts and tested for trypanocidal activity primarily against Trypanosoma congelense. None of the derivatives showed any useful level of activity although several compounds of the type were active at near toxic doses.[28]

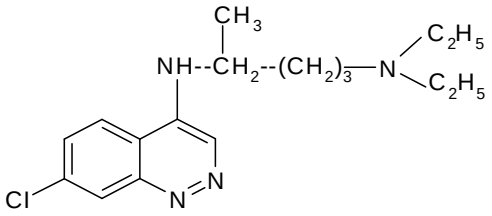


56

Where, R1 = H or Me
R2 = Me or Et; X = I.

Kenford J R et al, have reported in 1947, a variety of 4-dialkylaminoalkylcinnolines as antimalarial drugs by condensing an appropriate 4-phenoxycinnoline with an aliphatic amine at about 130 ^{0}C. These aminocinnolines

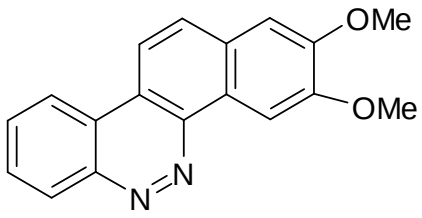
have been tested for anti-malarial activity against *Plasmodium gallinaceum* in chicks and these compounds showed better activity.[29]



57

7-chloro-4-(4-diethylamino-1-methylbutylamino)-cinnoline

Younong Y et al, have reported in 2003 the synthesis of substituted Dibenzo[c, h] cinnolines and screened them for Topoisomerase I as targets for anticancer agents.[30]



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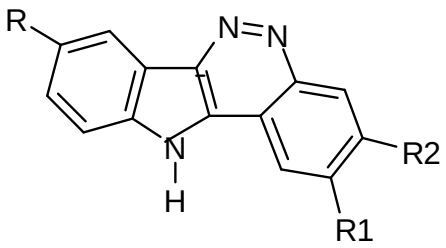
In 1999, Barraja and co-workers have reported Indolo[3, 2-c] cinnolines and tested them to evaluate for antiproliferative, antifungal and antibacterial activity.



59

Where (a) $R=R_1=R_2=H$; (b) $R=R_2=H$, $R_1=Cl$ (c) $R=R_1=H$, $R_2=Cl$

3. Identification and Characterization

The synthesized compounds and derivatives were identified and characterized by following methods:

- Thin Layer Chromatography (TLC)
- Melting Point Determination
- Infrared Spectroscopy (IR)
- Nuclear Magnetic Resonance Spectroscopy (NMR)

1. Thin Layer Chromatography (TLC)

Purity of the compounds was checked by thin layer chromatography using Merck Silica Gel 60 GF 254 as stationary phase. The mobile phase used for TLC was n-Hexane: Ethyl Acetate 1: 2. The spots were visualized by using UV light at 254 nm or iodine chamber. Different staining reagent like Ehrlich's Reagent, Ninhydrin, Potassium Permanganate, Phosphomolybdic acid (PMA), *p*-Anisaldehyde were also used.

2. Melting Point Determination

The melting point of the organic compound was determined by open capillary tube method using Thiel's tube or 'Thermonik' melting point apparatus.

3. Infrared Spectroscopy (IR)

The IR spectra of the synthesized compounds were recorded on a Fourier Transform IR spectrometer (model Shimadzu 8700) in the range of 400-4000 cm^{-1} as KBr pellets.

4. Nuclear Magnetic Resonance Spectroscopy (NMR)

The NMR spectral data of the compound was carried out in Bruker 200 MHz spectrospin NMR at AstraZeneca Pharma India Limited, Bangalore or 400 MHz at IISc, Bangalore. The solvent used for NMR was $CDCl_3$ or DMSO-d_6 and chemical shifts (δ) was reported in parts per million downfield from internal reference tetramethylsilane (TMS).

UV spectroscopy

Absorbance of the synthesized compound was recorded on ultraviolet visible spectrometer (model Shimadzu 8700) in range of 400-800 nm.

Semi auto analyzer

Absorbance of the synthesized compound was recorded on semi auto analyzer (model Prietest touch) in range of 510-520 nm.

(a). Antimicrobial Activity

Study of Anti-Microbial Activity by Agar Diffusion Method: In our current study, anti anti-microbial activity was carried out by agar diffusion method. Here responses of micro-organisms to the synthesized compounds were measured and compared with the response of the standard reference drug. The standard drug used in the present work was Amoxicillin. [33]

Micro-Organisms Used

The two micro-organisms were used are (Gram +ve). *Bacillus subtillis* and (Gram–ve) *Escherichia coli*

Composition of Muller Hinton Agar

Beef extract	30 g
Casamino acids	17.5 g
Starch	1.5 g
Agar	17 g
Distilled water	1000 ml
Final pH	7.3

Preparation of Test solutions

Each test compound was dissolved in Dimthyl formamide to get a concentration of 50 µg/ml. this concentration was used for testing anti-microbial activity.

Preparation of Muller Hinton Agar media

The beef extract was taken in 1000 ml beaker and made-up the volume up to 1000 ml with distilled water. To this mixture known quantity of beef infusion, agar, starch and Casamino acids were added and dissolved by heating the mixture. The pH was adjusted to 7.3 and finally the media was sterilized by autoclaving at 121 °C for 15 minutes at 20 psi pressure. Afterwards the mixture was cooled to 45 °C and then inoculums were added to the sterile borer. 0.1 ml of test solution and standard solution at a concentration of 50µg/ml were taken. A standard Amoxicillin was maintained with same concentration in each plate and a control having only DMF in one plate. Then the petri dishes were incubated at 37 °C for 24 hours and zone of inhibition was observed and measured for each sample.

Preparation of Inoculum:

The suspensions of all the organisms were prepared as per the standard procedure (McFarland Nephelometer Standard). A 24 hours culture was used for the preparation of bacterial suspension. Suspensions of organisms were made in sterile isotonic solution of Sodium Chloride (0.9% w).

Discussion

6-sulphonamido cinnolines was obtained in good yield by Friedel Craft reaction involving cyclisation. Sulphanilamide (60) with sodium nitrite in presence of Conc. HCl at 0-5°C form diazonium salt (**61**), which on treatment with cyanoacetamide gives aryl hydrazine (cyano) acetamide (**62).** This was reacted with anhydrous $AlCl_3$ in the presence of chlorobenzene to form 4-amino-6-sulphonamido-3-cinnolino carboxamides (**63).** Which was further refluxed with formamide to give sulphonamido cinnolino-pyramidine **(72).** 4-amino-6-sulphonamido-3-cinnolino carboxamides in THF was stirred with various anilines (**e-k)** which gave different urea derivatives **77 (e-k).** Sulphonamido cinnoline**(63**) 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 7**6(a-d**).4-Hydrazino-6-sulfamoyl-cinnoline-3-carboxylic acid amide **(75**) was synthesized by sulphonamido cinnoline(63) with hydrazine hydrate in presence of ethylene glycol as a solvent. Synthesis of 6-sulphonamide cinnoline derivatives (**63)** identified and characterized by physical methods and spectral method UV, IR, and NMR spectra. TLC were derivatized using either Ninhydrin, P- anisaldehyde, Ehrlich's.The amine group was identify by chemical test (diazotization), All the compounds were confirmed by elemental analysis (**table no-3**),Apart from this presence of peak and other functional groups were identified by I R such as 2222.07 cm^{-1} (C≡N) in IR spectra, (**scheme no. 14 and figure no-1)** conversion of nitrile to amine group was confired by peak 3433.41 cm^{-1} (**figure no. 2)**and 1664 cm^{-1} (C=O) str, sulphanilamido proton signal in ^1H NMR-spectra**(δ)** 14.1(s .NH_2,2H atI)., and 8.17(s, $CONH_2$,2H at IV) was identified (**figure no. 18) .**The disappearence of methylene proton of diazo nitrile acetamide **(62)** in ^1H NMR may indicate the formation of cyclic procduct **(63).** 3375.54 cm^{-1} (NH str.) broad peak indicates the formation of tricyclic ring **74** (**scheme 16 figure no. 3)** 3525 cm^{-1} (O-H) str. due to hydroxyl peak (**scheme no 19 , figure no 9**) indicates the formation of cinnoline schiff's base(**63a)** ,752 cm^{-1} (C-Cl) due to halogen peak (**scheme 21 figure no. 12**) Indicates the formation of cinnoline Schiff's base and 1320, 1150 cm^{-1} **(**SO_2) (scheme**. no. 14**, **figure no. 1**) indicates the prasance of sulphonamide group (62). 1597.11 **,**1450 (N=O) due to nitro group (**scheme no.21 figure no 13,14**).indicates the formation of cinnoline urea derivatives (**63e, 63g and 63j**) , 827.26 ,752 cm^{-1} (Cl) due to halogen peak (**scheme no.20, figure no. 15,16**,) confirmed the synthesis of cinnoline urea derivatives(**63f, 63h** and **63k**)

Pharmacologacal evaluaction.

- All the synthesized compounds were tested for antibacterial activity as compared with standard drug Amoxicillin against *Bacillus subtillis* and *Escherichia coli.* **63, 72, 76c**, **73** and **74** showed good activity and other compounds exhibited weak activity.
- All the compounds were Screened for *in-vitro* anti-inflammatory activity of BSA using Ibuprofen as standard drug , Compounds **72**, **76a,76c, 73** and **74** showed good anti-inflammatory activity. Other synthesized compounds (**63, 75, 77e** and**77f)** exhibited weak activity.
- All the compounds (**72, 73.74.75 76(a-d)** and **77(e-k)** Screened for in-vitro Antioxidant activity by using DPPH as reducing agent, compounds **63, 72.**and 7**6c** showed good antioxidant activity. Remaining compound (**63,75, 76a, 76b, 76d. 77f, 77k, 71**) resulted in weak activity.

Attempt was made to explore structure activity relationship of synthesized 6- sulphonamido cinnoline derivatives. Sulphonamido cinnoline urea derivatives were tasted against different microbes namely *E. coli* and *B. subtillis.* The presence electro withdrawing group like nitro at Meta position demonstrated very good activity against (E. coli) however this compound was mild activity against *B. subtillis.*

Cinnoline Schiff's base derivatives was tested against different microbes namely *E. coli* and *B. subtillis* .The presence of electron donating group like Hydroxy at ortho position demonstrated very good activity against (E. coli) however this compound showed mild activity against B.subtillis. Sulphonamido-Cinnolino-pyrimidine derivatives (**72**,**73** and**74**) Substituted pyrimidine ring a cinnoline molecules demonstrated good activity against (E. coli) however this compound was showed mild activity against B. subtillis.

Cinnoline pyrimidine derivatives (**72, 73**, and **74**) were evaluated for against Bovine serum Denaturation. Substituted pyrimidine ring in cinnoline molecule demonstrated good activity. Cinnoline schiff's base derivatives against BSD present electron donating group like (OH) at ortho and Meta position demonstrated very good activity.

4. Conclusion

The novel class of sulphonamido cinnolines 63 **(a-k**), were synthesized are need to explored and optimized study for better pharmacological activity Keeping antibacterial, anti-inflammatory and antioxidant as supported by previous published reports of some of the compound belong into this class. Wide range of electron withdrawing group at meta position on the phenyl ring as R in case of urea derivatives **77(e-k**) and electron donating group at ortho position on the phenyl ring as R Schiff base **76 (a-d)**) derivatives need to explored further and optimized for the betterment of antibacterial activity. In the similar fused pyrimidine ring with cinnoline ring bearing (OH) group at 4^{th} is position required to be studied further to dovelop a novel class of antioxidant In order to ameliorate anti-inflammatory activity a wide spectrum of electron donating substituents at

Para (**76**a) and orhto (**77c)** position on phenyl ring as R need to be investigated as pharmacophore development for these classes of molecules.

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