IJBPAS, July, 2021, 10(7): 2430-2440

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

A REVIEW ON CINNOLINE SYNTHESIS, ITS DERIVATIVES AND THEIR BIOLOGICAL ACTIVITIES

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Received 5th Aug. 2020; Revised 19th Sept. 2020; Accepted 15th Oct. 2020; Available online 1st July 2021

https://doi.org/10.31032/IJBPAS/2021/10.7.5578

ABSTRACT

The cinnoline is a very significant bicyclic heterocycle that is used with its fascinating medicinal properties as the subunit of several compounds. The review represents its many pharmacological activities such as antihypertensive, antithrombotic, antitumor, antisecretory, anticancer, antibacterial, anti-inflammatory, antiparasitic, antimicrobial, antibacterial, cytotoxic, molluscicidal, antimalarial – anti-*Plasmodium falciparum*, antileukemic. In this review, an endeavor has been made to study the synthesis of cinnoline, its derivatives, and their biological activities that are reported in the scientific world.

Keywords: Cinnoline, biological activity, derivatves

INTRODUCTION

Cinnoline is the aromatic heterocyclic compound. The cinnoline solid is pale yellow in colour with melting point 24-25^{0}C, and was first noticed by Von Richter in the year 1883 **[1]**. Cinnoline synthesis can be done with o-aminophenyl-propanoic and $NaNO_2$/HCl, by maintaining proper temperature conditions for reduction **[10]**.

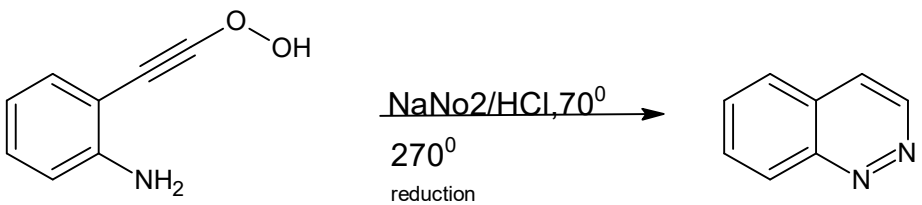
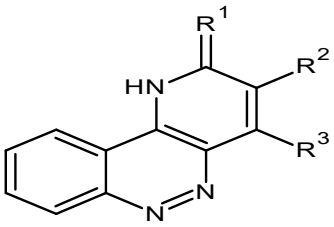


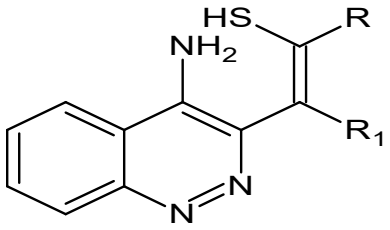
Figure 1: Cinnoline synthesis

Amer *et al* **[2]** studied derivatives of cinnoline in the different fields, cinnoline and benzo and heterocyclic analogs exhibit biological activity, including antihypertensive, antithrombotic, antitumor, antisecretory, and bactericidal **[1a-f]** activities. Due to their antibacterial, antihistamine and insecticide properties, 4-amino-cinnoline have recently become essential. These derivatives were commonly used as intermediates for the synthesis of possible biological activity **1[aa-ae]** of fused cinnoline. Previously, with a cinnoline ring as the central nucleus, these authors documented the synthesis of condensed tricyclic systems of potential biological activity.



1 a-f, 1 aa-ae,

1a:R^1=NH_2 ,R^2=CN ,R^3=Ph
1b:R^1=OH ,R^2=CN
1c:R^1=CH_3 ,R^2=$COCH_3$
1d:R^1=CH_3 ,R^2=COOEt
1e:R^1=OH , R^2=COOEt
1f:R^1=OH , R^2=SH

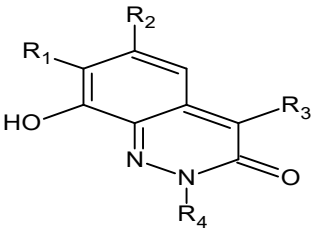


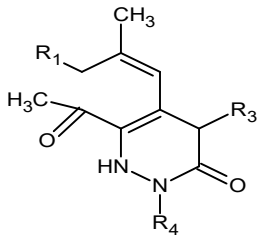
R:COOH
R_1:Ph

1aa:R^1=H , R_3=NH_2
1ab:R^1=H , R_3=OH
1ac:R^1=H , R_3=$NHCOCH_3$
1ad:R^1=SH , R_3=NH_2
1ae:R^1=NHPh , R_3=SH

Figure 2: Cinnoline Derivatives with different substituents

Nazmy, *et al* **[3]** reported that due to recurrent chemoresistance, there is an immediate continual need for novel anti-cancer agents. Newly synthesized cinnoline are examined for their potential anticancer activities and proposed mechanism in this context. In the current research, a simple and effective densely synthesized synthesis of the multicomponent reaction of ethyl 5-cyano-4-methyl-1-aryl-6-oxo-1,6-dihydropyridine-3-carboxylates with aromatic aldehydes and nitromethane in dioxane /piperidine under controlled microwave heating was developed using functionalized cannolis **[3]**.





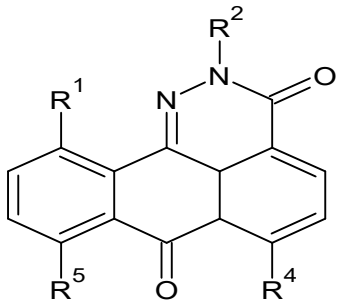
2a-v,

2a:R_2=C_6H_5 ,R_4=furfural
2b:R_2=C_6H_5 ,R_4=C_6H_5
2c:R_2=C_6H_5 ,R_4=p-Cl-C_6H_4
2d:R_2=C_6H_5 ,R_4=p-OCH_3-C_6H_4
2e:R_2=C_6H_5 ,R_4=p-NO_2-C_6H_4
2f:R_2=C_6H_5 ,R_4=m-NO_2-C_6H_4
2g:R_2=C_6H_5,R_4=o-NO_2-C_6H_4
2h:R_2=p-CH_3-C_6H_4 ,R_4=furfural
2i:R_2=p-CH_3-C_6H_4 ,R_4=C_6H_5
2j:R_2=p-CH_3-C_6H_4 ,R_4=p-Cl-C_6H_4
2k:R_2=p-CH_3-C_6H_4 ,R_4=o-Cl-C_6H_4
2l:R_2=p-CH_3-C_6H_4 ,R_4=3,4,5$(OMe)_3$-C_6H_2
2m:R_2=p-CH_3-C_6H_4,R_4=p-OCH_3-C_6H_4
2n:R_2=p-CH_3-C_6H_5,R_4=p-NO_2-C_6H_4
2o:R_2=p-CH_3-C_6H_4,R_4=m-NO_2-C_6H_4
2p:R_2=p-CH_3-C_6H_4,R_4=p-NO_2-C_6H_4
2q:R_2=p-CH_3-C_6H_4,R_4=furfural
2r:R_2=p-CH_3-C_6H_4,R_4=C_6H_5
2s:R_2=p-CH_3-C_6H_4,R_4=p-Cl-C_6H_4
2t:R_2=m-Cl-C_6H_4,R_4=Furfural
2u:R_2=m-Cl-C_6H_4,R_4=p-Cl-C_6H_4
2v:R_2=m-Cl-C_6H_4 ,R_4=p-OCH_3-C_6H_4

R_3=CN
R_1=NO_2

Figure 3: Derivatives of Cinnoline with Anticancer Property

Stefańska, *et al* **[4]** reported a sequence of derivatives of anthrapyridazone with one or two basic side chains were synthesized at different locations in the tetracyclic chromophore. In synthesis, the key intermediates are 2,7-5dihydro-3H-dibenzo[de,h]cinnoline-3,7-diones 1,12-dihydro-3H- dibenzo[de,h]cinnoline-3,7-diones 1, Monosubstituted and 15 monosubstituted with sufficient alkylaminoalkylamines at position 2(3j,3m-q) or 6 (3a-f) or disubstituted at position 2 and 6 (4g-j) or 2and 8 (3r-v). *In vitro* cytotoxic activity against murine leukemia (L1210) and humming was demonstrated in all analogs. The compound was also involved in the multidrug-resistant human leukemia (K562/DX) cell line with depending on the composition of the compound, the resistance was tested *in vivo* for murine P388 leukemia and demonstrated comparable antileukemic activity to that of mitoxantrone **[4]**.



3a-w, 3aa-al

3a:R^1=H,R^2=H,R^3=H,R^5=H

3b:R^1=H,R^2=H,R^3=H,R^5=H,R^4=NR_2R_3 R^5=NHR_2

3c:R^1=H,R^2=H,R^3=H,R^5=H

3d:R^1=H,R^2=H,R^3=H,R^5=H

3e:R^1=H,R^2=H,R^3=H,R^5=H

3f:R^1=H,R^2=H,R^3=CH_3,R^5=H

3g:R^1=H,R^2=$CH_2CH_2N(CH_3)_2$,R^3=H,R^5=H

3h:R^1=H,R^2=$CH_2CH_2N(CH_3)_2$,R^3= H,R^5=H

3i:R^1=H,R^2=CH_2CH_2-c-$N(CH_2)_5$,R^3= H ,R^5=H

3J:R^1=H,R^2=$CH_2CH_2N(CH_3)_2$,R^3=H,R^5=H

3k:R^1=OH,R^2=$CH_2CH_2N(CH_3)_2$,R^3=H,R^5=OH

3l:R^1=OH,R^2=H,R^3=H,R^5=OH

3m:R^2=$CH_2CH_2N(CH_3)_2$,R^3=H

3n:R^2=$CH_2CH_2N(C_2H_5)_2$,R^3=H

3o:R^2=$CH_2CH_2CH_2N(CH_3)_2$,R^3= H

3p:R^2=CH_2CH_2-c-$N(CH_2)_5$,R^3= H

3q:R^2=CH_2CH_2-c-$N(CH_2)_4$,R^3= H

3r:R^2=$CH_2CH_2N(CH_3)_2$,R^3= H

3s:R^2=$CH_2CH_2N(C_2H_5)_2$,R^3= H

3t:R^2=$CH_2CH_2CH_2N(CH_3)_2$,R^3= H

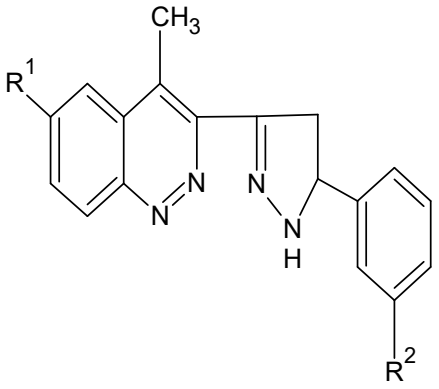
3u:R^2=$CH_2CH_2N(CH_3)_2$,R^3= H

3v:R^2=CH_2CH_2-c-$N(CH_2)_4$,R^3= H

3w:R^2=CH_3,R^3=H

Figure 4: Derivatives of Cinnoline with Antileukemic Activity

Unnissa, *et al* **[5]**, synthesized 4-methyl-3-acetylcholine-6-sulfonamide and hydrazine chalcones. Anti-malarial and anti-bacterial activity to obtain new congeners such as cinnoline-based pyrazole analogs the potent antimalarial and anti-microbial agents. Both analogs exhibited antimalarial *in vitro Plasmodium falciparum* activity and all the analogs demonstrated strong antibacterial activity against different types of micro-organisms **[5]**.

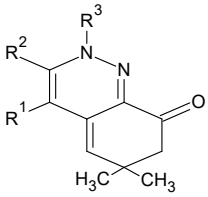


4a-k

4a:R^1=H_2NO_2S,R^2=1-methyl-4-nitrobenzene
4b:R^1=H_2NO_2S,R^2=4-methylphenol
4c:R^1=H_2NO_2S,R^2=1-chloro-4-methylbenzene
4d:R^1=H_2NO_2S,R^2=1-methoxy-4-methylbenzene
4e:R^1=H_2NO_2S,R^2=2-methoxy-4-methylphenol
4f:R^1=H_2NO_2S,R^2=[(1*E*)-prop-1-en-1-yl]benzene
4g:R^1=H_2NO_2S,R^2=N,N,4-trimethylaniline
4h:R^1=H_2NO_2S,R^2=1-fluoro-3-methylbenzene
4i:R^1=H_2NO_2S,R^2=1-chloro-2-methylbenzene
4j:R^1=H_2NO_2S,R^2=1-chloro-3-methylbenzene
4k:R^1=H_2NO_2S,R^2=1-methyl-2-nitrobenzene

Figure 5: Derivatives with Antimalarial activity

Abdelrazek, *et al*, synthesized pyrano[2,3-c]pyrazole derivatives 5a-c,aa-ac,5a-d . In general, these newly synthesized compounds demonstrate a mild molluscicidal activity **[6]**.

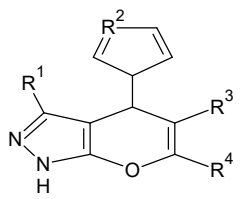


5a-c, aa-ac

5a:R^1=NC,R^2=NH_2,R^3=Ph
5b:R^1=NC,R^2=NH_2,R^3=4-Me-C_6H_4
5c:R^1=NC,R^2=NH_2,R^3=4-Cl-C_6H_4

5aa:R^1=NC,R^2=RN,R^3=AC
5ab:R^1=NC,R^2=RN,R^3=AC
5ac:R^1=NC,R^2=RN,R^3=AC

5a-d

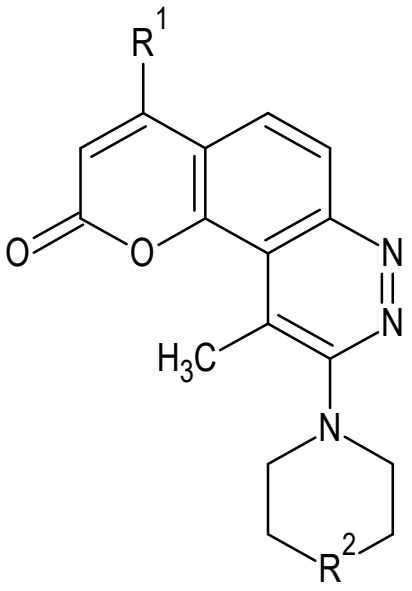


5a:R^1=Me,R^2=O,R^3=CN,R^4=NH_2
5b:R^1=Ph,R^2=O,R^3=CN,R^4=NH_2
5c:R^1=Me,R^2=S,R^3=CN,R^4=NH_2
5d:R^1=Ph,R^2=S,R^3=CN,R^4=NH_2

Figure 6: Derivatives with Molluscicidal activity

Al-zagameem, *et al*, synthesized pyrano[2,3-f]cinnolines and studied the antitumor activity on breast cancer, compounds are 6a-m **[7]**.

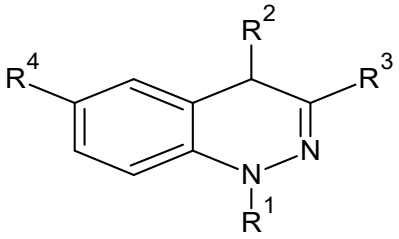
6a-m



6a:R^1=Me,R^2=O
6b:R^1=Me,R^2=S
6c:R^1=Me,R^2=CH_2
6d:R^1=Me,R^2=N-Me
6e:R^1=Me,R^2=N-Et
6f:R^1=Me,R^2=N-Pr
6g:R^1=Me,R^2=N-(p-FC_6H_4)
6h:R^1=Me,R^2=N-(o-FC_6H_4)
6i:R^1=Me,R^2=N-CH_2Ph)
6j:R^1=Me,R^2=N-(2-pyrimidyl)
6k:R^1=Me,R^2=N-(p-ClC_6H_4)
6l:R^1=Me,R^2=N-(p-$MeOC_6H_4$)
6m:R^1=Me,R^2=N-Ph

Figure 7: Antitumor Activity Derivatives

Giovannoni, M. P. *et al*, reported the therapeutics for inflammatory disease therapy. The compounds are (7a-s,7aa-ae,7aaa-are,7A) that can effectively inhibit the human proteolytic activity of neutrophils elastane (HNE) **[8]**.



7a-s ,7aa-ad,7aaa-aae,7A

7a:R^1=$CO_cC_3H_5$,R^2=OH,R^3=COOEt,
7b:R^1=CH_3,R^2=OH,R^3=COOEt
7c:R^1=CH_2-m-CH_3-ph,R^2=OH,R^3=COOEt
7d:R^1=CO-m-CH_3-ph,R^2=OH,R^3=COOEt
7eR^1=CO-m-CH_3-ph,R^2=OH,R^3=COOH
7f:R^1=CO-m-CH_3-ph,R^2=OH,R^3=Ph
7g:R^1=CO-m-CH_3-ph,R^2=OH,R^3=$_cC_3H_5$
7h:R^1=CO-m-CH_3-ph,R^2=OH,R^3=C_3H_7
7i:R^1=CO-m-CH_3-ph,R^2=OH,R^3=CH_2OH
7j:R^1=CO-m-CH_3-ph,R^2=OH,R^3=Cl
7k:R^1=CO-m-CH_3-ph,R^2=OH,R^3=Br
7l:R^1=CO-m-CH_3-ph,R^2=OH,R^3=i
7m:R^1=CO-m-CH_3-ph,R^2=OH,R^3=H
7n:R^1=$COCH_3$,R^2=OH,R^3=H
7o:R^1=COC_2H_5,R^2=OH,R^3=H
7p:R^1=COC_3H_7,R^2=OH,R^3=H
7q:R^1=COC_4H_9,R^2=OH,R^3=H
7r:R^1=$CO_cC_3H_5$,R^2=OH,R^3=H
7s:R^1=$CO_cC_5H_9$,R^2=OH,R^3=H

7aa:R^2=3-methylbenzoicacid,R^3=ClR^4=H
7ab:R^2=3-methylbenzoicacid,R^3=Br,R^4=H
7ac:R^2=3-methylbenzoicacid,R^3=i,R^4=H
7ad:R^2=3-methylbenzoicacid,R^3=H,R^4=NO_2

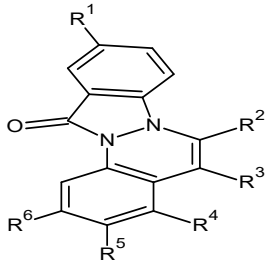
7aaa:R^1=3-methylbenzal,R^2=OH,R^4=NO_2
7aab:R^1=3-methylbenzal,R=OH,R^4=Cl
7aac:R^1=3-methylbenzal,R=OH,R^4=Br
7aad:R^1=3-methylbenzal,R=OH,R^4=i
7aae:R^1=3-methylbenzal,R=OH,R^4=NHCO-m-CH_3-Ph
7A:R^1=3-methylbenzal,R^2=ethanol

Figure 8: Derivatives with Anti-inflammatory Effect

Zhang, X., Bai *et al* synthesized the 12H-indazolo[2,1-a]cinnoline-12-ones compounds [B] Cytotoxic activity of these skeleton compounds and found highly cytotoxic activity of certain compounds **[9]**.

[A]

R^2=Ph
R^3=COOEt



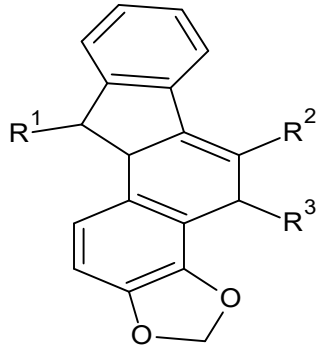
8a-c,

8a:R^1=H
8b:R^1=F
8c:R^1=OMe

8A:R^5=F
8B:R^5=Cl
8C:R^5=Br
8D:R^5=l
8E:R^5=Me
8F:R^5=OMe

8aa: R^6,R^4=OMe

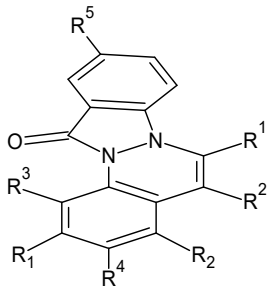
[B]



8a:R^1=OH,R^2=Ph,R^3=COOEt

8b:R^1=OH,R^2=CH_3,R^3=COOEt

[C]



8aa-af,8A-8B,8Aa-Af,8AA,8aA,8aaa,8aAa-aAc

8aa:R^1=fluorobenzene,R^2=COOEt
8ab:R^1=iodobenzene,R^2=COOEt
8ac:R^1=toluene,R^2=COOEt
8ad:R^1=anisole,R^2=COOEt
8ae:R^1=anisole,R^2=COOEt
8af:R^1=furan,R^2=COOEt

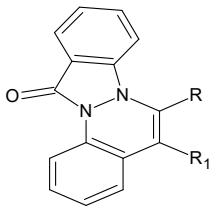
8A:R^1=CH_3,R^2=COOEt,R^3=OMe
8B:R^1=CH_3,R^2=COOEt R^3=H
8Aa:R^1=CH_3,R^2=COOEt,R^4=F
8Ab:R^1=CH_3,R^2=COOEt,R^4=Cl
8Ac:R^1=CH_3,R^2=COOEt,R^4=Br
8Ad:R^1=CH_3,R^2=COOEt,R^4=i
8Ae:R^1=CH_3,R^2=COOEt,R^4=Me
8Af:R^1=CH_3,R^2=COOEt,R^4=Ome

8AA:R^2=COOEt,R^5=Ome
8aA:R_1,R_2=OMe,R^1=CH_3,R^2=COOEt
8aaa:R^3=F,R^2=COOMe,R^1=CH_3
8aAa:R^1=CH_3,R^2=COOMe,R^4=H
8aAb:R^1=CH_3,R^2=COOMe,R^4=Et
8aAc:R^1=CH_3,R^2=COOMe,R^4=OCF_3

8a1:R^1=CH_3,R^2=COOMe

8aa1:R^1=CH_3,R^2=COOMe,$R_1R_2R_4$=Ome

[D]

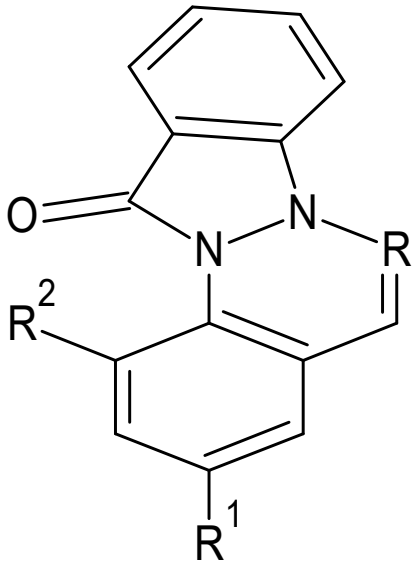


8a-b

8a:R=Et,R_1=COOMe

8b:R=cyclopropyl,R_1=dimethoxy(OXO)phoshanium

[E]



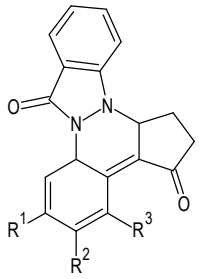
8a-c,8aa-ac,aaa-aae

8a:R=cyclohexanone,R^1=H
8b:R=cyclohexanone,R^1=F
8c:R=cyclohexanone,R^1=OMe

8aa:R=cyclopentanone,R^2=F
8ab:R=cyclopentanone,R^2=OMe

8aaa:R^1=H,R=cyclopentanone
8aab:R^1=C,lR=cyclopentanone
8aac:R^1=Br,R=cyclopentanone
8aad:R^1=i,R=cyclopentanone
8aae:R^1=OMe,R=cyclopentanone

[F]

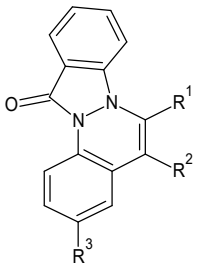


8a-aa

8a:R^1=Ome,R^3=Ome
8aa:R^1=Ome,R^2=Ome,R^3=Ome

8a-b,8aa-ab

[G]



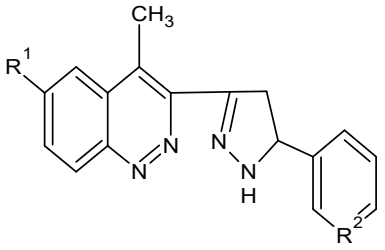
8a:R^1=Ph,R^2=COOEt,R^3=Ph
8a:R^1=Ph,R^2=COOEt,R^3=CN
8a:R^1=Ph,R^2=COOEt,R^3=morphollnyl

8aa:R^1=Ph,R^2=2-hydroperoxyethan-1-ol
8ab:R^1=Me,R^2=2-hydroperoxyethan-1-ol

Figure 9: Highly Cytotoxic Derivatives of Cinnoline

Unnissa, S. H. *et al* synthesized 4-methyl -3-acetylcinnoline-6-sulfonamido chalcones and hydrazines. Antimalarial and antibacterial agents are the compound 9a-j, both are analogous and exhibited antimalarial *in vitro Plasmodium falciparum* activity, and all analogous demonstrated strong antibacterial activity against different pathogenic microbes **[10]**.

9a-j



9a:R^1=H_2NO_2S,R^2=1-methyl-4-(nitomethyl)benzene
9b:R^1=H_2NO_2S,R^2=4-methylPhenol
9c:R^1=H_2NO_2S,R^2=1-chloro-4-methylbenzene
9d:R^1=H_2NO_2S,R^2=1-methoxy-4-methylbeneze
9e:R^1=H_2NO_2S,R^2=2-methoxy-4-methylphenol
9f:R^1=H_2NO_2S,R^2=1-methyl-3-[(1Z)-prop-1-en-1-yl]benzene
9g:R^1=H_2NO_2S,R^2=N,N,4-trimethylaniline
9h:R^1=H_2NO_2S,R^2=1-fluoro-3-methylbenzene
9i:R^1=H_2NO_2S,R^2=1-chloro-3-methylbenzene
9j:R^1=H_2NO_2S,R^2=1-methyl-2-(nitromethyl)benzene

Figure 10: Novel Antimalarial Derivatives

CONCLUSION

From this review, it can be concluded that cinnoline and its derivatives are useful chemical entities for various biological activities. More scientific endeavors are required towards their formulation development and stability studies as per standard protocols.

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