WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 3, 1289-1296. Research Article ISSN 2277– 7105

SYNTHESIS AND EVALUATION OF DERIVATIVES OF HETEROCYCLE CINNOLINE

Dr. P.R. Logeshkumar*[1], Dr. P. Vasanthkumar[2], K. Tharangini[3], K. Priyanka[3], M. Sunanda[3], J. Manjula[3] S. Varun Kumar[3], V. Hareeshkumar[3], M. Chandrashekar[3], M. Madhu Sudhana[3]

[1]Associate Professor, Department of Pharmaceutical Chemistry, Sri Krishna Chaithanya College of Pharmacy, Nimmanapalli Road, Madanapalle, Chittoor (Dt), Andhra Pradesh-517325, India.

[2]Professor and Principal, Sri Krishna Chaithanya College of Pharmacy, Nimmanapalli Road, Madanapalle, Chittoor (Dt), Andhra Pradesh-517325, India.

[3]B. Pharmacy, Sri Krishna Chaithanya College of Pharmacy, Nimmanapalli Road, Madanapalle, Chittoor (Dt), Andhra Pradesh-517325, India.

Article Received on
7 Jan. 2020,
Revised on 28 Jan. 2020,
Accepted on 18 Feb. 2020
DOI: 10.20959/wjpr20203-16932

***Corresponding Author**
Dr. P. R. Logesh Kumar
Department of Pharmaceutical Chemistry, Sri Krishna Chaithanya College of Pharmacy, Nimmanapalli Road, Madanapalle, Chittoor (Dt), Andhra Pradesh-517325, India.

ABSTRACT

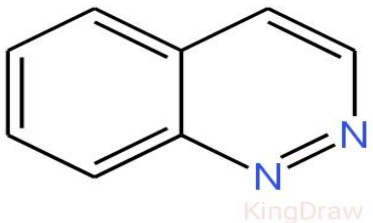
Cinnoline is also known as 1,2 diazanaphthalene or benzo-1,2 – diazene. Cinnoline itself is toxic. cinnoline nucleus is very important bicyclic heterocycle that is used as the structural sub unit of many compounds. Cinnoline derivatives exhibit broad spectrum of pharmacological activities such as antibacterial, antifungal, antimalarial, anti inflammatory, analgesic, anxiolytic and antitumour activites. It is soluble in water, ethanol, methanol, DMSO, and DMF. It is a pale yellow solid of geranium like odour. The starting compound of cinnoline is Aniline and Sodium nitrite. Some of the cinnoline derivatives are 4-phenyl cinnoline, Ethyl cinnoline, Methyl cinnoline, Cinoxacin.

KEYWORDS: 1,2-diazanaphthalene, Heterocycle, Anti-fungal, Anti-malarial, Anti-inflammatory, Anti-analgesic, Anti-tumor, Anti-bacterial.

INTRODUCTION

Cinnoline 1, 1,2-diazanaphtalene or benzo[c]-1,2-diazine (Hantsch-Widmann system), C8H6N2 is a nitrogenous organic base, obtained from certain complex diazo compounds (Fig. 1). Their system is an isosteric relative to either quinoline or isoquinoline. Therefore, in many cases the synthesized compounds were designed as analogs of the previously obtained quinoline or isoquinoline derivatives. Cinnoline itself is toxic and shows antibacterial activity against Escherichia coli.[1] None of its derivatives have been found in nature. The synthesis of its nucleus was first carried out by V. Richter in 1883, after whom this heterocyclic system is named.[2] Although its derivatives have been reviewed in many books and journals, only some of them reported biological properties.[3–6] This review includes papers and patents after 1945 because earlier data are scarce. In 1957, Jacobs in his review on cinnoline and related compounds pointed out that this ring system was the least known of the condensed, bicyclicaromaticheterocyclescontainingtwonitrogenatoms. Since then a significant interest in the synthesis of compounds possessing the cinnoline ring system has developed. Some cinnolines have been screened and have received approval as bioactive drugs or are still under clinical trials. Of all substituted cinnolines, which have been prepared, mainly aminocinnolines are known to havebiologicalactivity. With the view of discovering a new antimalarial drugs such as chloroquine analogs, the derivatives of 4-aminocinnolines 2 (Fig. 2) were synthesized by Keneford et al. Biological tests demonstrated that some of them showed significant activity.[7] A year later in 1948, Kornfeld synthesized a series of 1,2-dihydrocinnolines to investigate compounds with possible estrogen-like activity, but the compound 3 (Fig. 2) exhibited only a weak estrogen activity.[8] A new group of 3,4-substituted cinnolines 4 (Fig. 2) structurally related to early obtained quinoline derivatives were synthesized as antimicrobial agents. Some of the tested compounds exerted bacteriostatic activity.

CINNOLIN



Molecular formula : $C_8H_6N_2$

Molecular weight : 130 gm

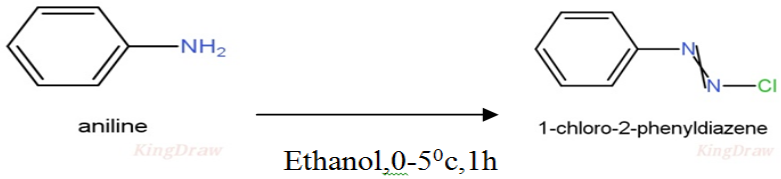
Melting point : 38°C

Boiling point : 0.35114°[151.4⁺_13.0°C at 760mmHg]

Solubility : Soluble in water, Ethanol, Methanol, DMSO, DMFetc.

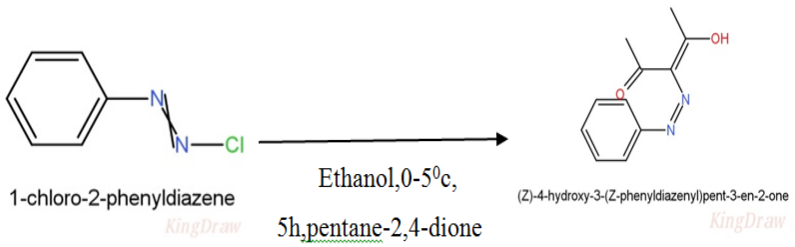
Appearance : Pale yellow solid, Geranium odour.

SCHEME AND MATERIALS METHOD



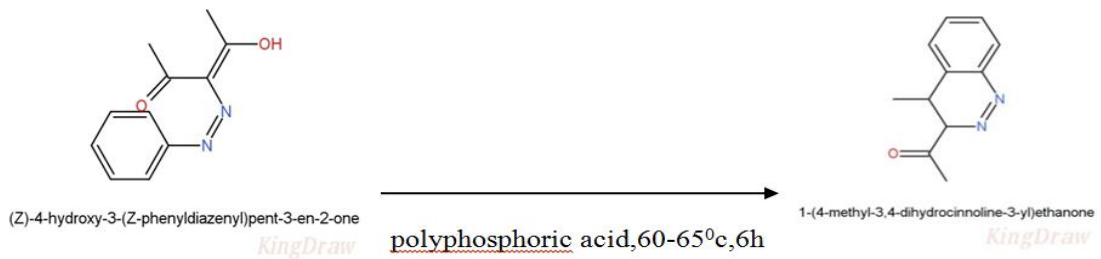
Step 1: Synthesis of 1-chloro-2-phenyl diazene.

- 1-chloro-2-phenyl diazene is prepare by dissolving sodium nitrite(0.1 mole) in 26ml of water.
- Added drop wise to a solution of aniline (10ml of in 1N HCL) at 0°c under stirring for about 30mins.
- Reflux for 1hr.Then orange coloured precipitate is collect by filtration and dried.



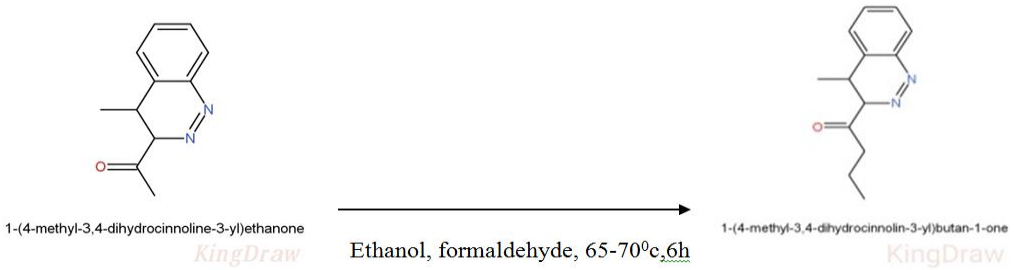
STEP-2: Synthesis of (Z)-4-hydroxy-3-{(Z)-phenyldiazenyl}pent-3-en-2-one.

- To a solution of compound (0.2mole) in ethanol, pentane-2,4-dione(0.2 mole) is added.
- The mixture is refluxed for 5hours.
- The solvent is evaporated and the solid obtained is recrystalised from petroleum ether.



STEP 3: Synthesis of 1-[4-methyl-3,4-dihydrocinnoline-3-yl]ethanone.

- Compound 2(0.1mole) in ethanol(10ml),20ml of polyphosphoric acid is added
- The mixture is maintained under reflux for 6hours.
- After cooling, the mixture is poured on ice and the solid formed is collected by filtration, washed with cold water and recrystalised from ethanol.



Step-4: Synthesis of 1-[4-methyl-3,4-dihydrocinnolin-3-yl]butan-1-one.

- Compound 3(0.1mole) in 30ml of ethanol and 30ml of formaldehyde.
- The mixture is maintained under reflux for 6hours.
- The solvent is evaporated and the solid obtained is recrystalised from petroleum ether.

Chemicals

Aniline, Sodium nitrite,1-chloro-2-phenyldiazene,(Z)-4-hydroxy-3-(Z-phenyl diazenyl)pent-3-en-2-one,1-(4-methyl-3,4-dihydrocinnolin-3-yl)ethanone,1-(4-methyl-3,4-dihydrocinnoline-3-yl)butan-1-one.

Apparatus

Round bottom flask, Reflex condenser, Measuring cylinder, Beakers, Funnel, Petri plate, Glass rods, Water bath, Weghing balance, Tripod stand.

Physical Characterisation

Molecular formula : $C_8H_6N_2$

Molecular weight : 130gm

Melting point : 38^0c

Boiling point : 0.35114^0[151.4+/-13.0^0c at 760mmHg]

Solubility : Soluble in water, ethanol, methanol, DMSO, DMF etc

Apperance : Pale yellow solid, Geranium odour.

BIOLOGICAL SCREENING

In-Vitro Anti-Inflammatory Activity

Inflammation is normal protective response to tissue injury caused by physical trauma, noxious chemicals or microbiological agents and local response of living mammalian tissue to injurious agents, which may be due to physical agents like heat, cold, radiation, trauma; Chemical agents like organic and inorganic; Infective agents like bacteria, virus, parasites; Immunological agents like antigen-antibody reactions, cell mediated reaction. In the present study invitro anti-inflammatory activity was checked for the synthesized compounds.

HRBC Membrane Stabilisation method

The method involves the stabilization of human red blood cell membrane by hypotonicity induced membrane lysis.

Principle

The lysosomal enzymes released during inflammatory condition produce a variety of disorders. The extra cellular activity of these enzymes is said to be related to acute or chronic inflammation. The anti-inflammatory agents act by either inhibiting the lysosomal enzymes or by stabilizing the lysosomal membrane since the human red blood cell membrane are similar to lysosomal membrane components. The prevention of hypotonicity induced HRBC membrane lysis is taken as a measure of anti-inflammatory activity of the drug.

Reagents

- HRBC suspension : 10%
- Alsiever solution
- Isotonic saline : 0.85%
- Phosphate buffer : 0.15M,pH-7.2
- Hypotonic saline : 0.36%

Preparation of Alsievier's solution: 2g dextrose + 0.8g sodium citrate + 0.05g citric acid + 0.42g sodium chloride was made up with distilled water to 100ml.

Preparation of 0.5 ml of 10% HRBC Suspension

To 3 ml of blood, add 3 ml of Alsievier's solution and centrifuge at 3000 rpm for 20 minutes then packed cells were washed with isotonic saline and later 10% v/v suspension of the packed cells was made with isotonic saline.

Preparation of Hypotonic Saline

0.36g of sodium chloride in 100 ml of distilled water.

Preparation of Isotonic Saline

0.85g of sodium chloride in 100 ml of distilled water.

SPECTRAL ANALYSIS

^{1}HNMR Interpretation

^{1}HNMR Spectral data Absorption position (in PPM)	
7.27 - 7.53	m, 6H, CH
6.77 – 6.89	d, 6H, CH
5.47	s, 3H, CH_2
4.8	d, 3H, NH

RESULTS AND DISCUSSION

Synthesis

The present study report the synthesis of cinnoline derivatives nucleophillic substitution of aniline with sodium nitrite was carried out stepwise at different temperature by various amines. The first step involves substitution of ethyl aceto acetate. The final cinnoline derivative in the synthesized compound 3 was replaced by formaldehyde. Since the report regarding this compound suggest a cinnoline posses a good bioactive moiety.

Physical Characterization

Melting points of the synthesized compound was taken in open capillary tubes and was uncorrected and were found to be in the range 115-130˚C.

TLC was performed using precoated silica gel plates of 0.25mm thickness. Eluents used were chloroform, ethanol (2:8) spots were visualized in U.V. light.

At room temperature solubility of newly synthesized compounds were determined by various organic solvents and it was found that all compounds were freely soluble in Methanol, Ethanol, DMSO and DMF.

IN-VITRO ANTI-INFLAMMATORY ACTIVITY

The synthesized compounds are to be used for this study. They are to be made into doses of 1000 µg/ml with DMSO (5.0%) solution. Diclofenac sodium is taken as standard. The reaction mixture (4.5 ml) consist of 2 ml of hypotonic saline (0.36% sodium chloride), 1 ml

of 0.15 M phosphate buffer (Ph 7.4), 1 ml of the test solution (1000 µg/ml) in normal saline and 0.5 ml of HRBC suspension in normal saline. For control test, 1 ml isotonic saline is to be used instead of test solution while product control lacked RBC. The mixture is then incubated at 56˚C for 30 minutes, then to be cooled under running tap water and centrifuged at 3000 rpm for 20 minutes. The absorbances of the supernatants are read at 560 nm.Percent membrane stabilization activity is calculated as follows:

$$\% \text{ stabilization} = \frac{\text{OD of test control-OD of test sample}}{\text{OD of test control}} \times 100$$

S.No	Compound code	Percentage Stabilization
1	formaldehyde derivatives	77
2	STD (Diclofenac)	87.4

CONCLUSION

In the present study certain cinnoline derivatives were synthesized and characterized by^{1}HNMR. The synthesized compound show characteristic absorption peaks –in ^{1}HNMR spectra. Expected molecules in (m+) fragments were observed for the entire compounds in mass spectra.

The synthesized compound was subjected to biological evaluation. The compound were evaluated for anti-oxidant studies revealed that the substitution of different aromatic amines to parent cinnoline nucleus show the moderate activity.

REFERENCES

1. V. Murugesan, V Sivamurugan, G Abraharam Rajkumar & Banumathi Arabindoo, “Selective and clean oxidation of alcohols with benzimdazolium fluorochromate (BIFC) under solvent free conditions”, Indian journal of Chemistry, January, 2005; 44B: 144-147.
2. E Rajanarendar, D Karunakar & M Srinivas, “Synthesis of imidazole, coumarin and isoxazole containing new triheterocyclic compounds and their derivatives”, Indian Journal of Chemistry, March, 2005; 44B: 563-567.
3. Biswanath Das, M Ravinder Reddy & N Ravindranath, “A substituted imidazole derivative from Jatropha curcas.” Indian journal of Chemistry, May, 2005; 44B: 1119-1120.
4. P K Dubey, A Naidu, V Anandam & G Hemasunder, “Synthesis of 1-(n-hexyl-5-one)-2-chlorobenzimidazole.” Indian journal of Chemistry, June, 2005; 44B: 1239-1242.

5. R T Pardasani, P Pardasani, B Gupta A V Londhe & S Kohli, "Synthesis and semiempirical calculationsof isatylidine, thioisatylidine and acenapthylidine derivatives of imidazolidine, thiazolidine, oxazolidine and pyrimidinetrione." Indian journal of Chemistry, June, 2005; 44B: 1252-1256.
6. P M Shafi, T D Sobha, & P A M Basheer, "Synthesis and reactions of 4-(aminoaryl)-methylene-2-aryl-2-imidazolin-5-one." Indian journal of Chemistry, June, 2005; 44B: 1298-1300.
7. P Hanumantha Rao & T V Maruthikumar, "A Novel synthesis of 1-(1-aza-2-arylvinyl)-2-[(1E)-2-arylvinyl]-4-(phenyl methylene)-2-imidazolin-5-ones" Indian journal of chemistry, July, 2005; 44B: 1497-1499.
8. P Hanumantha Rao, T Venkata Maruthikumar & V Prabhakar Reddy, "Microwave induced solvent-free synthesis of 1-aryl-2-(1E)-arylvinyl-4-arylmethylene-2-imidazolin-5-ones." Indian journal of Chemistry, September, 2005; 44B: 1931-1932.
9. V Rajeswar Rao & P Vijaya kumar, "Synthesis and biological activity of some3-imidazo[1,2-a]pyridin-2-yl-chromen-2-one and 3-indolizin-2-yl-chromen-2-one." Indian journal of Chemistry, October, 2005; 44B: 2120-2125.
10. V V Mulwad & B P Choudhari, "synthesis and antimicrobial screening of 5H, 7H-N-(coumarin-6-yl)-2,8-diphenyl-5,7-dioxo-4,5,6,7-tetrahydrobenzimidazo(5,6-c)-furan and 5H, 7H-N-(coumarin-6-yl)-2,8-diphenyl-5,7-dioxo-6-(7-methoxy-4-methylcoumarin-6-yl)-4,5,6,7-tetrahydrobenzimidazo(5,6-c)pyrrole" Indian journal of Chemistry, January, 2006; 45B: 314-317.
11. Y A Ammar, Abdullah M Al-Sehemi & A M Sh El-Sharief, "propionic acids in organic synthesis:nove synthesis of benzimidazole, 3,1-benzoxazine,3-aminoquinazole and 3-aminotheno[2,3-d]pyrimidine derivatives containing 2-naphthyl propionyl moiety" Indian journal of Chemistry, February, 2006; 45B: 450-455.
12. M R yadav, D S Puntambekar, K P Sarathy, S Vengurlekar & R Giridhar, " Quantitative structure activity relationship studies of diarylimidazoles as selective COX-2 inhibitors." Indian journal of Chemistry, February, 2005; 45B: 475-482.