e - ISSN - 2249-7668
Print ISSN - 2249-7676

International Journal of
Pharmacology & Toxicology

www.ijpt.org

SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF SOME CINNOLINE DERIVATIVES

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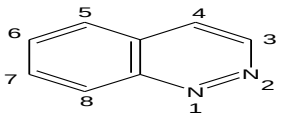
ABSTRACT

The review of literature showed that cinnoline derivatives were found to elicit many pharmacological actions like anti-hypertensive, antithrombotic, antihistamine, antileukemic, CNS activity, anti tumor, antibacterial and antisecretory activity. Imidazole can be found in many other drugs such as dacarbazine, metronidazole, cimetidine, flumazenil, thyroliberin, methimazole, pilocarpine and etomidate which are used as antineoplastic antibiotic, antiulcerative, benzodiazepine antagonist, prohormone, antihyperthyroid, muscarinic receptor.In the substituted Cinnoline Imidazole series, the compounds which are halogen mainly Chloro Substituted were showed potent antibacterial, anti-inflammatory and anti-fungal activity than other compounds. However Methyl substituted compound also showed more potent antimicrobial activity and anti-inflammatory activity.

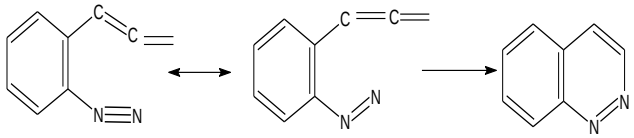
Keywords: Cinnoline, Imidazole, Anti-inflammatory activity.

INTRODUCTION

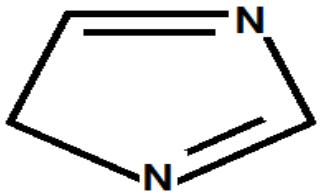
Cinnoline is a pale yellow solid, m.p. 24-25°C and was first discovered by Von Richter in 1883. He also prepared a cinnoline derivative from 2-aminophenylpropionic acid via intramolecular cyclization of the diazonium salt. The review of literature showed that cinnoline derivatives were found to elicit many pharmacological actions like anti-hypertensive, antithrombotic, antihistamine, antileukemic, CNS activity, anti tumor, antibacterial and antisecretory activity (Abbady MS. They are reactive by virtue of the presence of a benzene ring and the electrophillic attack takes place in this ring. Cinnolines are the six-membered heterocyclic compounds having two hetero atoms in the ring [1-5]. They are also called as 1, 2- benzodiazine or benzopyridazine or 1, 2- diazanaphthalene or phenodiazine. (VI)



The main approach for the synthesis of cinnoline is electrophilic attack by diazoniumcation on carbon – carbon center of unsaturation as given below.



Imidazole



Imidazole is an organic compound with the formula $C_3H_4N_2$. This aromaticheterocyclic is a diazole and is classified as an alkaloid. Imidazole refers to the

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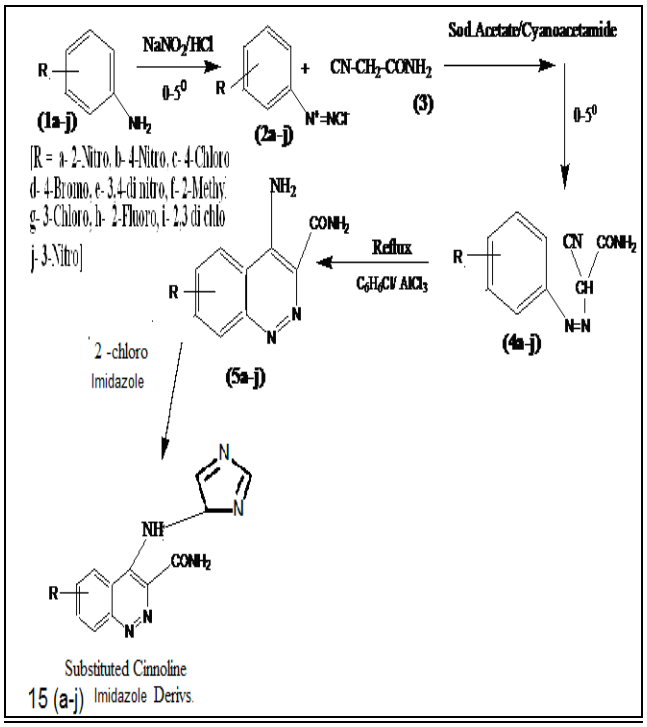
parent compound whereas imidazoles are a class of heterocycle with similar ring structure but varying substituents [6-10]. This ring system is present in important biological building blocks such as histidine, and the related hormone histamine. Imidazole can serve as a base and as a weak acid. Many drugs contain an imidazole ring, such as antifungal drugs and nitroimidazole.

During the past decade, imidazole derivatives have occupied a unique place in the field of medicinal chemistry. They have wide range of biological activities. They are well known analgesics, anti-inflammatory, antiparasitic, anthelmintic, platelet aggregation inhibitors and antiepileptic agents [11-15]. Imidazole can be found in many other drugs such as dacarbazine, metronidazole, cimetidine, flumazenil, thyroliberin, methimazole, pilocarpine and etomidate which are used as antineoplastic antibiotic, antiulcerative, benzodiazepine antagonist, prohormone, antihyperthyroid, muscarinic receptor [16-22].

1. Synthesis of new series of substituted cinnoline derivatives condensed with Imidazole Moieties.
2. Characterization of newly synthesized compounds by analytical and spectral methods viz., IR spectra, NMR spectra and Mass spectra.
3. Anti-inflammatory activity of some of the synthesized compounds.

MATERIALS AND METHODS

The Methodology Used For the Synthesis of Substituted Cinnoline imidazole Series is as follows : 15 (a - j)



The synthesis of substituted cinnoline Imidazole derivatives by the described above method remitted in products with good yield.

Methodology for Anti-inflammatory

The anti-inflammatory activity was assessed by rat paw edema method wherein the procedure of plethysmographic measurement of edema produced by planter injection of 1% w/v formalin in the hind paw of the rat was followed. The method described by Wilhelm and Domenoz as modified by Sisodia and Rao was used for measuring the paw volume. Suspension of phenylbutazone containing 40 mg/ml of drug was prepared in 2% gum acacia and used as standard drug. Suspensions of test compounds at a concentration of 40 mg/ml were also prepared in 2% gum acacia. The dose concentration of both standard drug and the test compounds was 100 mg/kg body weight. 1% w/v of formalin solution prepared and 0.1 ml of it in each case was injected in the planter region of left hind paw of albino rats [23-29].

Albino rats of either sex weighing 150-200 grams were used and divided into groups of sixalbino rats in each group. First group served as control, second group was used for standard drug phenylbutazone and the remaining groups served for compounds under investigation. An identification mark was made on both the hind paws just beyond tibiotorsal junction so that every time the paw was dipped in mercury column upto a fixed mark to ensure constant paw volume. Immediately after 30 minutes of drug administration, 0.1 ml of 1% w/v formalin was injected in the planter region of left paw of the rats. The right paw was used as reference for non inflammated paw for comparision. The paw volume of all the test animals was measured after 2nd and 4th hours of drug administration. The percentage of increase in edema over the initial reading was also calculated. The increase in edema of animals treated with standard test compounds were compared with the increase in the edema of untreated control animal with the corresponding intervals of 2nd and 4th hours. Thus the percentage inhibition of edema at known intervals in treated animals was calculated as given below.

$$\text{Percentage inhibition} = \frac{Vc - Vt}{Vc} \times 100$$

Vc = volume of paw edema in control animals
Vt = volume of paw edema in treated animals

Data analysis

The data were subjected to analysis of variance (ANOVA) as per statistical methods using SPSS (1996) software package.

All the Synthesized compounds have shown anti-inflammatory activity to a certain extent as compared to standard drug Phenylbutazone. Among the tested

compounds15DSDc, 15DSDf and 15DSDi have shown good activity by formalin induced rat paw edema method.

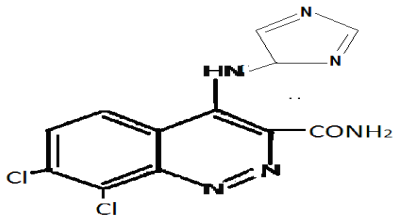
RESULTS AND DISCUSSION

In the substituted Cinnoline Imidazole series, the compounds which are halogen mainly Chloro Substituted were showed potent antibacterial, anti-inflammatory and anti-fungal activity than other compounds. However Methyl substituted compound also Showed more potent antimicrobial activity and anti-inflammatory activity.

In the present work the representative products were characterized by their infrared (IR) spectra, proton magnetic resonance (PMR) spectra and mass spectra. Some intermediates were characterized by measuring their melting point and comparing with literature value, wherever possible. The IR spectra were recorded by NICOLETT-IMPACT-400FT-IR SPECTRO PHOTOMETER using a thin film supported on KBrpellets.The PMR spectra were recorded on JEOL-JMS D-300 (300 MHz) NMR spectro meter. All spectra were obtained in Deuturated Methanol and chemical shift values are reported as values in ppm relative to TMS (δ = 0) as internal standard. Mass spectra were recorded on JEOL SX102 MS System operating at 70 ev.

Sample 15DSDi

C.No. 15DSD$_i$ _ 7,8-Di-chloro-4(-5-amino- Imidazole) cinnoline-3-carboxamide



IR (KBr) in cm^{-1}

Peak at 3466.1 cm^{-1} corresponds to NH stretching
Peak at 3341.5 cm^{-1} corresponds to asymmetric NH_2 group.
Peak at 3236.2 cm^{-1} corresponds to CH stretching.
Peak at 1671.9 cm^{-1} corresponds to C = O stretching.
Peak at 1500.6 cm^{-1} corresponds to aromatic C = C stretching.
Peak at 1671.9 cm^{-1} corresponds to C = N stretching.
Peak at 1208 - 1671 cm^{-1} corresponds to imidazole

H^1-NMR δ in ppm

δ 8.10 – 8.25 (2H, d, of cinnolines)
δ 7.51 – 7.67 (3H, d, Imidazole)
δ 14.11 (1H, s, of NH)
δ 10.35 (2H, s, of CONH2)

Mass in m/z

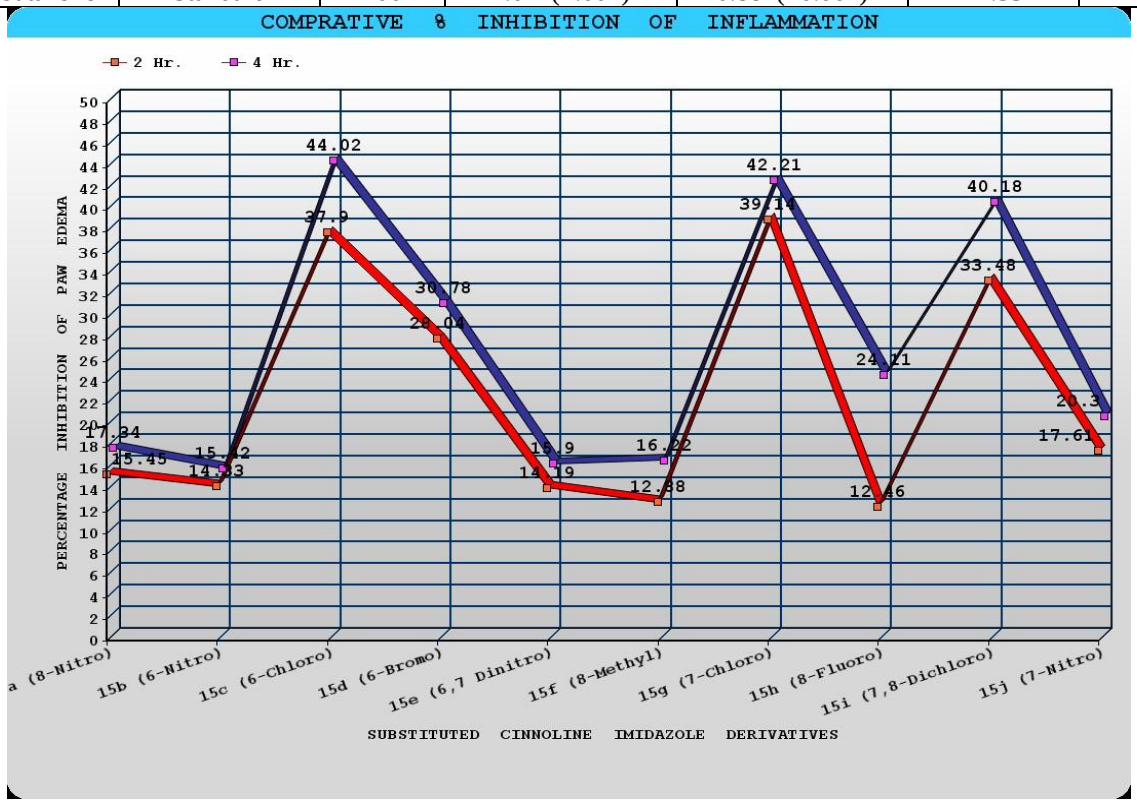
Molecular ion peak at m/z = 323 mHz is because of molecular formula $C_{12}H_8Cl_2N_6O$. Base peak is at m/z = 154 mHz. Fragment ion peak is observed at m/z = 256 because of $C_9H_5Cl_2N_4O$, m/z = 241 because of $C_9H_4Cl_2N_3O$, m/z =82 because of $C_3H_4N_3$.

Table 1. Physical data of substituted 4(-5-amino-Imidazole) cinnoline-3-carboxamide derivatives: (15a –j)

Sl. No.	Comp. No	Physical nature	M.P(°C)	Yield (%)
8 -Nitro-4(-5-amino-Imidazole) cinnoline-3-carboxamide	**15DSD$_a$**	Pale brown crystals	212-214°C	55.89%
6- Nitro-4(-5-amino-Imidazole) cinnoline-3-carboxamide	**15DSD$_b$**	Dark Yellow crystals	105-107°C	67.98%
6- Chloro-4(-5-amino-Imidazole) cinnoline-3-carboxamide	**15DSD$_c$**	Green crystals	184-186°C	57.34%
6-Bromo -4(-5-amino-Imidazole) cinnoline-3-carboxamide	**15DSD$_d$**	Light green-brown crystals	158-160°C	45.08%
6,7- di nitro-4(-5-amino-Imidazole) cinnoline-3-carboxamide	**15DSD$_e$**	Dark orange crystals	151-153°C	61.14%
8- Methyl-4(-5-amino-Imidazole) cinnoline-3-carboxamide	**15DSD$_f$**	Dark red crystals	154-156°C	54.78%
7 –Chloro- 4(-5-amino-Imidazole) cinnoline-3-carboxamide	**15DSD$_g$**	Golden violet crystals	166-168°C	70.39%
8-Fluoro-4(-5-amino-Imidazole) cinnoline-3-carboxamide	**15DSD$_h$**	Light brown crystals	148-150°C	66.61%
7,8- DiChloro-4(-5-amino-Imidazole) cinnoline-3-carboxamide	**15DSD$_i$**	Off white crystals	217-219°C	58.82%
7- Nitro1H-Cinnoline -4(-5-amino-Imidazole) cinnoline-3-car	**15DSD$_j$**	Orange Crystals	197-199°C	62.45%

Table 2. Result of Anti-inflammatory Activity

Compound	Substitution	Dose Mg/kg	Mean value (+S.E) of edema at different intervals		Percentage inhibition At Different intervals	
			2nd Hour	4th hour	2nd hr	4th hr
15DSDa	8 –Nitro	100	1.66 (±0.002)	1.62 (±0.001)	15.45	17.34
15DSDb	6- Nitro	100	1.68 (±0.015)	1.66 (±0.002)	14.33	15.42
15DSDc	6- Chloro	100	1.15 (±0.001)	0.90 (±0.003)	37.90	44.02
15DSDd	6-Bromo	100	1.50 (±0.032)	1.45 (±.0.003)	28.04	30.78
15DSDe	6,7- di nitro	100	1.68 (±0.015)	1.65 (±0.026)	14.19	15.90
15DSDf	8- Methyl	100	1.70 (±0.601)	1.63 (±0.005)	12.88	16.22
15DSDg	7 –Chloro	100	1.13 (±0.002)	1.01 (±0.001)	39.14	42.21
15DSDh	8-Fluoro	100	1.70 (±0.001)	1.51 (±0.006)	12.46	24.11
15DSDi	7,8- DiChloro	100	1.20 (±0.003)	1.11 (±0.001)	33.48	40.18
15DSDj	7- Nitro	100	1.62 (±0.005)	1.58 (±0.004)	17.61	20.30
Phenyl butazone	Standard	100	1.01 (±.001)	0.88 (±0.002)	42.35	46.6



CONCLUSION

In the substituted Cinnoline Imidazole series, the compounds which are halogen mainly Chloro Substituted were showed potent anti-inflammatory activity than other compounds.

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