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Synthesis, Characterization and Antiinflammatory activity of Cinnolines (pyrazole) derivatives

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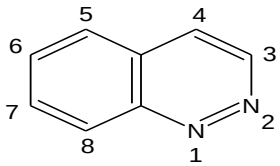
Abstract: *In the substituted Cinnoline Pyrazole series, the compounds which are halogen mainly Chloro, Bromo and Fluoro Substituted were showed potent antibacterial, anti-inflammatory and anti-fungal activity than other compounds. Especially Chloro Substituted Compounds Showed more potent anti-inflammatory activity among all the substituted cinnoline pyrazole compounds.*
Keywords*: cinnoline, pyrazole, anti-inflammatory activity.*

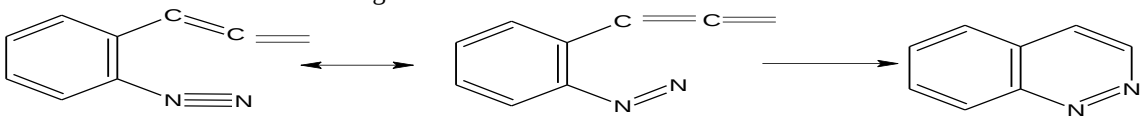
I. Introduction

Cinnolines: 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. 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. They are also called as 1, 2- benzodiazine or benzopyridazine or 1, 2-diazanaphthalene or phenodiazine. (VI)



(VI)

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



Pyrazoline:

Pyrazole refers both to the class of simple aromatic ring organic compounds of the heterocyclic diazole series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions, and to the unsubstituted parent compound. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons. The term pyrazole was given to this class of compounds by Ludwig Knorr in 1883. In medicine, derivatives of pyrazoles are used for their analgesic, anti-inflammatory, antipyretic, antiarrhythmic, tranquilizing, muscle relaxing, psychoanaleptic, anticonvulsant, monoamineoxidase inhibiting, antidiabetic and antibacterial activities.

Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals. The recent success of pyrazole COX-2 inhibitor has further highlighted the importance of these heterocycles in medicinal chemistry. A systematic investigation of this class of heterocyclic lead revealed that pyrazole containing pharmacoactive agents play important role in medicinal chemistry**.** The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead. The treatment of pain continues to be the subject of considerable pharmaceutical and clinical research. Microbial infections often produce pain and inflammation. Chemotherapeutic, analgesic and anti-inflammatory drugs are prescribed simultaneously in normal practice. The compound possessing all three activities is not common. It has been reported that pyrazoline possess analgesic, anti-inflammatory and antimicrobial activities. In view of these above, an attempt has been undertaken for the synthesis of substituted Cinnoline pyrazole derivatives containing potent, anti-inflammatory and anti-microbial activities.

II. Review Of Literature

Priyadarsini P (2012) prepareds new substituted pyrazoles from o-hydroxyacetophenone and cinnamic acids as starting material through1,3-diketones as intermediates. These intermediates on reaction with hydrazines in alkaline media produce pyrazoles. The antimicrobial activity of synthesized pyrazoles. In the most cases having Chloro substitution on the styryl ring was found to be more efficient.

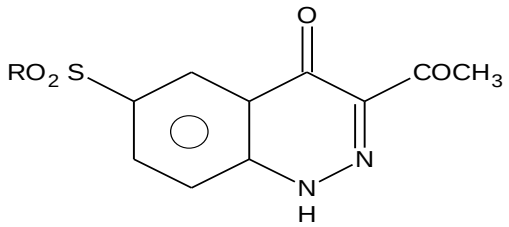
Dutta S (2010) Synthesized a series of 2-substituted-4,5-diphenyl imidazoles by refluxing benzil with different substituted aldehydes and screened for anthelmintic activity. The compounds showed significant anthelmintic activity compared to the standard drugs.

Iradyan MA et al. (2007) reported potent anti-tumor activity in some amino imidazole compounds.
Barbara stefa Ska, et al,(2003) synthesized 2, 7- dihydro-3H-dibenzo (de, h) cinnoline 3, 7-dione derivatives. And screened for anti leukemic activity.

Hipparagi S.M. and Nargund L.V.G (2003) synthesized cinoxacin derivatives substituted with imidazole by phase transfer catalysis from 3-chloro, 4 fluoro aniline. Their antibacterial activity has been screened against Escherichia coli, P. aeruginosa, Bacillus subtilis and staphylococcus aureus.

Saravanan J and Manjunatha KS (1998) prepared some 4- {5- substituted -2- furanyl)amino-7- substituted oxazolo-6- fluoro cinnoline-3-carboxylic acid as potent antimicrobial agents.

Balbi A (1998) synthesized thirty-six novel pyrazole derivatives and studied their antiproliferative activity in human ovarian adenocarcinoma A2780 cells, human lung carcinoma A549 cells, and Four of these substances found potent against cancer.
M.S. Abbady et al, (1993) prepared 3-acetyl, 6-sulphonyl-1H cinnoline, 4-one derivatives(18) by the intramolecular cyclisation of the corresponding hydrazones with $Alcl_3$. They have been screened for antibacterial activity.



III. Material And Method

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

Table : Physical data of substituted 4(-5-amino-pyrazole) cinnoline-3-carboxamide derivatives:

Sl. No.	Comp. No	Physical nature	M.P(°C)	Yield (%)
8 -Nitro-4(-5-amino-pyrazole) cinnoline-3-carboxamide	**14DSD$_a$**	Dark Yellow crystals	204-206°C	75.43%
6- Nitro-4(-5-amino-pyrazole) cinnoline-3-carboxamide	**14DSD$_b$**	Reddish brown crystals	114-116°C	51.44%
6- Chloro-4(-5-amino-pyrazole) cinnoline-3-carboxamide	**14DSD$_c$**	Pale Yellow crystals	196-188°C	64.23%
6-Bromo -4(-5-amino-pyrazole) cinnoline-3-carboxamide	**14DSD$_d$**	Light orange crystals	178-180°C	42.56%
6,7- di nitro- 4(-5-amino-pyrazole) cinnoline-3-carboxamide	**14DSD$_e$**	Off white crystals	167-169°C	53.12%
8- Methyl-4(-5-amino-pyrazole) cinnoline-3-carboxamide	**14DSD$_f$**	Dark green crystals	192-194°C	32.45%
7 –Chloro- 4(-5-amino-pyrazole) cinnoline-3-carboxamide	**14DSD$_g$**	Golden brown crystals	175-177°C	67.34%
8-Fluoro-4(-5-amino-pyrazole) cinnoline-3-carboxamide	**14DSD$_h$**	Light brown crystals	184-185°C	71.65%
7,8- DiChloro-4(-5-amino-pyrazole) cinnoline-3-carboxamide	**14DSD$_i$**	Reddish white crystals	177-179°C	45.32%
7- Nitro1H-Cinnoline -4(-5-amino-pyrazole) cinnoline-3-carboxamide	**14DSD$_j$**	Dark orange Crystals	180-182°C	73.29%

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.

Albino rats of either sex weighing 150-200 grams were used and divided into groups of six albino 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 2^{nd} 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

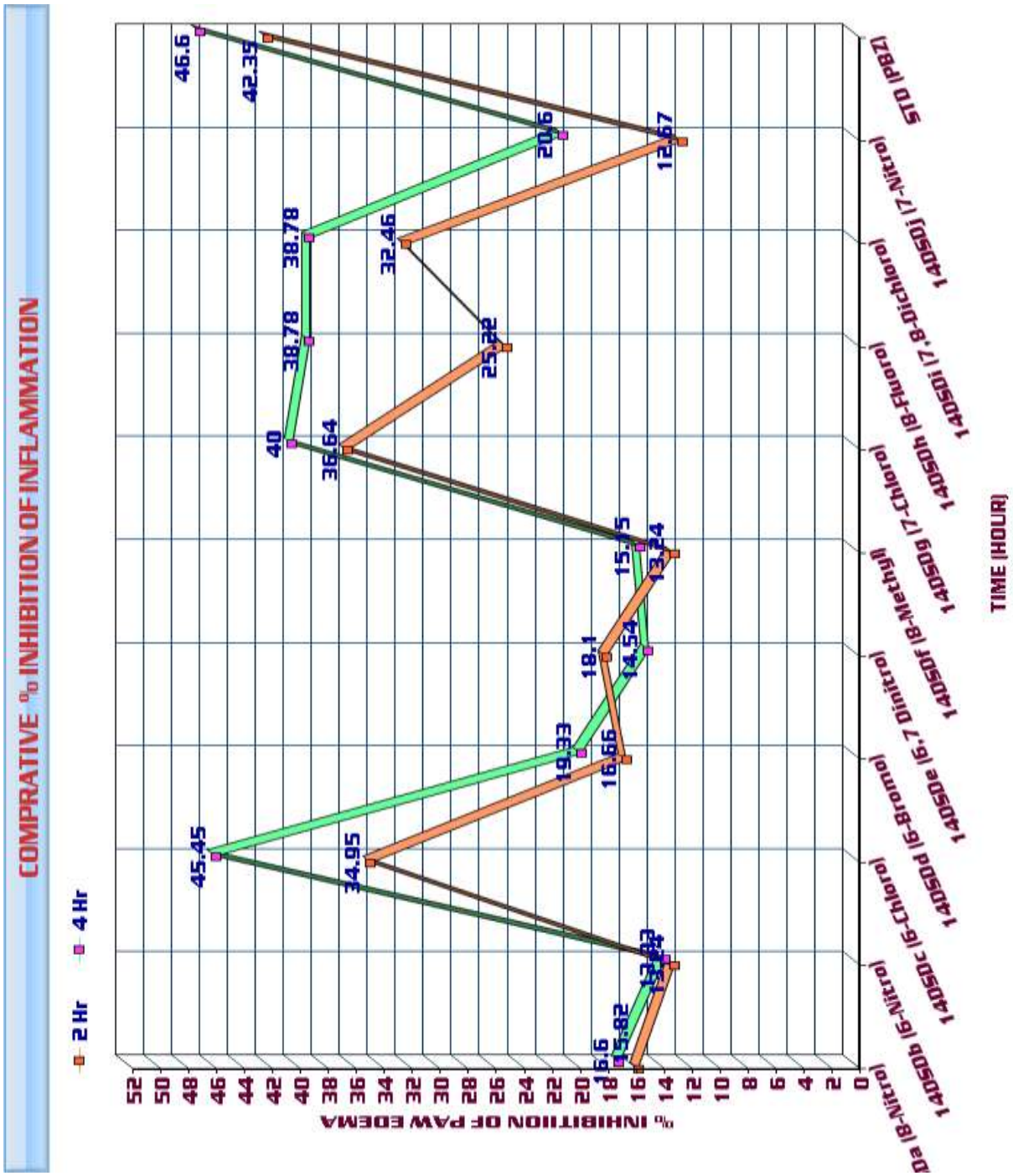
The data were subjected to analysis of variance (ANOVA) as per statistical methods using SPSS (1996) software package.

Compound	Substitution	Dose Mg/kg	Mean val ue (+S.E) of edema at different intervals		Percentage inhibition At Different intervals	
			2nd Hour	**4th hour**	**2nd hr**	**4th hr**
14DSDa	8 –Nitro	100	1.35 (±0.002)	1.31 (±0.001)	16.66	15.82
14DSDb	6- Nitro	100	1.46 (±0.015)	1.33 (±0.002)	13.24	13.33
1s4DSDc	6- Chloro	100	1.14 (±0.001)	0.90 (±0.003)	34.95	45.45
14DSDd	6-Bromo	100	1.52 (±0.032)	1.43 (±.0.003)	16.66	13.33
14DSDe	6,7- di nitro	100	1.61 (±0.015)	1.41 (±0.026)	18.10	14.54
14DSDf	8- Methyl	100	1.65 (±0.601)	1.55 (±0.005)	13.24	15.15
14DSDg	7 –Chloro	100	1.16 (±0.002)	1.01 (±0.001)	36.64	40.00
14DSDh	8-Fluoro	100	1.11 (±0.001)	0.99 (±0.006)	25.22	38.78
14DSDi	7,8- DiChloro	100	1.31 (±0.003)	1.01 (±0.001)	32.46	38.78
14DSDj	7- Nitro	100	1.52 (±0.005)	1.40 (±0.004)	12.67	20.60
Phenyl butazone	Standard	100	1.01 (±.001)	0.88 (±0.002)	42.35	46.6

All the Synthesized compounds have shown anti-inflammatory activity to a certain extent as compared to standard drug Phenylbutazone. Among the tested compounds **14DSDc, 14DSDg, 14DSDh and 14DSDi** have shown good activity by formalin induced rat paw edema method.

IV. Result And Discussion

In the substituted Cinnoline Pyrazole series, the compounds which are halogen mainly Chloro, Bromo and Fluoro Substituted were showed potent antibacterial, anti-inflammatory and anti-fungal activity than other compounds. Especially Chloro Substituted Compounds Showed more potent anti-inflammatory activity among all the substituted cinnoline pyrazole compounds.



V. Conclusion

On the basis of results it is clear that cinnoline derivative pyrazoline have significant anti-inflammatory effect.

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