IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)
e-ISSN: 2278-3008, p-ISSN:2319-7676. Volume 10, Issue 2 Ver. IV (Mar -Apr. 2015), PP 72-77
www.iosrjournals.org

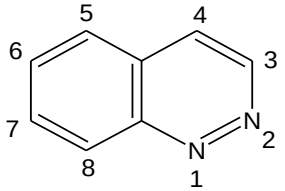
Synthesis, Characterization and Pharmacological evaluation of some Cinnoline (Furan) derivatives

Mishra Pankaj, Saxena Vikas, Kesheri Minu, Saxena Abhishek
**Department of Pharmaceutical chemistry Shridhar university pilani Rajasthan India*

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.*
Furan 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 furan 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, furan, anti-inflammatory activity.*

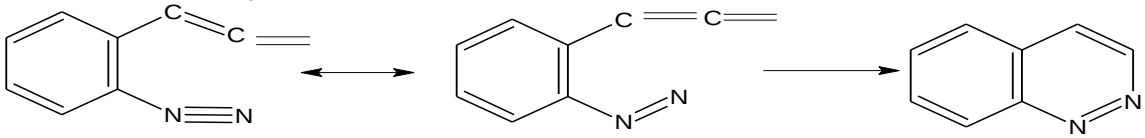
I. Introduction

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.



Furan:
Furan is a heterocyclic organic compound, consisting of a five-membered aromatic ring with four carbon atoms and one oxygen. The class of compounds containing such rings are also referred to as furans. The parent compound is typically derived by the thermal decomposition of pentose-containing materials, cellulosic solids especially pine-wood. Furan is a colorless, flammable, highly volatile liquid with a boiling point close to room temperature. It is toxic and may be carcinogenic. Catalytic hydrogenation (see redox) of furan with a palladium catalyst gives tetrahydrofuran.
The name furan comes from the Latin *furfur*, which means bran. The first furan derivative to be described was 2-furoic acid, by Carl Wilhelm Scheele in 1780. Another important derivative, furfural, was reported by Johann Wolfgang Döbereiner in 1831 and characterised nine years later by John Stenhouse. Furan itself was first prepared by Heinrich Limpricht in 1870, although he called it *tetraphenol.*

Objectives
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.

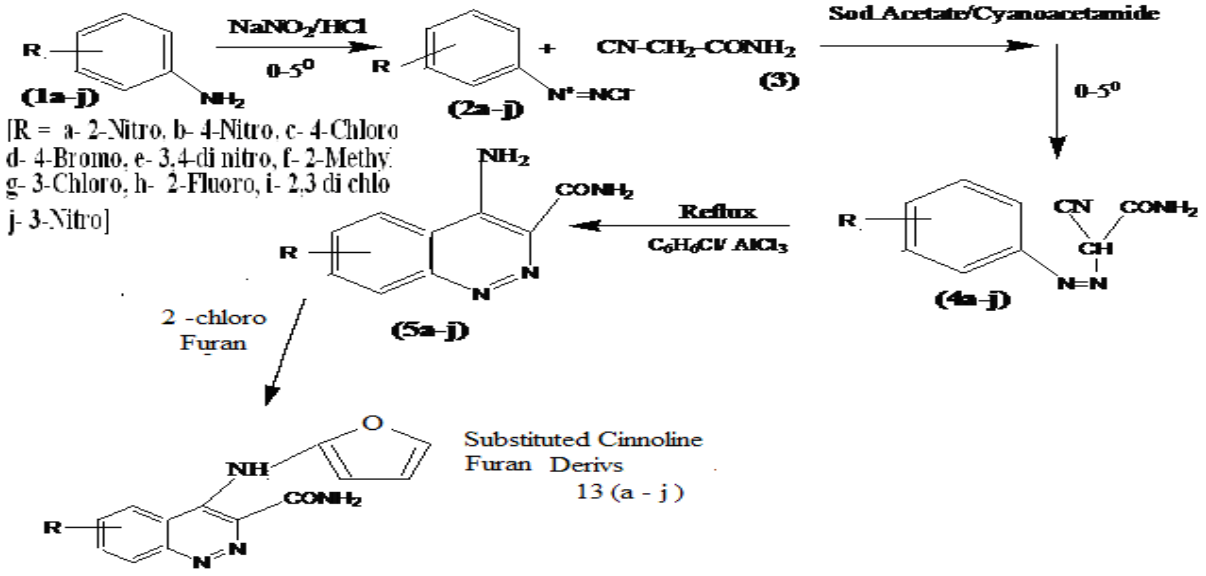
II. Review Of Literature

Narayana et al., (2006) Studied antibacterial and antifungal studies on some new acetylcinnolines and cinnolinyl thiazole derivatives. They are reported antibacterial and antifungal activity.
Iradyan MA et al. (2007) reported potent anti-tumor activity in some amino imidazole compounds.

Saxena et al., (2009) Synthesis, characterization and biological activities of substituted cinnoline culphonamides. They are reported that these derivatives particularly halogen substituted cinnoline derivatives showed potent antimicrobial activity.
Dutta et al., (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.
Patel et al., (2011) Studied synthesis and microbial evaluation of pyrazoline derivatives. They are reported that anti microbial activities.
Priyadarsini et al., (2012) prepared 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.
Chaudhary et al., (2014) Studied synthesis and biological screening of some cinnoline derivatives. They are reported that newly synthesized compounds were screened for their anti-inflammatory and antibacterial activity.

III. Material And Method

The Methodology Used For the Synthesis of Substituted Cinnoline imidazole Series is as follows : 13 (a - j)



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

Table : 3.0. Physical data of substituted 4(-2-amino-furan) cinnoline-3-carboxamide derivatives: (13a –j)

Compound Name	Com. No	Physical nature	M.P(°C)	Yield (%)
8-Nitro-4(-2-amino-2- furan) cinnoline-3-carboxamide	**13DSD$_a$**	Light Brick crystals	182-183°C	67.39%
6-nitro- 4(-2-amino- furan)cinnoline-3-carboxamide	**13DSD$_b$**	Yellow crystals	178-179°C	83.87%
6-chloro-4(-2-amino- furan) cinnoline-3-carboxamide	**13DSD$_c$**	Pale green Crystals	212-214°C	63.17%
6-bromo-4(-2-amino- furan) cinnoline-3-carboxamide	**13DSD$_d$**	Parrot Color crystals	202-204°C	72.92%
6,7 di nitro- 4(-2-amino- furan) cinnoline-3-carboxamide	**13DSD$_e$**	Dark Brownish red	196-198°C	81.05%
8-methyl- 4(-2-amino-2- furan) cinnoline-3-carboxamide	**13DSD$_f$**	Light red crystals	206-208°C	56.58%
7 chloro- 4(-2-amino- furan) cinnoline-3-carboxamide	**13DSD$_g$**	Violet green crystals	234-236°C	50.44%
8-Fluoro- 4(-2-amino- furan) cinnoline-3-carboxamide	**13DSD$_h$**	Orange yellow crys	205-207°C	45.23%
7,8-Di-chloro-4(-2-amino- furan) cinnoline-3-carboxamide	**13DSD$_i$**	Light Yellow cryst	261-263°C	49.77%
7- Nitro- 4(-2-amino-furan) cinnoline-3-carboxamide	**13DSD$_j$**	Light Brown Crystals	188-190°C	75.38%

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.

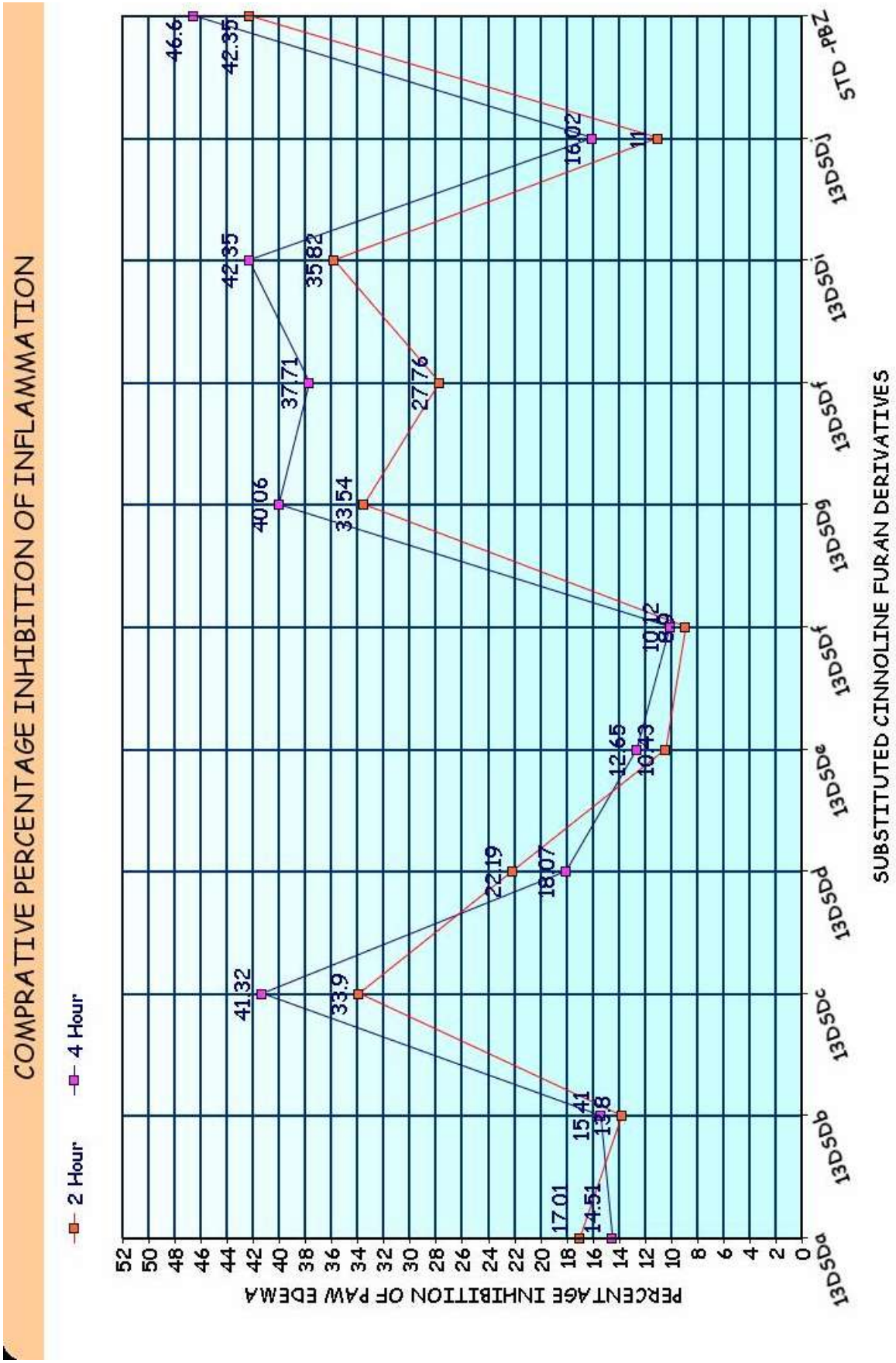
All the Synthesized compounds have shown anti-inflammatory activity to a certain extent as compared to standard drug Phenylbutazone. Among the tested compounds **15DSDc, 15DSDf and 15DSDi** have shown good activity by formalin induced rat paw edema method.

Result of Anti-inflammatory Activity

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**
13DSDa	8 -Nitro	100	1.39 (±0.032)	1.30 (±0.001)	17.01	14.51
13DSDb	6- Nitro	100	1.45 (±0.019)	1.39 (±0.003)	13.80	15.41
13DSDc	6- Chloro	100	1.12 (±0.004)	1.02 (±0.004)	33.90	41.32
13DSDd	6-Bromo	100	1.35 (±0.039)	1.42 (±.0.003)	22.19	18.07
13DSDe	6,7- di nitro	100	1.60 (±0.032)	1.53 (±0.021)	10.43	12.65
13DSDf	8- Methyl	100	1.64 (±0.0004)	1.59 (±0.006	8.90	10.12
13DSDg	7 –Chloro	100	1.12 (±0.005)	1.03 (±0.004)	33.54	40.06
13DSDh	8-Fluoro	100	1.30 (±0.001)	1.07 (±0.012)	27.76	37.71
13DSDi	7,8- DiChloro	100	1.10 (±0.007)	1.01 (±0.032)	35.82	42.35
13DSDj	7- Nitro	100	1.51 (±0.002)	1.38 (±0.001)	11.00	16.02
Phenyl butazone	Standard	100	1.01 (±.003)	0.88 (±0.043)	42.35	46.6

IV. Result and Discussion

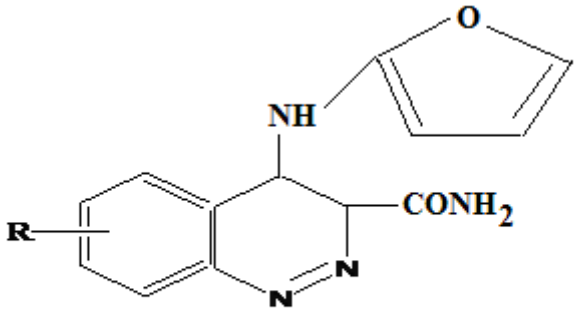
In the substituted Cinnoline furan series, the compounds which are halogen mainly Chloro Substituted were showed potent antibacterial, anti-inflammatory and anti-fungal activity than other compounds. However Methyl substituted compound also Showed more potent antimicrobial activity and anti-inflammatory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



SUBSTITUTED CINNOLINE FURAN DERIVATIVES

- **IR (KBr) in cm $^{-1}$ (Figure-13.1)**

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 1631.9 cm^{-1} corresponds to C = O stretching.
Peak at 1470.6 cm^{-1} corresponds to aromatic C = C stretching.
Peak at 1113.0 cm^{-1} corresponds to C = S stretching.
Peak at 861.6 to 1298.5 corresponds to furan

- **H^1-NMR δ in ppm (figure.13.2)**

δ 7.96– 8.01 (2H, d, of cinnolines)
δ 7.4– 7.52 (3H,m, Furan)
δ 11.20 (1H, s, of NH)
δ 9.9 – 10.01 (2H, s, of $CONH_2$)

- **Mass in m/z (Figure-13.3)**

Molecular ion peak at m/z = 326 mHz is because of molecular formula $C_{13}H_{10}Cl_2N_4O_2$. Base peak is at m/z = 160 mHz. Fragment ion peak is observed at m/z = 312 because of $C_{13}H_{10}Cl_2N_3O_2$, m/z = 241 because of $C_9H_4Cl_2N_3O$, m/z = 83 because of C_4H_4ON.

Acknowledgement

. The authors are grateful to Brig (Dr) PS Siwach Vice Chancellor of Shridhar university, Pilani, Rajasthan, India, Dr. Minu Keshri, Assistant Professor and Head Reaserch & Consultancy, Dr. Puja Rawat. Ph.D Coordinator of Shridhar university for providing the necessary laboratory facilities and precious suggestions.

Reference

[1]. Abbady MS, Sh M, Radwan and Bakhite EA. Synthesis and antimicrobial activity of some cinnoline derivatives containing sulphonamido group. Indian. J Chem. 1993; 32 (B) : 1281 – 1284
[2]. Bevan JA. Essential of pharmacology. 2nd edn; 1981.
[3]. Bansal RK. Heterocyclic chemistry, synthesis, Reactions and Mechanisms. Wiley Eastern Ltd, New delhi; 1990 : 242.
[4]. Busch M, Klett M. Synthesis of cinnoline derivatives. Ber 1892; 25 : 2847
[5]. Bracher F and Papke T. Synthesis of antifungal thiophene congeners of morpholine and allylamine type. Pharmazine. 1995 Aug;50(8):525-7
[6]. Fusco, raffaello, Piselli, Fulvio L, Boschi, Pier Marino, Eur. CO7D237/28. A process for the preparation of antibacterial 1-alkyl-3-carboxyl–4-cinnolines. Chem. Abstr 1988; 110 : 75540.
[7]. Harman S. Lowrie. Synthesis of 3-Phenyl-4-dialkyl amino alkoxy Cinnolines. Chem. Abstr 1966; 64 : 176
[8]. Jevons S, and Leeming MRG. Antifungal Activity of Tioconazole (UK-20,349), A new imidazole derivative. Antimicrob Agents Chemother. 1979 April; 15(4):
[9]. Joule JA and Mills K. Heterocyclic Chemistry. 4th edn. 2000 ; 194-197.
[10]. Katritzky AR and Pozharskii AF. Hand book of Heterocyclic chemistry.2nd edn. 2000: 629-630.
[11]. Kanner CB and Pandit UK. Reaction of ß-amino-α, ß-unsaturatesters and amides with aryl diazonium salts. Tetrahedron 1981; 37: 3513 – 35
[12]. Morley JO and Matthews TP.Synthesis and antimicrobial activity of 2- chloro-3,5- dinitrothiophene. Org. Biomol. Chem, 2006,4,359-366
[13]. Nargand LVG, Gopkumar P, Shivakumar B, Jayachandran E, Nagappa
[14]. AN, and Gurupadaiah BM. Synthesis and biological activity of 6–fluoro-7- (substituted) –(2–N-P–Anilino sulphonamido) Benzothiazoles. Ind. J Het. Chem 2001; 11
[15]. Stanczak A, Ochocki, Pakulska W. Synthesis and biological activity of some 4- amino – 3- cinnoline carboxylic acid derivatives. Part 5: pyrimido [5, 4 – c] cinnolines and triazepino [7, 6, - c] cinnoline. Pharmazie 1998; 53(12): 834 – 838.
[16]. Amer AM, Atti IAG, Mobayad ME and Asker S. On the chemistry of cinnoline III : condensation reactions of (4 - amino cinnolin – 3- yl) – Phenyl – methanone and 4- amino - 3- cinnoline – carbonitrile. Polish J. Chem. 2000; 74 : 681 – 686.

[17]. Nargand LVG, Gopkumar P, Shivakumar B, Jayachandran E, Nagappa AN, and Gurupadaiah BM. Synthesis and biological activity of 6– fluoro -7-(substituted) –(2 –N- P – Anilino sulphonamido) Benzothiazoles. Indian. J. Het. Chem.. 2001; 11: 39 – 42.

[18]. Vingkar SK, Bobade AS and Khadse BG. Synthesis and Antimicrobial activity of 6-Chlorocinnolino thiazoles. Indian. J. Het. Chem. 2001; 11: 35-38.

[19]. Stefaska B, Arciemiuk M, Maria M. Bontemps G, Dzieduszycka M, Kupiec A, Martelli S and Borowski E. Synthesis and biological evaluation of 2, 7-Dihydro –3H- dibenzo [de, h] cinnoline –3, 7- dione derivatives, a novel group of anticancer agents active on a multidrug resistant cell line. Bioorganic and Medicinal chemistry 2003; 11(4): 561-572.

[20]. Vingkar SK, Bobade and Khadse BG. Synthesis and Antimicrobial activity of 3-2 (alkyl / aryl, 4-substituted thiazolo).-6- fluoro cinnoline – 4- ones. Indian drugs 2001; 38(7): 347-350.

[21]. Hipparagi SM, and Nargund LVG. Synthesis of cinoxacin derivatives by phase transfer catalysis as antibacterial agents. Indian. J. Het. Chem. 2003; 13 : 123 - 126

[22]. Pattan SR, Patel RB, Ali MA, Butle SR and Pattan JS. Synthesis of some substituted 2-amino/acetamido-4-aryl thiazolyl –5- substituted sulphides and sulphones and their antibacterial and antifungal activity. Indian. J. Het. Chem. 2004; 13: 265 – 268.

[23]. Pattan SR, Ali MS, Pattan JS and Reddy VVK. Synthesis of some fluoro cinnoline derivatives and evaluation for their antifungal and antibacterial activities. Indian. J. Het. Chem.. 2004; 14:157-158.

[24]. Dua R et al. Synthesis and antimicrobial activity of some 2-[(2- substituted-phenyl-5-methyl-1, 3-thiazolidin-4-one)-5-(2'-methylamino-4-phenyl-1', 3'-thiazolyl]-1, 3, 4-thiadiazoles**,** Int. J. Res. Pharm. Sci., 2010,1, 358-364.

[25]. Dutta S. Synthesis and anthelmintic activity of some novel 2-substituted-4,5-diphenyl imidazoles. Acta Pharm.,2010, 60(2), 229-35.

[26]. Mohareb NRM, Fleita DH and Sakka OK. Synthesis of Hydrazide-Hydrazone Derivatives and Their Utilization in the Synthesis of Coumarin, Pyridine, Thiazole and Thiophene Derivatives with Antitumor Activity, Molecules, 2011,16(1),16-27.

[27]. Busch M and Klett M. Synthesis of cinnoline derivatives. Ber 1892; 25 : 2847.

[28]. Schofield K, Simpson JCE. Synthesis of cinnoline derivatives. J. Chem. Soc 1945 ; 512.

[29]. Castle RN and Onda M. Synthesis of tertiary amino alkyl 4- cinnolyl ethers. J. Org. Chem. 1960; 26 : 2374.

[30]. Barber HJ, Kenneth Washbourn DR and Wragg WR. Brit. 762, 184. Synthesis of cinnolines derivatives. Chem.Abstr.1956; 52: 459.

[31]. Lowrie HS. U.S. 3, 297, 694,. Synthesis of Dialkyl amino alkyl amino amides of 3-phenyl cinnoline-4- carboxylic acids. Chem. Abstr.1967; 66: 76020.

[32]. Lowrie HS. Synthesis of 3,(4-Dialkylamino alkoxy phenyl) cinnolines. Chem. Abstr 1966; 64: 17616.

[33]. Bhusare SR, Pawar RP and Vibhute YB. Synthesis and antibacterial activity of some new-2- (substituted phenyl sulphonamido) –6- substituted benzothiazoles. Indian. J. Het. Chem. 2001; 11:79-80.

[34]. Chandrashekar B, Roy K and De AU. Synthesis of some new p-toluene sulfonamido glutaramides. Indian. J.Het Chem. 2001;10:237-238.

[35]. Pattan SR, Narendra SN and Angadi J. Synthesis and biological activity of 2-amino [5^1-(4^1-sulphonyl benzylidene]-2,4-thiazolidine dione] –7-(substituted)-6- fluoro benzothiazoles. Indian. J. Het. Chem. 2002; 11: 333-334.

[36]. Bhusari KP, Khedekhar PB, Umathe SN, Bahekar RH, Ramrao RA. Synthesis and antibacterial activity of some substituted 2-(4-amino phenyl sulphonamido) Benzothiazoles. Indian J. Chem 2000; 9; 213-216.