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Synthesis, characterization and pharmacological evaluation of cinnoline (thiophene) derivatives

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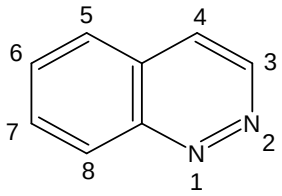
Abstract
The review of literature showed that cinnoline derivatives were found to elicit many pharmacological actions like anti-hypertensive, antithrombotic, antihistamine, antileukemic, CNS activity, anti-tumor, antibacterial and antisecretory activity.
In the substituted Cinnoline thiophene series, 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 antimicrobial activity and anti-inflammatory activity among all the substituted cinnoline thiophene compounds.

Keywords: *cinnoline, thiophene, anti-inflammatory activity.*

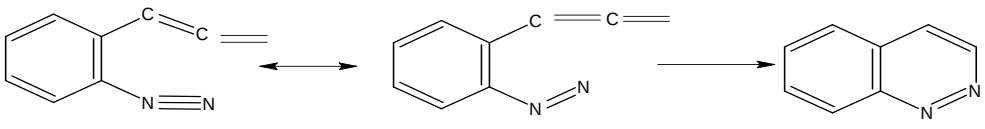
Introduction

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 electrophilic 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- benzodiazepine or benzopyridazine or 1, 2- diazanaphthalene or phenothiazine. (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.



Thiophene

In medicinal chemistry, thiophene derivatives have been very well known for their therapeutic applications. The simple thiophenes are stable liquids which closely resemble the corresponding benzene compounds in boiling point and even in smell. They occur in coal tar distillates. The discovery of thiophene in coal tar benzene provides one of the classic anecdotes of organic chemistry. Thiophene was discovered as a contaminant in benzene. It was observed that isatin (1Hindole-2, 3- Dione) forms a blue dye if it is mixed with sulfuric acid and crude benzene. Victor Meyer was able to isolate the substance responsible for this reaction. The compound was found to be a heterocyclic compound-Thiophene. Are important heterocyclic compounds that are widely used as building blocks in many agrochemicals and pharmaceuticals as seen in examples such as the NSAID lornoxicam, the thiophene analog of piroxicam.

Objectives

1. Synthesis of new series of substituted cinnoline derivatives condensed with Thiophene 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.

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) [26] 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) [19] 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.

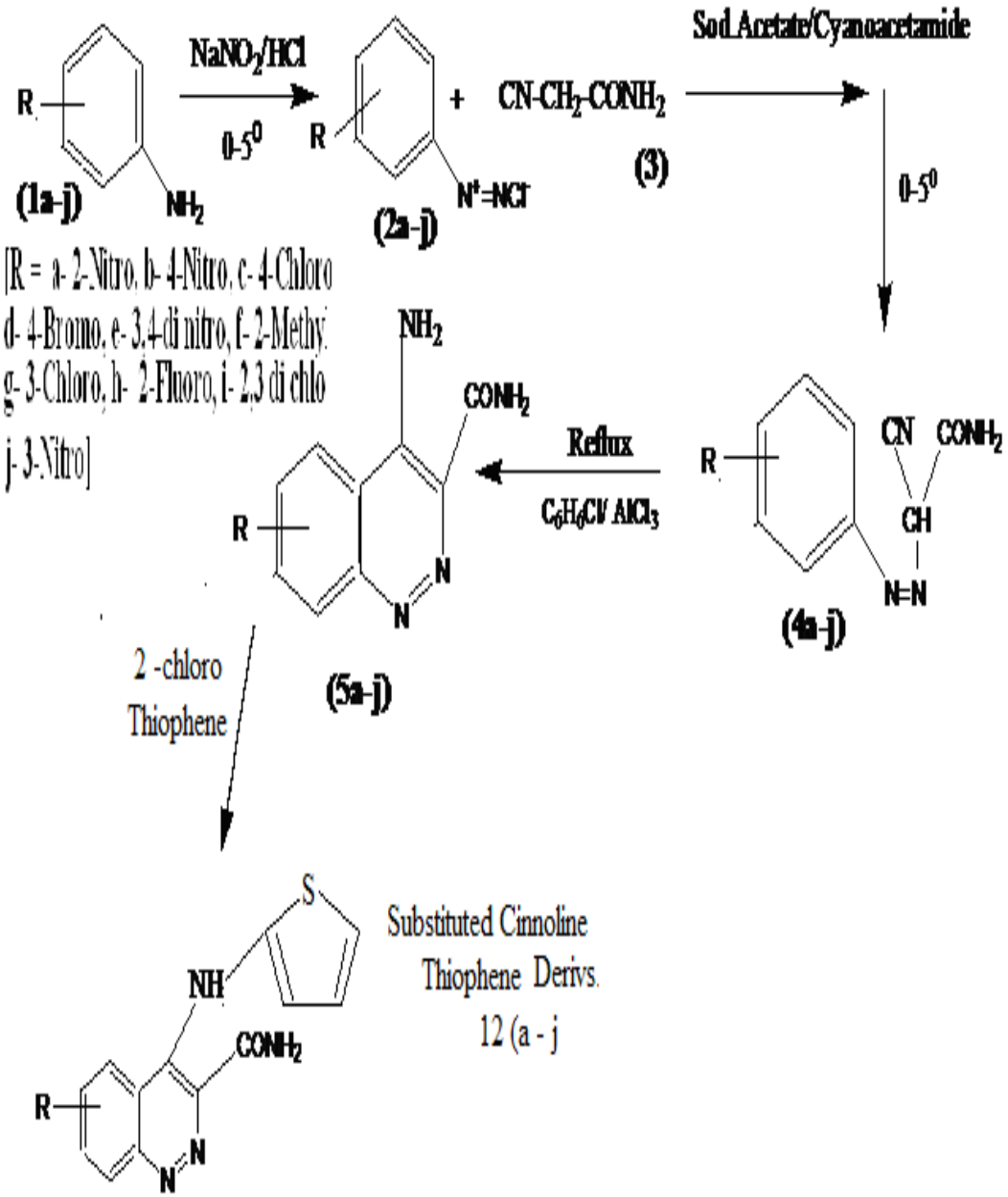
Patel *et al.*, (2011) Studied synthesis and microbial evaluation of pyrazoline derivatives. They are reported that anti-microbial activities.

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.

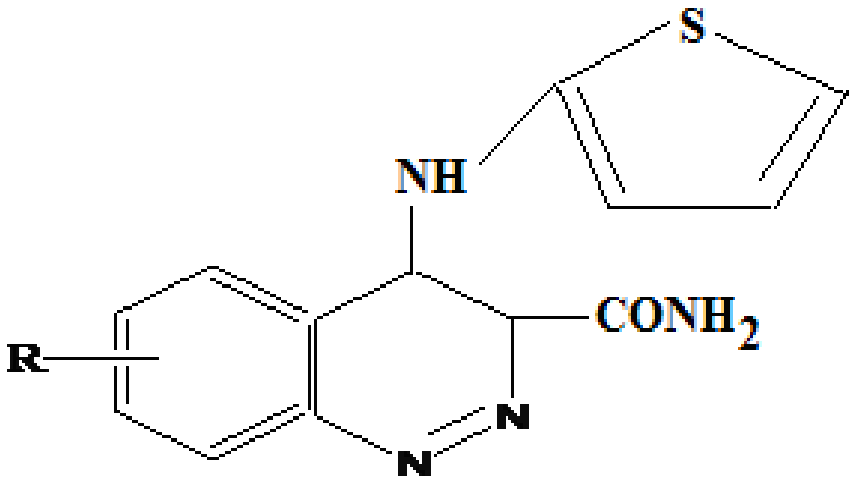
Material and Method

The Methodology Used for the Synthesis of Substituted Cinnoline imidazole Series is as follows:



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

Results of Scheme



SUBSTITUTED CINNOLINE THIOPHENE DERIVATIVES

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

Table 1.0: Physical data of substituted 4(-2-amino-thiophene) cinnoline-3-carboxamide derivatives

Compound Name	Com. No	Physical nature	M.P (°C)	Yield (%)
8-Nitro-4(-2-amino-2- thiophene) cinnoline-3-carboxamide	$12DSD_a$	Dark Yellow crystals	184-185 °C	73.78%
6-nitro- 4(-2-amino thiophene)cinnoline-3-carboxamide	$12DSD_b$	Pale Yellow crystals	188-189 °C	67.12%
6-chloro-4(-2-amino- thiophene) cinnoline-3-carboxamide	$12DSD_c$	Greenish yellow	246-248 °C	59.87%
6-bromo-4(-2-amino- thiophene) cinnoline-3-carboxamide	$12DSD_d$	Brown crystals	220-222 °C	64.34%
6,7 di nitro- 4(-2-amino- thiophene) cinnoline-3-carboxamide	$12DSD_e$	Greenish yellow	203-204 °C	61.83%
8-methyl- 4(-2-amino-2- thiophene) cinnoline-3-carboxamide	$12DSD_f$	white crystals	221-222 °C	67.40%
7 chloro- 4(-2-amino- thiophene) cinnoline-3-carboxamide	$12DSD_g$	Yellow Brown crys.	226-228 °C	64.80%
8-Fluoro- 4(-2-amino- thiophene) cinnoline-3-carboxamide	$12DSD_h$	Grenish yellow crys	198-200 °C	60.81%
7,8-Di-chloro-4(-2-amino- thiophene) cinnoline-3-carboxamide	$12DSD_i$	Creamish white cryst	265-267 °C	71.12%
7- Nitro- 4(-2-amino-thiophene) cinnoline-3-carboxamide	$12DSD_j$	Pale yellow Crystals	178-180 °C	58.71%

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 tibiotarsal 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.

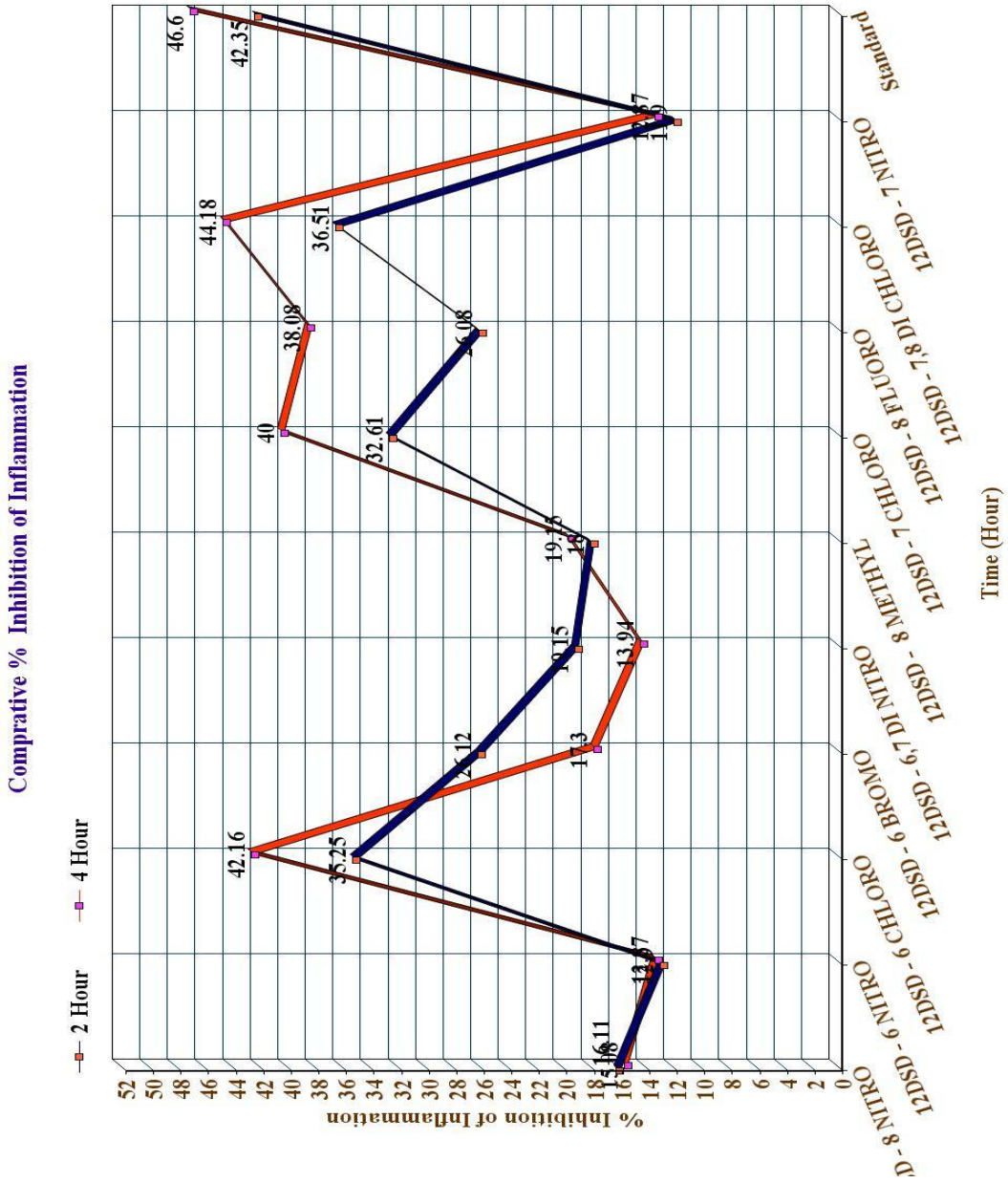
Result of Anti-inflammatory Activity

Compound	Substitution	Dose Mg/kg	Mean value (+S.E) of edema at different intervals 2nd Hour 4th hour		Percentage inhibition At Different intervals 2nd hr 4th hr	
12DSDa	8 –Nitro	100	1.41 (±0.064)	1.31 (±0.002)	16.11	15.08
12DSDb	6- Nitro	100	1.48 (±0.015)	1.38 (±0.002)	12.90	12.87
12DSDc	6- Chloro	100	1.11 (±0.001)	1.01 (±0.003)	35.25	42.16
12DSDd	6-Bromo	100	1.31 (±0.032)	1.40 (±.0.003)	26.12	17.30
12DSDe	6,7- di nitro	100	1.59 (±0.015)	1.43 (±0.026)	19.15	13.94
12DSDf	8- Methyl	100	1.60 (±0.601)	1.59 (±0.005)	18.00	19.15
12DSDg	7 –Chloro	100	1.14 (±0.002)	1.02 (±0.001)	32.61	40.00
12DSDh	8-Fluoro	100	1.32 (±0.001)	1.09 (±0.006)	26.08	38.08
12DSDi	7,8- iChloro	100	1.10 (±0.003)	1.00 (±0.001)	36.51	44.18
12DSDj	7- Nitro	100	1.53 (±0.005)	1.38 (±0.004)	11.90	12.87
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 12DSDc, 12DSDd, 12DSDg, 12DSDh and 12DSDi have shown good activity by formalin induced rat paw edema method.

Result and Discussion

In the substituted Cinnoline thiophene 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 antimicrobial activity and anti-inflammatory activity among all the substituted cinnoline thiophene compounds.



Results Characterization

The characterization requires the identification of molecular frame work, the nature of functional groups that are present and their location within the skeletal structure and finally the establishment of any stereo chemical relationships, which might exist.

The problem of characterization of organic compounds has been revolutionized by the progressive adoption of the wide range of spectroscopic techniques, which are now available. These have been applied extensively in the preparative section to confirm the structure of the expected products. The same were applied in present work to confirm the structure of newly synthesized compounds

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.

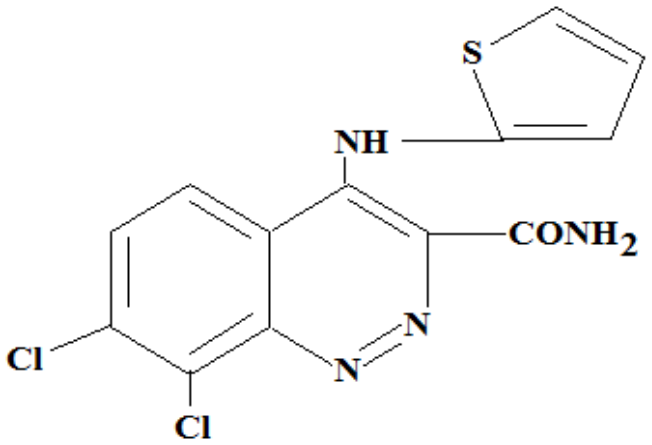
The PMR spectra were recorded on JEOL-JMS D-300 (300 MHz) NMR spectro meter. All spectra were obtained in Deuterated Methanol and chemical shift values are reported as values in ppm relative to TMS (= 0) as internal standard.

Mass spectra were recorded on JEOL SX102 MS System operating at 70 ev.

The IR, NMR and MASS spectra of one Compound from each Series is given in figure 12.1 to 12.3 for the representative compounds.

Spectral Features

12DSDi : 7,8-Di-chloro-4(-2-amino-thiophene) cinnoline-3-carboxamide



- **IR (KBr) in cm $^{-1}$ (Figure-12.1)**

Peak at 3481.7 cm^{-1} corresponds to NH stretching
Peak at 3361.4 cm^{-1} corresponds to asymmetric NH_2 group.
Peak at 3106.9 cm^{-1} corresponds to CH stretching.
Peak at 1631.9 cm^{-1} corresponds to C = O stretching.
Peak at 1505.2 cm^{-1} corresponds to aromatic C = C stretching.
Peak at 997.00 cm^{-1} corresponds to C = S stretching.
Peak at 840 - 1113 cm^{-1} corresponds to thiophene

- **H^1-NMR δ in ppm (figure.12.2)**

δ 7.9 – 8.1 (2H, d, of cinnolines)
δ 7.5 – 7.67 (5H, m, Thiophene)
δ 13.60 (1H, s, of NH)
δ 10.6 – 10.7 (2H, s, of $CONH_2$)

- **Mass in m/z (Figure-12.3)**

Molecular ion peak at m/z = 341 mHz is because of molecular formula $C_{13}H_{10}Cl_2N_4SO$. Base peak is at m/z = 160 mHz. Fragment ion peak is observed at m/z = 327 because of $C_{13}H_{10}Cl_2N_3SO$, m/z = 241 because of $C_9H_4Cl_2N_3O$, m/z = 101 because of C_5H_8SH.

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References

1. Armarego WLF. Stereo chemistry of Heterocyclic compounds. 2nd edn. A Wiley – Interscience publication, 1977, 238-240.
2. Amer AM, Atti IAG, Mobayad ME, 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.
3. Alam M, Siddiqui N. Synthesis of new benzothiozole incorporated sulphonamides as potential anticonvalsants. Indian. J Het Chem. 2004; 13:361-364.
4. Adamczeski M, Quinoa E, Crews P. Unusual anthelminthic oxazoles from a marine sponge, J Am Chem Soc. 1988; 110(5):1598-1602.
5. Abbady MS, Radwan SM, Bakhite EA. Synthesis and antimicrobial activity of some cinnoline derivatives containing sulphonamido group. Indian. J Chem. 1993; 32B:1281-1284.
6. 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.
7. Bhusare SR, Pawar RP, Vibhute YB. Synthesis and antibacterial activity of some new-2- (substituted phenyl sulphonamido) –6- substituted benzothiazoles. Indian. J Het Chem. 2001; 11:79-80.
8. Badawi AM, Ali HE, Ismail DA. Synthesis, Characterization, and anti-tumor Activity of four novel sulphonamide compounds, Australian Journal of Basic and Applied Sciences. 2008; 2(2):301-309.
9. Baumgarten HE, James LF. The stolle-Becker synthesis, Ber 1924; 26:1536.
10. Bansal RK. Heterocyclic chemistry, synthesis, Reactions and Mechanisms, (Wiley Eastern Ltd., New Delhi, 1990, 242.
11. Bevan JA. Essential of pharmacology. 2nded^n; 1981
12. Bansal RK. Heterocyclic chemistry. 3rd edn. New age international publishers, 2001, 448-450.
13. Bhandarkar SK. Pharmacology and Pharmacotherapeutics. 7th edn. Himalya publication, 2001, 622-623.
14. Curd FHS, Hepworth W. Synthesis of (4-amino – 6-cinnolyl) guanidine dimethiodide, Chem. Abstr, 1952; 46:11-25.
15. Chaudhary P, Sharma PK, Sharma A, Varshney J. Recent advances in Pharmacological activity of benzothiazole derivatives, Int. J of Pharm. Research. 2010; 2:20-23.
16. Castle RN, Onda M. Synthesis of tertiary amino alkyl 4-cinnolyl ethers. J Org Chem. 1960; 26:2374.

17. Chandrashekar B, Roy K, De AU. Synthesis of some new p-toluene sulfonamido glutaramides. Indian. J Het Chem. 2001; 10:237-238.
18. Dua R. 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.
19. Dutta S. Synthesis and anthelmintic activity of some novel 2-substituted-4, 5-diphenyl imidazoles. Acta Pharm. 2010; 60(2):229-35.
20. Dutta S, Singh SK, Mariappan G, Pandey L. Synthesis and antimicrobial activity of some 2-substituted-4, 5-diphenyl imidazole, International Journal of Applied Chemistry. 2009; 01:56-58.
21. 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.
22. Gonzalez IC, Davis LN, Smith CK, Novel thiophenes and analogues with anthelmintic activity against Haemonchus contortus, Bioorganic & med. Chem. 2004; 14(15):4037-4043.
23. Garg LC, Atal CK. Anthelmintic activity of Calotropain and Bromelanin. Ind. J Pharmacy. 1963; 25:422.
24. Gopkumar P, Shivakumar B, Jayachandran E, Nagappa AN, Nargund LVG, 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.
25. Hipparagi SM, Nargund LVG. Synthesis of cinoxacin derivatives by phase transfer catalysis as antibacterial agents. Indian. J Het Chem. 2003; 13:123-126.
26. Iradyan MA. Synthesis and anti-tumor activity of some bis[2-chloroethyl]amino imidazole derivatives, Pharm. Chem. J 2007; 18(7):462-466.
27. Jauregg W, Theodor S, franz J, Ulrich Swiss. 471795. Antipyretic derivatives of 1, 2- malonyl – 1, 2- dihydro – cinnoline. Chem. Abstr. 1969;, 71:81393.
28. Joule JA, Mills K. Heterocyclic Chemistry. 4th edn. 2000, 194-197.
29. Kanner CB, Pandit UK. Reaction of ß-amino-α, ß-unsaturated esters and amides with aryl diazonium salts. Tetrahedron 1981; 37:3513-3518.
30. Katritzky AR. Hand book of Heterocyclic chemistry Ist edn, 1985, 466-467.
31. Kadam SS, Bothara KC. Principle of medicinal chemistry 10thednn. New Delhi, Nirali Prakashan publishers. 2002, 49-56.
32. Katritzky AR, Pozharskii AF. Hand book of Heterocyclic chemistry. 2nd edn. 2000, 629-630.
33. Kaspady M, Narayanaswamy VK, Raju M. Synthesis, Antibacterial Activity of 2, 4-disubstituted oxazoles and thiazoles as bioisosteres, Letters in Drug Design & Discovery 2009; 6:21-28.
34. Lowrie HS. Synthesis of 3-Phenyl-4-dialkyl amino alkoxy Cinnolines, Chem. Abstr 1966; 64:17-61.
35. Lowrie HS. Synthesis of 3, (4-Dialkylamino alkoxy phenyl) cinnolines. Chem Abstr. 1966; 64:17616.
36. Mohareb NRM, Fleita DH, 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.
37. Manna P, Singh R, Narang KK, Manna SK. Synthesis, antifungal, antitumor and anti-inflammatory activities of some new 5-substituted arylimino-2-N-P-Tolyl sulphonyl-3-oxo-1,2,4-thiadiazolidines. Indian. J Het Chem. 2004; 13:249-252.
38. Nagarajan K, Shah RK, Shenoy SJ. Synthesis and Reactions of 4, 6, 7, 8 – Tetrahydro- 5 (IH) – cinnolinones. Indian J Chem. 1986; 25B:697-708.
39. Nargand LVG, Gopkumar P, Shivakumar B, Jayachandran E, Nagappa AN, 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.
40. Pattan SR, Patel RB, Ali MA, Butle SR, 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.
41. Pattan SR, Ali MS, Pattan JS, Reddy VVK. Synthesis of some fluoro cinnoline derivatives and evaluation for their antifungal and antibacterial activities. Indian J Het Chem. 2004; 14:157-158.
42. Prasad KS, Shivakumar S, Vinay KB, Chandrashekhar SC, Jayalakshmi B, Revanasiddhapa HD. Antimicrobial and anthelmintic activity of Sulphonamides of 1,3 dioxalone, International Journal of Chemistry Research. 2011; 2(1):28.
43. Richter VV. Von Richter (Cinnoline) synthesis. Ber. 1883; 16:677.
44. Raymond N, Ward H, White N. Heterocyclic and related compounds. J Org Chem. 1959; 25:570.
45. Rao DS, Jayachandran E, Srinivasa GM, Kumar BK. Synthesis and Antimicrobial activity of 2-[N-P-Tolyl Sulphon hydrazino]6-fluoro-7- substituted (1,3)-benzothiazoles. Indian. J Het Chem. 2004; 14:65-66.
46. Schmidt Joerg H, Franke Joachim, scheffler Reingard, Toenjes Heinz, Kammann Guenter, Dietz Guenther. 4(1H)-oxocinnoline-3-carboxylic acid derivatives. Chem. Abstr. 1984; 101:7178b.
47. Stanczak A, Kwapiszewski W, Szadowska A, pakulska W. Synthesis and action on the central nervous system of some N_2 – substituted cinnoline derivatives. Pharmazie. 1994; 49(6):406-412.
48. Stanczak A, Pakulska W. Synthesis, Structures and biological activity of some 4 – amino – 3- Cinnoline – carboxylic acid derivatives part 3 : 1,3 – oxazino [5,4 – c] Cinnolines and Pyrimido [5, 4 – c] cinnolines. Pharmazie. 1997; 52(11):838-843.
49. 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.
50. Stefaska B, Arciemiuk M, Maria M, Bontemps G, Dzieduszycka M, Kupiec A *et al.* 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.
51. Shaw AY. Characterization of novel diaryl oxazole-based compounds as potential agents to treat pancreatic cancer. J Pharmacol Exp Ther. 2009; 331(2):636-47.