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Synthesis and Evaluation of New Novel Heterocycles Containing Benzothiazoles (1, 3) for Pharmacological Screening

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ABSTRACT

Various 1-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)-3-methyl-1*H*-pyrazol-5-ol containing different functional groups have been synthesized by condensing 7- Chloro-6-Fluoro-2-Hydrazinyl-1,3-Benzothiazole with Ethyl Aceto Acetate in presence of ethanol. The identities of compounds were confirmed on the basis of their spectral (IR, ^{1}HNMR and MASS) data. Further, they have been screened for their antimicrobial, and anti-inflammatory activities.

Keywords; Benzothiazole, Ethyl aceto acetate, Fluorine, Pyrazolo.

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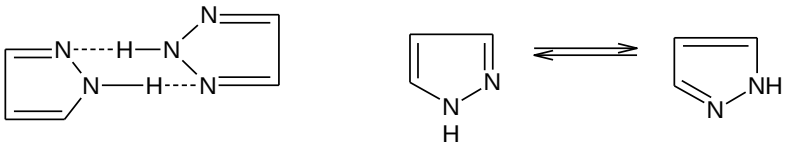
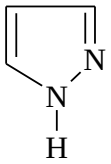
INTRODUCTION

The rapid progress of organic Fluorine chemistry [1-5] since 1950 has been translated as a pathfinder to invent useful biodynamic agents in Medicinal and Biochemistry. The new generation antibiotics like Norfloxacin, Ciproflaxacin, Flufloxacin, Sporfloxacin and Ofloxacin which were incorporated with fluorobenzene moiety proved their efficacy as potent bio active molecules.

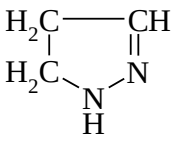
Pyrazole [6-10] is a colorless solid, m.p. 70°C. This high value (compared with 1-alkyl or aryl substituted pyrazoles) is due to intermolecular hydrogen bonding which results in a dimmer. Pyrazole is a tautomeric substance; the existance of tautomerism cannot be demonstrated in pyrazole itself, but it can be inferred by the consideration of pyrazole derivatives.



Pyrazole derivatives constitute an interesting class of organic compounds, which are associated with diverse chemical and pharmacological properties. Pyrazolines have received considerable attention in recent years. Pyrazoline derivatives occupy a unique place in field or medicinal chemistry due to a wide range or biological activities exhibited by them.



Pyrazole



Pyrazoline

Based on the above observations we have synthesized some Fluoro-Benzothiazolo-Pyrazolo derivatives starting with fluoro-chloro-aniline, in hope of getting pharmacological agents with broad spectrum of clinical activity.

MATERIALS AND METHODS

Melting points were determined by open capillary tube method and are uncorrected. T.L.C was run on silica gel G plates using butanol, ethyl acetate and chloroform (1:2:1) as developing solvent for the purity of the compounds. I.R. Spectra were recorded on Shimadzu FTIR Spectrophotometer by using NUJOL MULL technique.

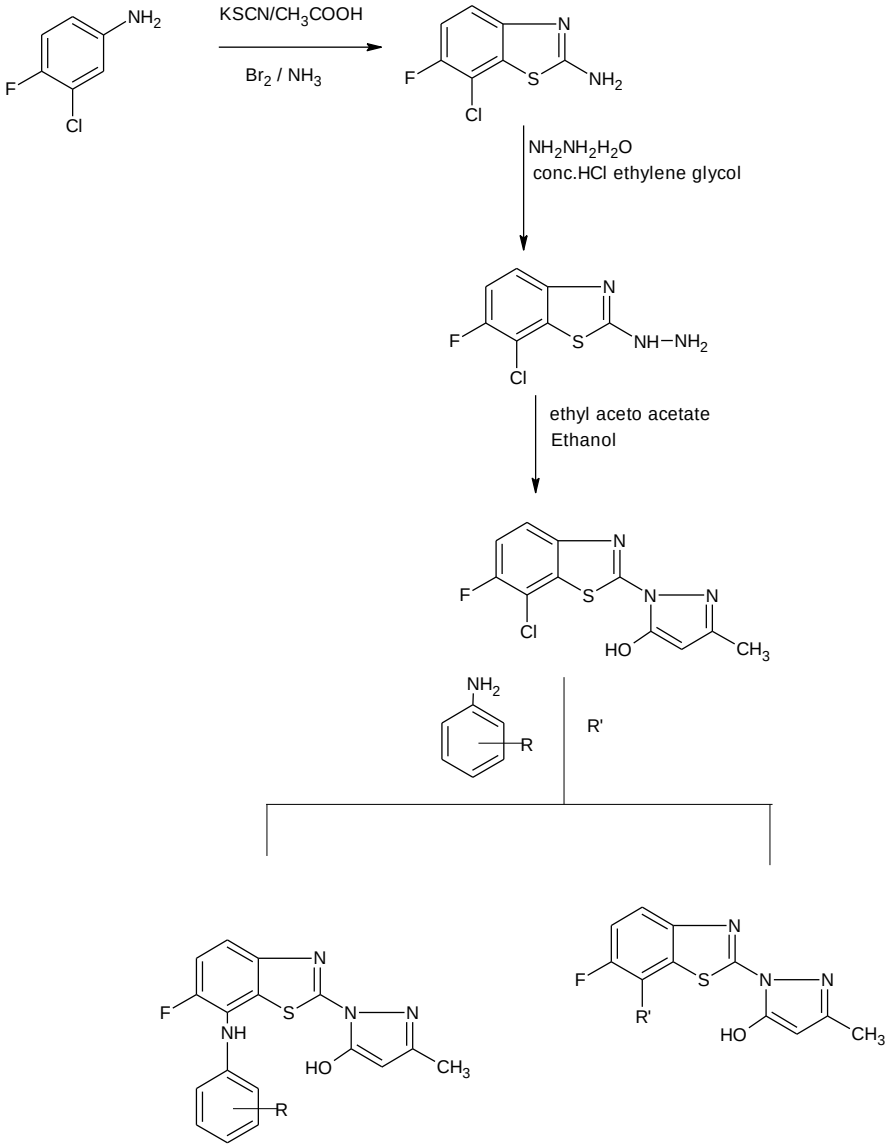
Synthesis of 1-(7-chloro-6-fluoro-1,3-benzothiazole-2-yl)-3-methyl-1H-pyrazol- 5-ol.

21.7 gm (0.1mol) of hydrazino benzothiazole mix with 13.6 ml (0.1mol) of ethyl aceto acetate in a round bottom flask into the 40 ml ethanol reflux for 2hrs and later excess of

ethanol was distilled of and poured onto the crushed ice. The product obtained was filter and recrystalised form ethanol.

To 0.01 mol of 1-(7-chloro-6-fluoro-1,3-benzothiazole-2-yl)-3-methyl-1H-pyrazol-5-ol was treated with equimolar quantities of various substituted aniline, morpholine, piperazine and diphenylamine refluxed for 2 hours in oil bath in presence of 30 ml N,N- dimethyl formamide (DMF). The mixture was cooled and poured in to crushed ice. The solid separated was filtered off, dried and crystallized from alcohol and benzene.

Scheme



R= o, m, p –nitro
= o, m, p –chloro
= H
= o, m, p-methyl

R = N-methyl piperazine
= morpholine

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Biological Activities [11-17]

Anti-microbial Activity

The synthesized compounds are screened against bacterias like *staphylococcus aureus (Gram +ve)* and *Escherichia coli (Gram -ve)* and *Bacillus subtillis (Gram +ve)* and *Pseudomonas aureus (Gram -ve)* and fungi like *Candida albicans* and *Aspergillus niger* to know their antimicrobial activity (by cup plate method).

Anti-inflammatory activity (*In-vitro*) [18-22]

The synthesized compounds are screened for anti-inflammatory activity by using inhibition of albumin denaturation technique which was studied according to Jayachandran E. and G.M. Sreenivasa with slight modification.

The standard drug and test compounds were dissolved in minimum amount of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solutions was less than 2.0%. Test solution (1 ml) containing different concentrations of drug was mixed with 1 ml of 1% mM Bovine albumin solution in phosphate buffer and incubated at 27 ^{0} ± 1 ^{0}C in incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60 ^{0} ± 1 ^{0}C in water bath for 10 min. After cooling the turbidity was measured at 660 nm (UV-Visible Spectrophotometer SL-159, Elico India Ltd.). Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average was taken. The Ibuprofen was used as standard drug.

RESULTS AND DISCUSSION

Anti-bacterial activity

Synthesis and pharmacological screening of 1-(7-chloro-6-fluoro-1,3-benzothiazole-2-yl)-3-methyl-1H-pyrazol-5-ol.were tested for the antibacterial activity against following bacteria;

a) i) *Staphylococcus aureus(gram +ve)* ii) *Streptococcus aureus(gram +ve)* and
b) iii) *Escherichia coli(gram –ve)*. iv) *psuedomonas(gram –ve)*.

The compounds R_1, R_2, R_5 ,R_6 ,R_7 ,R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, and R_{15} showed promising antibacterial activity and R_4 and R_{13} show significant antibacterial activity against *Staphylococcus aureus* (gram +ve) .

Compounds R_1 to R_{15}, showed promising antibacterial activity against, *E.coli* (gram –ve) and *pseudomonas aeruginosa (gram -ve)*

Compounds R_1 ,R_2,R_3,R_5,R_6,R_7,R_8,R_9,R_{10},R_{11},R_{12},R_{13},and R_{15} showed promising antibacterial activity and R_{14} shows significant antibacterial activity against *Streptococcus aureus* (gram +ve).

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ANTIBACTERIAL ACTIVITY

Sl. No	Name of the compounds	Mean zone of inhibition (in mm)*			
		Staphylococcus aureus		*Streptococcus aureus*	
		1 mg/ml	2 mg/ml	1 mg/ml	2 mg/ml
01	**Procaine penicillin**	20	21	18	20
03	R_1	10 (0.50)	12 (0.60)	10 (0.55)	13 (0.65)
04	R_2	10 (0.50)	10 (0.5)	9 (0.50)	12 (0.60)
05	R_3	9 (0.45)	14 (0.7)	10 (0.55)	11 (0.55)
06	R_4	16 (0.80)	11 (0.55)	14 (0.77)	15 (0.75)
07	R_5	11 (0.55)	12 (0.60)	14 (0.77)	15 (0.75)
08	R_6	14 (0.70)	10 (0.5)	13 (0.72)	15 (0.75)
09	R_7	12 (0.60)	14 (0.7)	11 (0.61)	14 (0.70)
10	R_8	12 (0.60)	13 (0.65)	10 (0.55)	13 (0.65)
11	R_9	12 (0.60)	10 (0.5)	12 (0.66)	15 (0.75)
12	R_{10}	9 (0.45)	13 (0.65)	12 (0.66)	14 (0.70)
13	R_{11}	10 (0.50)	14 (0.7)	11 (0.61)	13 (0.65)
14	R_{12}	9 (0.45)	12 (0.60)	10 (0.55)	11 (0.55)
15	R_{13}	10 (0.50)	16 (0.80)	12 (0.66)	13 (0.65)
16	R_{14}	11 (0.55)	12 (0.60)	15 (0.83)	16 (0.80)
17	R_{15}	10 (0.50)	9 (0.45)	13 (0.72)	15 (0.75)

ANTIBACTERIAL ACTIVITY

Sl. No	Name of the compounds	Mean zone of inhibition (in mm)*			
		E.coli		*Pseudomonas*	
		1 mg/ml	2 mg/ml	1 mg/ml	2 mg/ml
01	**Streptomycin**	23	24	20	21
03	R_1	13 (0.56)	16 (0.66)	10 (0.50)	12 (0.54)
04	R_2	11 (0.47)	14 (0.58)	15 (0.75)	17 (0.77)
05	R_3	10 (0.43)	11 (0.45)	12 (0.60)	14 (0.63)
06	R_4	14 (0.60)	16 (0.66)	11 (0.55)	12 (0.54)
07	R_5	12 (0.52)	15 (0.62)	11 (0.55)	13 (0.59)
08	R_6	12 (0.52)	15 (0.62)	11 (0.55)	14 (0.63)
09	R_7	10 (0.43)	14 (0.58)	11 (0.55)	12 (0.54)
10	R_8	14 (0.60)	15 (0.62)	11 (0.55)	12 (0.54)
11	R_9	13 (0.56)	15 (0.62)	12 (0.60)	14 (0.63)
12	R_{10}	11 (0.47)	12 (0.50)	10 (0.50)	11 (0.55)
13	R_{11}	10 (0.43)	13 (0.54)	10 (0.50)	12 (0.54)
14	R_{12}	10 (0.43)	14 (0.58)	11 (0.55)	13 (0.59)
15	R_{13}	10 (0.43)	13 (0.54)	11 (0.55)	12 (0.54)
16	R_{14}	11 (0.47)	13 (0.54)	14 (0.70)	15 (0.71)
17	R_{15}	13 (0.56)	14 (0.58)	13 (0.65)	16 (0.76)

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ANTIFUNGAL ACTIVITY

Sl. No	Name of the compounds	Mean zone of inhibition (*in mm*)*			
		Candida albicans		*Aspergillus fumigates*	
		1mg/ml	2mg/ml	1mg/ml	2mg/ml
01	**Ciclopiroxol amine**	22	24	18	20
02	R_1	17 (0.77)	18 (0.75)	12 (0.66)	13 (0.65)
03	R_2	15 (0.68)	18 (0.75)	16 (0.88)	17 (0.85)
04	R_3	13 (0.59)	15 (0.62)	12 (0.66)	17 (0.85)
05	R_4	16 (0.72)	17 (0.70)	16 (0.88)	18 (0.90)
06	R_5	15 (0.68)	17 (0.70)	16 (0.88)	17 (0.85)
07	R_6	17 (0.77)	19 (0.79)	13 (0.72)	15 (0.75)
08	R_7	17 (0.77)	18 (0.75)	15 (0.83)	16 (0.80)
09	R_8	15 (0.68)	17 (0.70)	14 (0.77)	16 (0.80)
10	R_9	16 (0.72)	17 (0.70)	17 (0.94)	18 (0.90)
11	R_{10}	14 (0.63)	15 (0.62)	17 (0.94)	18 (0.90)
12	R_{11}	18 (0.81)	19 (0.79)	15 (0.83)	17 (0.85)
13	R_{12}	14 (0.63)	17 (0.70)	16 (0.88)	17 (0.85)
14	R_{13}	16 (0.72)	18 (0.75)	17 (0.94)	18 (0.90)
15	R_{14}	14 (0.63)	16 (0.66)	14 (0.77)	17 (0.85)
16	R_{15}	17 (0.77)	18 (0.75)	13 (0.72)	15 (0.75)

$$\text{Activityindex} = \frac{\text{Test compound}}{\text{Standard compound}}$$

Anti-fungal activity

The compounds were tested for antifungal activity against *Candida albicans* and *Aspergillus fumigatus.*Among the compounds tested R_2,R_4, R_5,R_7,R_9, R_{10},R_{11}, R_{12}, and R_{13}showed significant antifungal activity against *Aspergillus fumigatus*.

CompoundsR_1,R_2,R_3,R_4,R_5,R_6,R_7,R_8,R_9,R_{10},R_{12}, R_{13},R_{14} and R_{15}showed promising antifungal.

Anti- inflammatory activity (*In-vitro model*)

Among the compounds tested R_8,R_9,R_{12},R_{13} and R_{15} showed promissing anti-inflammatory activity compared to standard drug Ibuprofen.

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ANTI-INFLAMMATORY ACTIVITY

Sl No	Name of the compounds	Absorbence value (Mean ± SE)	Inhibition of denaturation (in %)
01	**Control**	**0.087**	**-**
02	Diclofenac sodium	0.155	93.75%
03	R_1	0.109	25.00%
04	R_2	0.112	28.00%
05	R^3	0.125	43.67%
06	R_4	0.128	47.712%
07	R_5	0.130	49.42%
08	R_6	0.110	26.43%
09	R_7	0.118	35.62%
10	R_8	0.132	51.72%
11	R_9	0.135	55.17%
12	R_{10}	0.125	43.67%
13	R_{11}	0.127	45.97%
14	R_{12}	0.140	60.90%
15	R_{13}	0.131	50.57%
16	R_{14}	0.117	34.48%
17	R_{15}	0.133	52.87%

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