SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF IMIDAZOLIN-5-ONE DERIVATIVES AS POTENTIAL ANTIMICROBIAL AGENTS

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ABSTRACT

Various substituted 2-(2'-phenyl-4'-p-dimethylaminobenzylidenyl imidazolin-5'-one)-6-fluoro-7-substituted (1,3) benzothiazoles. and 2-(2'-phenyl-4'-o-hydroxy benzylidenyl-5'oxo imidazolin-1-yl amino) -6-fluoro-7-substituted (1,3) benzothiazoles. containing different functional groups have been synthesized by treating substituted 2-aminobenzothiazoles with oxozolone in presence of dry pyrirdine. The identity of compounds were confirmed on the basis of their spectral (UV-Visible, IR, ^{1}H NMR and Mass) data. Further, they have been screened for their antimicrobial activitiy.

Keywords: Fluorine, Benzothiazole, Imidazole, antimicrobial activitiy.

1. INTRODUCTION

We report here in the new and unreported yet the synthesis of fluoro benzothiazoles (Filler R, 1986) comprising imidazole derivatives of pharmacological activity of clinical importance in the areas of antibacterial (Anjani Solankee, 2003), antifungal (Purohit, 1999), anti-tuburcular (Desai, 2003), MAO inhibitors (Farzin hadizadeh,2005), anti-inflammatory (Nagalakshmi, 2008), anthelmintic (Jayachandran, 2003), anticonvulsant (Turner, 1965), anti-cancer (Solankee, 2001), analgesic (Biplab de, 1999), anti-viral (Deepika sharma, 2008). The chemistry and pharmacology of imidazole have been of great interest because, of its various biological activities, so that the biological and pharmacological activity of imidazole with fluoro benzothiazoles may be taken into account for synergism (Conte, 1995).

It is well known that the introduction of fluorine atom (Desbois Michel, 1987) into an organic molecule causes dramatic changes in its biological profile, mainly due to high electro negativity of fluorine, the strong carbon-fluorine bond and increased solubility in lipids. Therefore it was thought worthwhile to synthesize better kinds of drugs by incorporating imidazole in benzothiazole moiety.

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In search for new biodynamic potent molecule, it was thought worthwhile to incorporate some additional heterocyclic moieties in the imidazole nucleus and study their biological and pharmacological activity (Indian Pharmacopoeia, 1996), the review of literature reveal prompted us to synthesize substituted Fluorobenzothiazole, imidazole compounds and those will be screened for antimicrobial activity (Gurupadaiah, 1998).

2. MATERIALS AND METHODS

Chemicals and Reagents

4-fluoro-3-chloro aniline, Potassium thiocyanate, Glacial acetic acid, Bromine, Hippuric acid, Pyridine, N N amino Benzaldehyde, Ethanol, Ammonia, Benzene, Conc.Hydrochloric acid, Sodium acetate, N,Np-dimethyl formamide (DMF), Primary and secondary aromatic amines.

Experimental Section

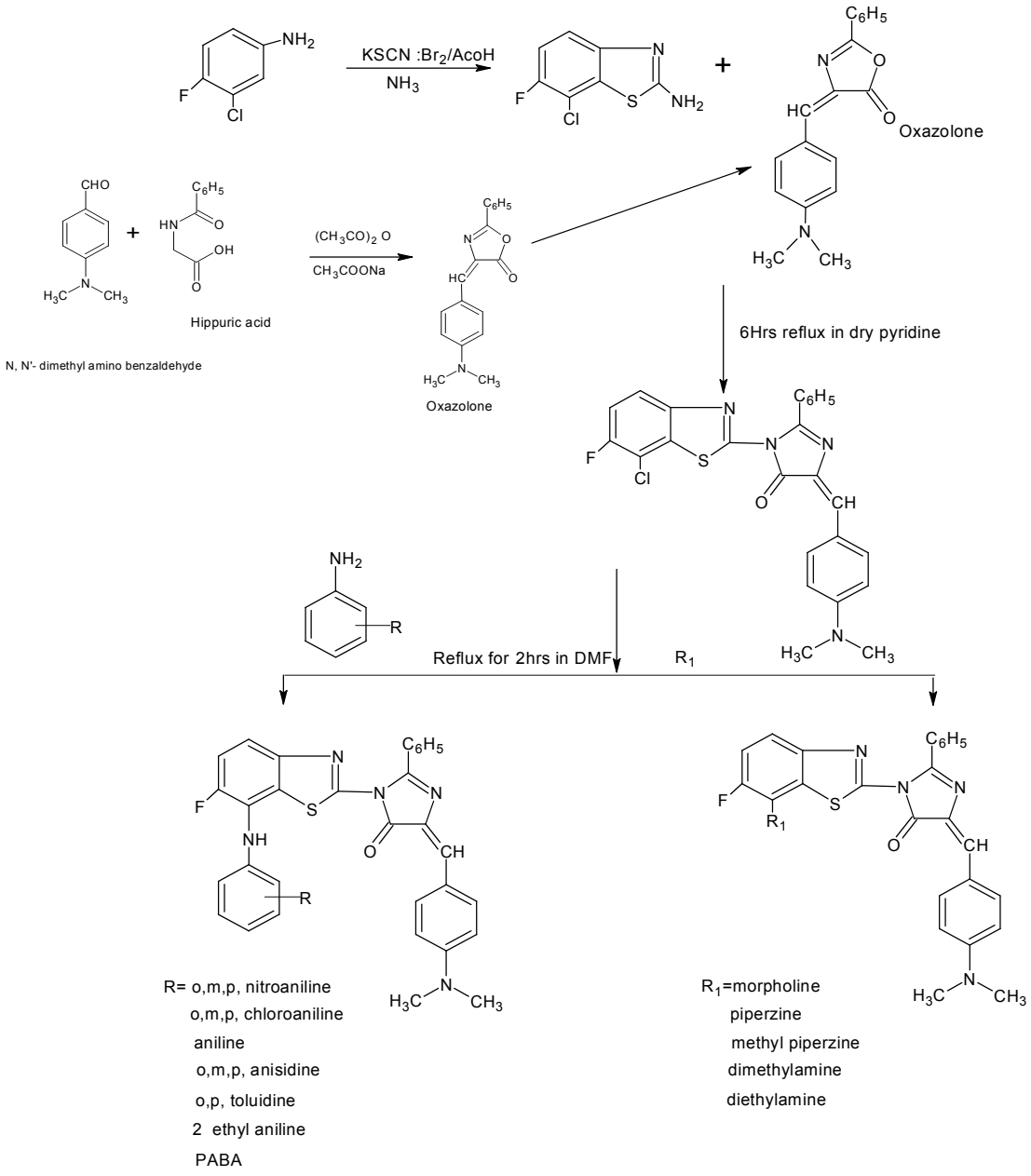
Step I: 4-fluoro-3-chloro aniline was treated with potassium thiocyanate (KSCN) in presence of glacial acetic acid and bromine to get 2-amino-6-fluoro-7-chloro-benzothiazole.

Step II: N, N'- Dimethyl amino benzaldehyde treated with benzoylglycine (Hippuric acid) in presence of dry acetic acid and anhydrous sodium acetate to get 2-phenyl-4-p-dimethylaminobenzylidenyl-5-oxazolone,

StepIII: 2-amino-6-fluoro-7-chloro-benzothiazole treated with 2-phenyl-4-p-dimethylaminobenzylidenyl-5-oxazolone, in presence of Pyridine to get 2-(2'-phenyl-4'-p-dimethylaminobenzylidenyl imidazolin-5'-one) 6-fluoro- 7-chloro, (1,3) benzothiazole.

Step IV: 2-(2'-phenyl-4'-p-dimethylaminobenzylidenyl imidazolin-5'-one)-6-fluoro-7-chloro, (1,3) benzothiazole was treated with various primary and secondary aromatic amines. in presence of N N' dimethyl formamide (DMF) yields various 2-(2'-phenyl-4'-p-dimethylaminobenzylidenylimidazolin-5'-one)-6-fluoro-7-substituted (1,3) benzothiazoles.

Scheme



General Procedures

Melting points were determined in open capillaries and are uncorrected. IR spectra (KBr pellet technique) were recorded using a Perkin-Elmer 237 spectrophotometer. ^{1}H NMR spectra were recorded on Bruker AM 400 instrument (at 400 MHz) using tetramethylsilane (TMS) as an internal standard and DMSO-*d6* as a solvent. Chemical shifts are given in parts per million (ppm). Splitting patterns are designated as follows: s- singlet, d- doublet, t- triplet, q- quartet and m-multiplet. Mass spectra (MS) were recorded on Schimadzu GC-MS operating at 70eV.

All the synthesized compounds were purified by recrystallization The reactions were followed up and the purity of compounds was monitored on pre-coated TLC plates and visualizing the spots in ultraviolet light.

In vitro antimicrobial study

Synthesised compounds were screened for antibacterial and antifungal activities at two different conc (50µg/ml, 100µg/ml) against Staphylococcus aureus, Escherichia coli, Steptococci, Pseudomonas aeruginosa, Candida albicans and Aspergillus flavus by cup plate method (diffusion technique) using Procaine penicillin, Streptomycin, Cefazolin Sodium, Sporafloxin and Griseofulvin respectively as standards. The results are the mean value of zone of inhibition measured in millimeter of two sets. The results are tabulated.

Table No. 1 Antibacterial activity

Sl. No	Name of the compounds	Mean zone of inhibition (in mm*)							
		S. aureus		*E. coli*		*Pseudomonas*		*Streptococci*	
		50µg	100µg	50µg	100µg	50µg	100µg	50µg	100µg
01	Procaine penicillin	19	22	-	-	-	-	-	-
02	Streptomycin	-	-	19	24	-	-	-	-
O3	Cefazolin Sod	-	-	-	-	20	25	-	-
04	Sporafloxin	-	-	-	-	-	-	20	27
05	D_1	10(0.52)	12(0.54)	14(0.73)	17(0.70)	11(0.55)	13(0.52)	10(0.50)	13(0.48)
06	D_2	13(0.68)	16(0.72)	12(0.63)	15(0.62)	11(0.55)	14(0.56)	11(055)	14(0.51)
07	D_3	10(0.52)	13(0.59)	11(0.57)	14(0.58)	12(0.60)	16(0.64)	12(0.60)	15(0.55)
08	D_4	12(0.63)	15(0.68)	11(0.57)	15(0.62)	14(0.70)	19(0.76)	10(0.50)	13(0.48)
09	D_5	12(0.63)	15(0.68)	12(0.63)	15(0.62)	12(0.60)	14(0.56)	11(0.55)	14(0.51)
10	D_6	12(0.63)	14(0.63)	12(0.63)	16(0.66)	12(0.60)	16(0.64)	10(0.50)	14(0.51)
11	D_7	11(0.57)	13(0.59)	13(0.68)	17(0.70)	11(0.55)	15(0.60)	10(0.50)	13(0.48)
12	D_8	10(0.52)	13(0.59)	12(0.63)	15(0.62)	10(0.50)	15(0.60)	11(0.55)	14(0.51)
13	D_9	12(0.63)	15(0.68)	14(0.73)	17(0.70)	13(0.65)	17(0.68)	10(0.50)	14(0.51)
14	D_{10}	11(0.57)	15(0.68)	13(0.68)	15(0.62)	13(0.65)	16(0.64)	11(0.55)	13(0.48)
15	D_{11}	12(0.63)	14(0.63)	12(0.63)	15(0.62)	12(0.60)	17(0.68)	12(0.60)	15(0.55)
16	D_{12}	10(0.52)	13(0.59)	11(0.57)	14(0.58)	10(0.50)	14(0.56)	10(0.50)	13(0.48)
17	D_{13}	13(0.63)	15(0.68)	12(0.63)	17(0.70)	11(0.55)	15(0.60)	11(0.55)	13(0.48)
18	D_{14}	11(0.57)	14(0.63)	12(0.63)	16(0.66)	12(0.60)	16(0.64)	10(0.50)	14(0.51)
19	D_{15}	11(0.57)	14(0.63)	13(0.68)	16(0.66)	14(0.70)	17(0.68)	10(0.50)	13(0.48)
20	D_{16}	11(0.57)	14(0.63)	12(0.63)	14(0.58)	11(0.55)	15(0.60)	11(0.55)	14(0.51)
21	D_{17}	13(0.68)	15(0.68)	14(0.73)	18(0.75)	12(0.60)	16(0.64)	12(0.60)	15(0.55)
22	D_{18}	12(0.63)	15(0.68)	12(0.63)	16(0.66)	13(0.65)	17(0.68)	10(0.50)	14(0.51)
23	D_{19}	13(0.68)	17(0.77)	13(0.68)	16(0.66)	13(0.65)	17(0.68)	11(0.55)	14(0.51)

Activity Index = Test Compound / Standard compound

Table No. 2 Antifungal activity

Sl. No	Name of the compounds	Mean zone of inhibition (in mm*)			
		Candida albicans		*Aspergillus niger*	
		50µg	100µg	50µg	100µg
01	Griseofulvin	19	24	19	23
02	D_1	15(0.73)	20(0.83)	12(0.63)	15(0.65)
03	D_2	13(0.68)	16(0.66)	12(0.63)	16(0.69)
04	D_3	11(0.57)	15(0.62)	14(0.73)	17(0.73)
05	D_4	12(0.63)	17(0.70)	11(0.57)	14(0.60)
06	D_5	11(0.57)	13(0.54)	13(0.68)	16(0.69)
07	D_6	12(0.63)	16(0.66)	13(0.68)	17(0.73)
08	D_7	15(0.78)	18(0.75)	11(0.57)	14(0.60)
09	D_8	11(0.57)	15(0.62)	13(0.68)	17(0.73)
10	D_9	13(0.68)	15(0.62)	13(0.68)	16(0.69)
11	D_{10}	12(0.63)	15(0.62)	11(0.57)	13(0.56)
12	D_{11}	13(0.68)	17(0.70)	12(0.63)	16(0.69)
13	D_{12}	12(0.63)	15(0.62)	13(0.68)	17(0.73)
14	D_{13}	13(0.68)	17(0.70)	11(0.57)	16(0.69)
15	D_{14}	14(0.73)	17(0.70)	11(0.57)	15(0.65)
16	D_{15}	14(0.73)	18(0.75)	12(0.63)	17(0.73)
17	D_{16}	12(0.63)	15(0.62)	13(0.68)	17(0.73)
18	D_{17}	15(0.78)	19(0.79)	14(0.73)	18(0.78)
19	D_{18}	11(0.57)	14(0.58)	12(0.63)	14(0.60)
20	D_{19}	12(0.63)	16(0.66)	11(0.57)	14(0.60)

Activity Index = Test Compound / Standard compound

Sl. No	Compound Code	M.P/ B.P°C	% Yield	MOL. FORM	M.Wt.	Calculated %		
						C	H	N

3. RESULTS AND DISCUSSION

a) Anti-bacterial activity :

Synthesis and pharmacological screening of 2-(2'-phenyl-4'-p-dimethylaminobenzylidenyl imidazolin-5'-one)-6-fluoro-7-substituted (1,3) benzothiazoles. were tested for the antibacterial activity against following bacteria

a) i] *S.aureus*, ii] *streptococci* (gram +ve*)* and
b) iii] *E.coil*, iv] *Pseudomonas* (gram –ve).

The test compounds $D_{2,}$ D_{13}, $D_{15,}$ and $D_{19.}$ showed moderate antibacterial activity against *S.aureus* (gram +ve) compare to standard drug procaine penicillin.

Compounds D_1, $D\text{-}_9$, and $D_{17.}$ showed moderate antibacterial activity against, *E. coli* (gram –ve) compared to standard drugs and steptomycin.

Compounds D_3, D_{11}, and $D_{17.}$ showed moderate antibacterial activity against, streptococci. (gram +ve) compared to standard drugs and Sporafloxin.

Compound D_4 and $D_{15.}$ showed moderate activity against Pseudomonas (gram –ve) at both lower and higher concentration compare to standard drug Cetazolin Sodium.

b) Anti-fungal activity :

Synthesized compounds were tested for antifungal activity against Candida albicans and Aspergillus niger. Among the compounds tested; D_1, D_7, and $D_{17.}$ showed good activity against Candida albicans at both concentration compare to standard Griseofulvin.

D_{13} and D_{17} showed significant activity against Aspergillus niger compared to standard Griseofulvin.

4. CONCLUSION

Result of present study demonstrate that, a new class of different aromatic aniline, PABA, piperzine, diphenylamine, N-methyl piperzine, o- toludine encompassing imidazole derivatives were synthesized and evaluated as antibacterial agents. The newly

synthesized heterocyclics exhibited promising antimicrobial activity against Staphylococcus aureus, streptococci, Pseudomonas aeruginosa and Escherichia coli. The antifungal studies against Candida albicans and Asperagillus niger showed significant activity at low and high concentration compared to standard. It can be concluded that this class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress.

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