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Der Pharma Chemica, 2011, 3(2): 305-309
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and anti-fungal screening of fluoro benzothiazolo imidazole derivatives

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ABSTRACT

Literature revealed that vast majority of benzothiazoles and imidazole compounds are known to possess pharmacologically proven therapeutic potentials. Though extensive research work is reported on benzothiazoles, very little is known so for about fluorobenzothiazole fused imidazolines with fluorine at 6th position.The reaction of 6- fluro-7-chloroaniline[1] with potassium thiocynate (KSCN) in presence of bromine and glacial acetic acid and ammonia to get 2-amino 6- fluro-7-chloro(1,3) benzothiazoles[2-5] (1) which was further treated with hydrazine hydrate in presence of ethylene glycol and sulphuric acid to yield 2-hydrazino-6-fluoro-7-chloro(1,3) benzothiazoles(2). It was reacted with prepared Oxazolone i.e.2-phenyl-4-benzylidine-5-oxazolone (3) to yield 2[2'- Phenyllidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- chloro(1,3) benzothiazole(4), which was treated with variety of aromatic anilines in presence of DMF to yield different derivatives (5a-5i). Purity of compounds was checked by TLC. Melting points were determined by open capillaries method and uncorrected. IR spectra (NaCl) are recorded on FTIR (Schimadzu-84005) spectrophotometer using nujol mull technique. [1]HNMR spectra are recorded on a spectrophotometer (Bruker AMX) at 500MHz, using TMS as internal reference. Griseofulvin was used as standard reference anti-fungal drug. All the results related to above data are given as MIC values in Table No. II.

Keywords: Flourine, Benzothiazole, Oxazalinone, Imidazoline, Anti-fungal Activity.

INTRODUCTION

Fluorobenzothiazoles were the effective therapeutic agents to be employed in development of novel pharmacologically active moieties. Imidazolinones exhibit diverse biological properties. In the recent years, the chemistry of oxazolones has received much attention due to their use as intermediates for synthesis of some heterocyclic systems. Hence in present study we made an attempt to link fluorobenzothiazoles with imidazoles for generating various derivatives having antimicrobial activity. Benzylidine derivatives were found to possess

MAO Inhibitory activity, therefore in the present work we have treated oxazolones benzothiazole ring to get biodynamic active leads.

MATERIALS AND METHODS

First Step

Synthesis of 2-amino-6-fluoro-7-chloro-(1,3)benzothiazole [2-5](1):

To the glacial acetic acid (20ml) which is cooled below room temperature, 8gm (0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of fluorochloroaniline was added. The mixture was placed in freezing mixture of ice and salt, mechanically stirred while 1.6ml of bromine in 6ml of glacial acetic acid was added, from a dropping funnel at such a rate that the temperature never rose beyond room temperature. After all the bromine was added (105min), the solution was stirred for 2 hours below room temperature and at room temperature for 10 hours, it was then allowed to stand overnight, during which period an orange precipitate settle at the bottom, water (6ml) was added quickly and slurry was heated at 85^0c on a steam bath and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid heated again to 85^0c and filtered hot. The combined filtrate was cooled and neutralized with concentrated ammonia solution to p^H 6. A dark yellow precipitate was collected. Recrystalised from benzene, ethanol of (1:1) after treatment with animal charcoal gave yellow plates of 2-amino-6-fluoro-7-chloro-(1,3) benzothiazole. After drying in a oven at 80^0c, the dry material (1gm 51.02%) melted at 210-212^0c. UV 307.4, 269nm, IR 1542cm^{-1}(aromatic C=C) and 3475cm^{-1} (NH_2); 1456 cm^{-1}(thiazole), 1215 cm^{-1}(aromatic-F), 712 cm^{-1}(aromatic-Cl).

Second Step

Synthesis of 2-Hydrazino-6-fluoro-7-chloro (1, 3) benzothiazole [4-5](2):

Concentrated HCl (10ml) was added drop wise with stirring to hydrazine hydrate (12ml, 0.2mol) at 5-10^0c followed by ethylene glycol (40ml). To the above solution 2-amino-6-fluoro-7-chloro (1,3) benzothiazole (0.01mol) was added in portion and the resulting mixture was refluxed for 2 hrs, cooled, poured in crushed ice. The solid separated, was filtered, dried and recrystalised from ethanol (Yield 76%). The dry material melted at 182^0c. IR (NaCl) 3476 cm^{-1}(Ar-NH_2 stretching), 3094 cm^{-1}(Ar-NH bending), 1632 cm^{-1} (C=N stretching), 1348 cm^{-1} (Ar-NH bending), 1194 cm^{-1}(C-F stretching), 688 cm^{-1}(C-Cl stretching).

Third Step

Synthesis of 2-Phenyl- 4-benzylidine-5-oxazol-5-one (oxazolone)[6] (3):

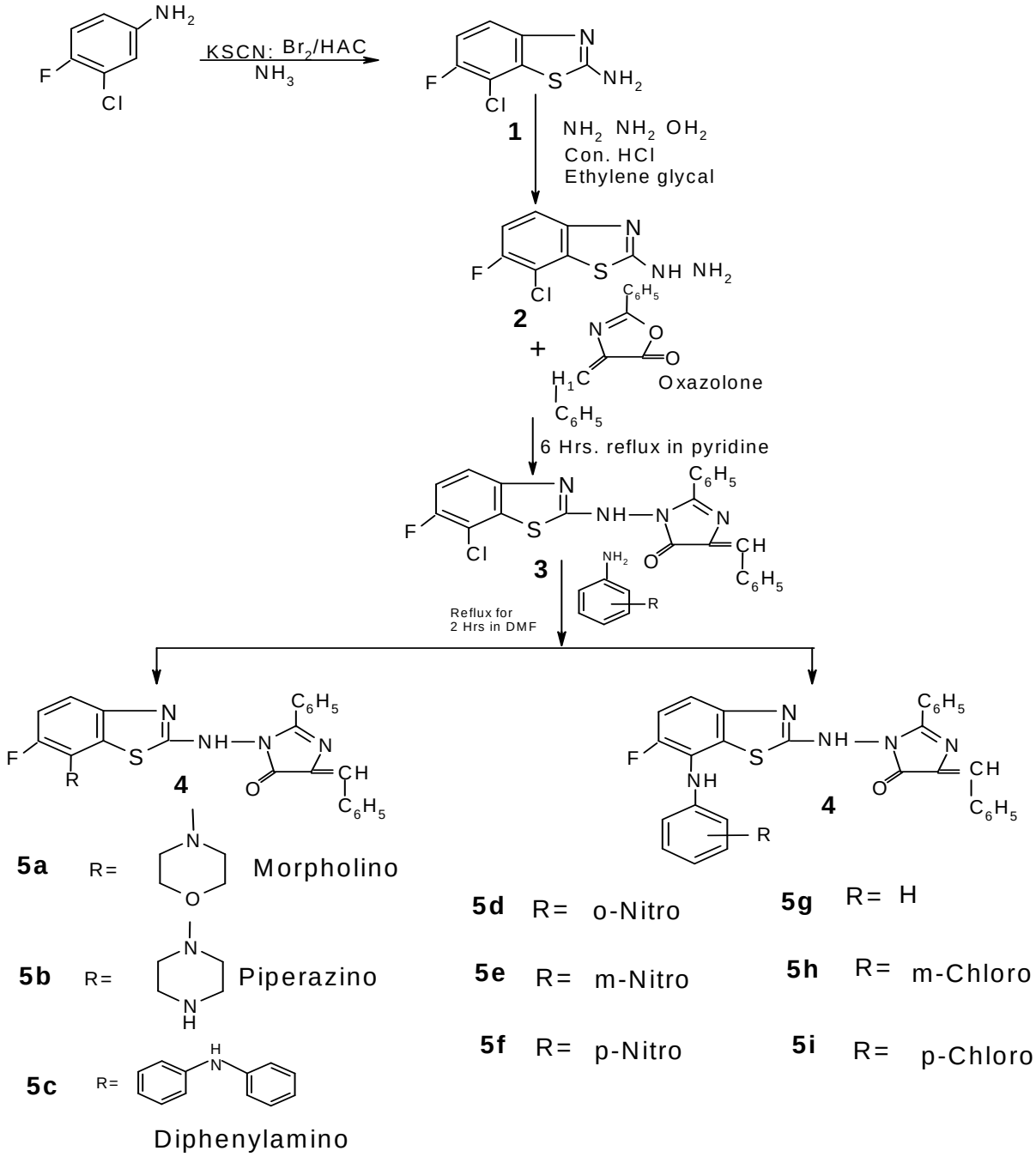
Redistilled benzaldehyde was treated with benzoyl glyciene (Hippuric acid) in presence of acetic anhydride (dry acetic acid) and anhydrous sodium acetate to get 4-benzylidene-2-phenyl-oxazol-5-one(oxazolone).Upon washing with ice cold alcohol and then with boiling water (Yield 80%),melted at 165-166^0C, IR (NaCl) 1790 cm^{-1}(Lactone carbonyl) and another bond at 1650 cm^{-1}(C=N stretching).

Synthesis of 2[2'- Phenyl -4'- benzidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7-chloro (1,3) benzothiazoles[2,5,7,8](4):

A mixture of 0.01 mol. of 2-hydrazino-6-fluoro-7-chloro benzothia-zole and 2-phenyl-4-benzylidene-5-oxazolinone (2.49g. 0.01mol) was refluxed in pyridine for 6-8 hours. excess of pyridine was distilled off and resulting mass was poured on to crushed ice and neutralised with dil HCl, filtered and product was recrystallised from ethanol. The dry material melted at

110-112^{0}c (72%).IR(NaCl) 3452 cm^{-1}(-NH stretching), 121 cm^{-1}(C-F), 677 cm^{-1}(C-Cl stretching),3091 cm^{-1}(C=C stretching),1601 cm^{-1}(C=O stretching).

Scheme



Preparation of various derivatives [2,5,9](5a-5i):

2[2'- Phenyl -4'- benzidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- chloro (1,3) benzothiazole (4) was treated with various aromatic amines Refluxed for 2 hrs. in presence of DMF (dimethyl formamide) yields various 2[2'- Phenyl -4'- benzidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- chloro (1,3) benzothiazole derivatives(5a-5i).

IR (NaCl) spectrum of 2[2'- Phenyl -4'- benzidinyl- 5'- oxo- imidazoline- 1yl- amino] -6 fluoro- 7- chloro (1,3) benzothiazole 3440 cm^{-1}(-NH stretching), 1640 cm^{-1}(imidazoline ring carbonyl), 1490 cm^{-1}(C=C stretching), 714 cm^{-1}(C-Cl), 1196 cm^{-1}(C-F strtching). Similarly the remaining 5b-5i compounds showed appropriate IR spectra confirming their structures. Similarly ^{1}HNMR spectra's of compounds 5g 6.8-8.5 δ (13 H), 5-5 δ (-NH group), 2.7-4.0 δ (8 H) multiplet. The analytical data of the synthesized derivatives is given in Table No. I.

Table No. I: Analytical Data of the Compounds (5a-5i)

Sr. No.	Comp. Code	% Yield	MP/BP (^{0}c)	Molecular Formula	Mol. Weight	Calculated (%)			Rf Value
						C	H	N	
01	5a	50%	117-118	$C_{27}H_{18}N_5O_2SF$	495	65.45	3.63	14.14	0.89
02	5b	72%	114-115	$C_{27}H_{19}N_6OSF$	494	65.58	3.84	17.00	0.63
03	5c	64%	126-127	$C_{35}H_{24}N_5OSF$	581	72.28	4.13	12.04	0.72
04	5d	60%	120-121	$C_{29}H_{19}N_6O_3SF$	550	63.27	3.45	15.72	0.62
05	5e	60%	143-144	$C_{29}H_{19}N_6O_3SF$	550	63.30	3.45	15.3	0.82
06	5f	68%	146-147	$C_{29}H_{19}N_6O_3SF$	550	63.30	3.45	15.3	0.73
07	5g	62%	140-142	$C_{29}H_{20}N_5OSF$	505	68.91	3.96	13.86	0.97
08	5h	67%	121-122	$C_{29}H_{19}N_6OSFCl$	540	64.44	3.51	12.96	0.94
09	5i	70%	105-106	$C_{29}H_{19}N_5OSFCl$	540	64.44	3.51	12.96	0.76

Antifungal activity[10, 11]

The synthesized compounds are screened against three selected fungal strains Candida albicans,Aspergillus flavus and Aspergillus niger by using diffusion method.

The 48 hours old fungal culture inoculated into nutrient broth by following aseptic techniques and incubated for 48 hours at 37 ± 2^0C in an incubator. This culture mixed with Potato-dextrose agar media (20%) and poured into petriplates.

After solidification five bores are made at equal distance by using sterile steel cork borer (8 mm in diameter). Into these cups different concentrations of standard drug and synthesized compounds along with control (Dimethyl formamide) introduced.

Table No II: Screening of Anti-Fungal Activity

Compounds	Mean Zone of Inhibition (in mm)		
	Candida albicans	***Aspergillus flavus***	***Aspergillus niger***
Griseofulvin	21	18	24
5a	19	12	20
5b	13	16	16
5c	17	18	17
5d	17	19	18
5e	16	17	16
5f	16	18	16
5g	17	19	16
5h	14	20	17
5i	13	15	14

After introduction of standard drug and compounds, these plates are placed in a refrigerator at 8 -10^0 C for two hours for proper diffusion of the drugs. After 2 hours of cold incubation, the petriplates are transferred to incubator and maintained at 37 ± 2^0 C for 24-36 hours.

After the incubation period, the plates were observed for zone of inhibition by using vernier scale. Results evaluated by comparing the zone of inhibition shown by the synthesized compounds with standard drug.

The results are the mean value of zone of inhibition measured in millimeter of two sets. The results are tabulated in the Table No.II. The standard drug and synthesized compounds were dissolved in minimum quantity of DMF and adjusted, to make up the volume with distilled water to get 50g/ml and 100g/ml concentrations. The Griseofulvin used as a standard drug.

CONCLUSION

In present investigation the newly synthesized compounds were screened for anti-fungal activity of which few compounds showed promising anti-fungal activity against the fungal strains compared to the standard drug Griseofulvin .

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