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SYNTHESIS, CHARECTERISATION OF 6-FLURO-7-CHLORO 2(5-FURYL 1,3,4-OXADIAZOL-2-YL) AMINO (1,3) BEZOTHIAZOLE DERIVATIVE AND ANTI-BACTERIAL ACTIVITY

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ABSTRACT

Benzothiazoles Incorporated with 1,3,4 oxadiazole derivatives have been synthesized and evaluated for their anti fungal activity. Structure of these compounds have been established by NMR, IR, Mass, U.V data. Significant anti-fungal activities were observed for members of this series.

Key words: Benzothiazole, Oxadiazole, Anti-fungal activity, anti -bacterial activity

INTRODUCTION

Benzothiazoles are bicyclic ring system with multiple applications. In the 1950s, a number 2-amino benzothiazoles were intensively studied as central muscle relaxants **[1]**.

It was found to interfere with glutamate neurotransmission in biochemical electrophysiological and behavioral experiments, after that benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity **[2]**.

Benzothiazoles with oxadiazoles were reported to possess various pharmacological activity of clinical impotence **[3]**. Oxadiazole derivatives are well known to have number of biological and antimicrobial activities. This also having antiinflammatory, anthelmentic and anticonvulsant activities **[4]**.

Discovering new drugs has never been a simple matter. In view of above considerations, we have selected Tailor made approach of drug design in search of new potent bio-active drug molecules. Chemical modification of drug molecules to locate the number of series having optimal effects and will probably continue to be the factor necessary, to make new drugs **[5-6]**.

The first successful attempts at actually designing a drug to work at a particular target happened nearly simultaneously in the 1970's with the discovery of cimetidine, a selective H_2-antagonist and captopril an angiotensin converting enzyme inhibitor. Since then, the art of rational drug design has undergone an explosive evolution, making use of sophisticated computational and structural methodology to help in the effort **[7]**.

To establish the structure of the drug molecules the new invention in the physico-chemical directions such as X-ray crystallography different types of chromatography, spectroscopic studies like NMR, IR, Mass, U.V immensely helpful for medicinal chemist.

The advances in the molecular biology, computer science, instrumentation technology gave an revolutionary turn to concept of chemotherapy leading to development or other area of drug design, QSAR studies etc. **[8-10]**.

MATERIALS AND METHODS

Chemical and reagents

Fluoro chloro aniline, Potassium thiocyanate, Glacial acetic acid, Bromine, 2-amino benzothiazole, Anhydrous K_2CO_3, $FeCl_3$, Ethyl chloroformate, Hydrazine hydrate,

Experimental section

First Step

General synthesis of 2-amino-6-fluoro-7-chloro-benzothiazole [11-14]

To glacial acetic acid (20ml) cooled below room temperature were added 8gm(0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of fluoro chloro aniline. The mixture was cooled in a water bath and 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 rises 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 0 c 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 0 c and

filtered hot. The combined filtrate was cooled and neutralised with concentrated ammonia solution to p^H 6 A dark yellow precipitate was collected. Recrystallized 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 ^{0}C, the dry material (1gm 51.02%) melted at 210-212^{0}c.

Second Step [15-16]

Preparation of 6-fluoro-7-chloro (1,3) benzothiazole 2-carbamates

2-amino benzothiazole (0.327 mol) 13.2 gm, absolute alcohol 30 ml. Anhydrous K_2CO_3 (2 gm) and ethyl chloroformate (0.0327 mol) 0.7 gm were added under cooling. The mixture was reflux for 7-8 hrs. the solution filtered and the residue washed with ethanol and the solvent evaporated under reduced pressure to get the product as solid which is crystalised from suitable solvent.

Third Step [17-19]

Preparation of 6-fluoro-7-chloro-2-semicarbazide (1,3) benzothiazoles

6-fluoro-7-chloro (1,3) benzothiazole 2-carbamates was added to 4 ml of hydrazine hydrate in ethanol (30 ml). The reaction mixture was heated under reflux for 5 hrs and cooled to room temperature. The carbamoylhydrazides separated were filtered, washed with ethanol (2 ml), dried and crystalized from suitable solvent.

Fourth Step [20-22]

Schiff basis of (1,3) benzothiazoles 6-fluoro-7-chloro-2-semicarbazides

2.6 gm of 6-fluoro-7-chloro-2-semicarbazide (1,3) benzothiazole disolved in absolute ethyl alcohol (12.6 ml) and furfuraldehyde 6.29 ml (0.015 mol) was added to a solution of 6-fluoro-7-chloro-2-semicarbazide (1,3) benzothiazole. The mixture was heated under reflux for 3 hrs and the solvent removed under reduced pressure to yield Schiff bases of (1,3) benzothiazole 6-fluoro-7-chloro-2-semi-carbazides which crystalised from suitable solvent.

Fifth Step [23-24]

Preparation of 6-fluoro-7-chloro-2-(5'-furyl 1',3'4'-oxadiazo2'yl)amino(1,3)benzothiazoles

5.2 gm (0.00132 mol) of (1,3) benzothiazoles 6-fluoro-7-chloro-2-semi carbazides was disolved in glacial acetic acid (10 ml) and $FeCl_3$ (1.5 gm) in water (50 ml) added to it with shaking. The mixture was shaken for 1 hr and diluted with water (100 ml) and kept at room temperature for 2 days. The solid separated was filtered washed with water dried and crystalised.

Sixth Step [25-26]

Preparation of 2(5'-furyl-1',3',4'-oxadiazol-2'-yl-amino)-6-fluoro-7-substituted (1,3) benzothiazoles

To 0.007 mol of 6-fluoro-7-chloro-2-(5'-furyl 1',3',4'-oxadiazol-2'yl) amino(1,3) benzothiazole was treated with equimolar quantity (0.0075 mol) of various substituted aromatic amines, PABA, morpholine, piperazine, P-toluidine, diphenylamine and N-methylpiperazine and refluxed for 2 hrs. in the presence of DMF (dimethyl formamide) then the mixture was cooled and poured in the crushed ice. The solid separated was filter off, dried and recrystalised from benzene and super dry alcohol (1:1).

Anti-bacterial activity (Table 6)

The antibacterial activities are performed by cup plate method (diffusion technique). The fresh culture of bacteria are obtained by inoculating bacteria into peptone water liquid media and incubated at 37 ± 2˚ C for 18 – 24 hours. This culture mixed with nutrient agar media (**Table 5**) (20%) and poured into petridishes by following aseptic techniques. After solidification of the media five bores are made at equal distance by using sterile steel cork borer (8 mm diameter). Into these cups different concentrations of standard drugs and synthesized compounds are introduced. Dimethyl formamide was used as a control. After introduction of standard drugs and synthesized compounds, the plates were placed in a refrigerator at 8-10°C for proper diffusion of drugs into the media. After two hours of cold incubation, the petriplates are transferred to incubator and maintained at 37 0 ±2 °C for 18-24 hours. After the incubation period, the petriplates were observed for zone of inhibition by using vernier scale. The results evaluated by comparing the zone of inhibition shown by the synthesized compounds with standard drugs. The results are the mean value of zone of inhibition measured in millimeter of two sets.

Antifungal activity

The synthesized compounds are screened against two selected fungal strains Candida albicans and Aspergillus niger by using diffusion method. The 48 hours old fungal culture inoculated into nutrient broth (**Table 8**) by following aseptic techniques and incubated for 48 hours at 37 0 ± 2°C 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. After introduction of standard drug and compounds, these plates are placed in a refrigerator at 8 0

-10°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°C for 24-36hours. After the incubation period, the plates were observed for zone of inhibition by using verniar 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 standard drug and synthesized compounds were dissolved in minimum quantity of DMF and adjusted, to make up the volume with DMF to get 50µg/ml and 100µg/ml concentrations. The Griseofulvin used as a standard drug.

INDENTIFICATION AND CHARACTERIZATION

The identification and characterization of the prepared compounds were carried out by the following procedure to ascertain that all prepared compounds had different chemical nature than the respective parent compounds.

Melting Point Determination

The melting points of the organic compounds were determined by open capillary tube method.

Thin Layer Chromatogrphy:

a. **Preparation of chromatoplate:** A uniform slurry of silica Gel-G in water was prepared in the ratio of 1:2.

b. **Preparation of Solvent System and saturation of Chamber:**

The solvent system used for the development of chromatogram was prepared carefully by mixing. Butanol: Ethyl acetate: Chloroform [1:2:1]

SPECTRAL STUDIES

1. Ultra Violet Spectra (**Table 1**)
2. IR Spectra (**Table 2**)
3. ^{1}HNMR Spectra (**Table 3**)

RESULTS AND DISCUSSION

Table 1: Analytical Data

Sl. No	Compound Code	M.P/B.P°C	% Yield	MOL. FORM	M.Wt.	C%	H%	N%
1	V F1	136-138	86%	$C_{19}H_{11}O_4SN_6F$	438	52.05	2.51	19.18
2	V F2	146-148	78%	$C_{19}H_{11}O_4SN_6F$	438	52.05	2.51	19.18
3	V F3	107-109	80%	$C_{19}H_{11}O_4SN_6F$	438	52.05	2.51	19.18
3	V F4	152-154	78%	$C_{19}H_{11}O_2SN_5FCl$	427.5	53.33	2.57	16.37
5	V F5	125-126	76%	$C_{19}H_{11}O_2SN_5FCl$	427.5	53.33	2.57	16.37
6	V F6	158-159	72%	$C_{19}H_{11}O_2SN_5FCl$	427.5	53.33	2.57	16.37
7	V F7	162-163	82%	$C_{17}H_{14}O_3SN_5F$	387	52.8	3.7	18.08
8	V F8	172-173	83%	$C_{17}H_{15}O_2SN_6F$	386	52.9	3.9	21.8
9	V F9	98-99	87%	$C_{25}H_{16}O_2SN_5F$	469	63.9	3.4	14.9
10	V F10	154-155	73%	$C_{20}H_{14}O_2SN_5F$	407	59.0	3.43	17.19
11	V F11	142-143	74%	$C_{20}H_{11}O_4SN_5F$	436	55.0	2.51	16.05
12	V F12	160-161	85%	$C_{18}H_{17}O_2SN_6F$	400	54.0	4.25	21.0

Table :2 Characteristics IR absorption bands of similar compounds (VF_1 toVF_{12})

Sl. No.	Sepc.no	Compound code	Ar-NH 2 cm -1	ArC=C cm -1	Cyclic C=N cm -1	C-F cm -1	C-Cl cm -1	NO_2 cm -1	CH_3 cm -1	C-N cm -1	C-OC cm -1	Benzo-thiazole cm -1
1	03	CFA	3433	1494	-	1259	762	-	-	-	-	-
2	04	2AB	3479	1460	1646	1193	685	-	-	-	-	1390
3	05	2HB	3476	1450	1632	1194	688	-	-	-	-	1390
4	06	VF1	3480	1375	1650	1200	725	-	-	1600	1070	1380
5	07	VF2	3450	1375	1650	1190	725	-	-	1600	1070	1380
6	08	VF3	3450	1375	1650	1190	725	-	-	1600	1070	1380
7	09	VF4	3460	1370	1660	1210	725	-	-	1620	1070	1300
8	10	VF5	3460	1370	1660	1210	725	-	-	1620	1070	1300
9	11	VF6	3460	1370	1600	1210	725	-	-	1620	1070	1300
10	12	VF7	3480	1360	1600	1190	-	-	-	1660	1075	1300
11	13	VF8	3470	1360	1600	1190	-	-	-	1660	1075	1300
12	14	VF9	3480	1350	1600	1190	-	-	-	1600	1075	1310
13	15	VF10	3475	1360	1600	1190	-	-	-	1600	1075	1320
14	16	VF11	3480	1360	1600	1190	-	-	-	1600	1075	1350
15	17	VF12	3480	1370	1600	1190	-	-	-	1600	1075	1350

Table 3: NMR Spectral Data of Compounds

Sl. No.	Spectra No.	Compound Code	Hydrogen	δ (ppm)	Multiplity	Solvent
1	34	F_3	*-Ar-H* -1H-NH -1H-NH	6.6-7.94 4.4 5.5	Multiplet Singlet Singlet	$CDCl_3$
2	35	F_6	*-Ar-H* -1H-NH -1H-NH	6.9-7.02 5.5 3.8	Multiplet Singlet Singlet	$CDCl_3$
3	36	F_8	*-Ar-H* -8H-CH_2	7.2-7.8 1.2-2	Multiplet Singlet	$CDCl_3$
4	37	F_{11}	-Ar-H -1H-NH -1H-NH	6.6-7.88 4.0 2.0	Multiplet Singlet Singlet	$CDCl_3$

Table 4: Preparation of peptone water liquid media

Ingredients	Quantity
Peptone	10 gm
Beef extract	10 gm
Sodium chloride	5 gm
Distilled water	Q. S. 1000 ml

Table 5: Preparation of assay medium

Ingredients	Quantity
Peptone	6.0 gm
Casein hydroxylate of soyabean	4.0 gm
Yeast extract	3.0 gm
Beef extract	1.5 gm
Dextrose (dehydrated)	1.0 gm
Agar	15.0 gm
Distilled water	Q. S. 1000 ml

The pH was adjusted to 7.4 ± .1 at 25^0C temperature.

Table 6: Antibacterial activity

Sl. No	Name of the compounds	*Mean zone of inhibition (in mm)*			
		Staphylococcus aureus		*Escherichia coli*	
		50µg	100µg	50µg	100µg
01	Procaine penicillin	20	25	-	-
02	Streptomycin	-	-	20	23
15	V F1	14 (0.7)	19 (0.76)	12 (0.6)	15 (0.65)
16	V F2	13 (0.65)	16 (0.64)	12 (0.65)	15 (0.65)
17	V F3	14 (0.7)	18 (0.72)	11 (0.55)	14 (0.60)
18	V F4	15 (0.75)	18 (0.72)	13 (0.65)	16 (0.69)
19	V F5	15 (0.75)	19 (0.76)	12 (0.55)	15 (0.65)
20	V F6	15 (0.75)	19 (0.72)	13 (0.65)	15 (0.65)
21	V F7	17 (0.85)	19 (0.72)	14 (0.7)	17 (0.73)
22	V F8	14 (0.7)	18 (0.72)	12 (0.55)	15 (0.65)
23	V F9	11 (0.55)	15 (0.6)	13 (0.65)	15 (0.65)
24	V F10	12 (0.6)	16 (0.69)	16 (0.8)	20 (0.86)
25	V F11	10 (0.5)	14 (0.54)	10 (0.5)	14 (0.6)
26	V F12	10 (0.5)	13 (0.49)	12 (0.6)	14 (0.6)

Table 7: Composition of nutrient broth

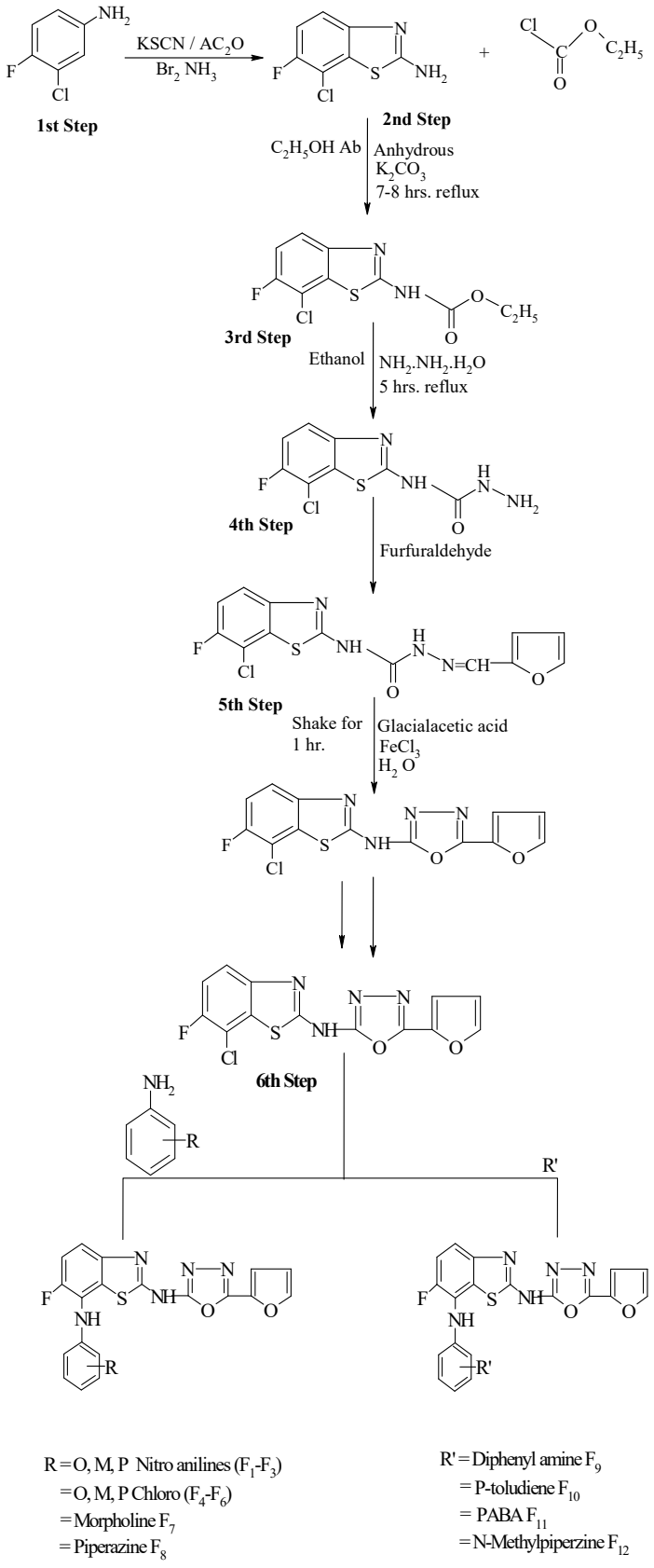
Ingredients	Quantity
Peptone	10.0 gm
Yeast extract	6.0 gm
Potassium dihydrogen phosphate	3.0 gm
Sodium chloride	5.0 gm
Glucose (anhydrous)	10.0 gm
Distilled water	Q. S. 1000.0 ml

pH of the media was adjusted to 7.4 (±.1) and autoclaved at 15lb/sq.inch. Pressure (121^{0}C) for 15 min.

Table 8: Antifungal activity

Sl. No	Name of the compounds	Mean zone of inhibition (in mm)			
		Candida albicans		*Aspergillus niger*	
		50µg	100µg	50µg	100µg
01	Griseofulvin	21	25	21	25
14	V F1	13 (0.61)	18 (0.74)	14 (0.66)	20 (0.8)
15	V F2	13 (0.61)	18 (0.72)	12 (0.57)	16 (0.65)
16	V F3	11 (0.51)	14 (0.56)	14 (0.66)	19 (0.76)
17	V F4	12 (0.56)	17 (0.68)	12 (0.57)	17 (0.7)
18	V F5	12 (0.56)	16 (0.64)	13 (0.61)	18 (0.72)
19	V F6	13 (0.61)	17 (0.68)	14 (0.66)	19 (0.76)
20	V F7	12 (0.56)	16 (0.64)	14 (0.66)	19 (0.76)
21	V F8	12 (0.56)	16 (0.64)	12 (0.57)	16 (0.65)
22	V F9	13 (0.61)	17 (0.68)	14 (0.66)	19 (0.76)
23	V F10	12 (0.56)	16 (0.64)	14 (0.66)	19 (0.76)
24	V F11	11 (0.51)	14 (0.56)	12 (0.57)	15 (0.6)
25	V F12	13 (0.66)	18 (0.72)	14 (0.66)	18 (0.72)

SCHEME-I


KSCN / AC2O
Br2 NH3
1st Step
2nd Step
C2H5OH Ab
Anhydrous
K2CO3
7-8 hrs. reflux
3rd Step
Ethanol
NH2.NH2.H2O
5 hrs. reflux
4th Step
Furfuraldehyde
5th Step
Shake for
1 hr.
Glacialacetic acid
FeCl3
H2 O
6th Step
R
R'
R = O, M, P Nitro anilines (F1-F3)
= O, M, P Chloro (F4-F6)
= Morpholine F7
= Piperazine F8
R' = Diphenyl amine F9
= P-toludiene F10
= PABA F11
= N-Methylpiperzine F12

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SUMMARY AND CONCLUSION

Scheme – I

In present work, fluorochloro aniline was treated with KSCN in presence of bromine in glacial acetic acid and ammonia to get 2-amino-6-fluoro-7-acid and ammonia to get 2-amino-6-fluoro-7-chloro (1,3)-benzothiazole, which was condensed with ethyl chloroformate in presence of anhydrous K 2 CO 3 to get ethyl, 6-fluoro, 7-chloro (1,3)-benzothiazole 2-carbamates to the above condensed product treatedwith hydrazine hydrate in presence of ethanol to get 6-fluoro, 7-chloro-2-semicarbazides (1,3)-benzothiazoles which is further condensed with furfuraldehyde in presence of ethanol it gives Schiff bases of (1,3)-benzothiazoles 6-fluoro, 7-chloro 2 semicarbazides which is further treated with FeCl 3 and glacialacetic acid (Cyclization) gives 6-fluoro-7-chloro 2(5'-furyl 1'3'4'3-oxadiazol-2-yl) amino (1,3) benzothiazole. To the above product different aromatic amine, morpholine, piperazine, dipheylamine p-toluidine, PABA and N-methyl piperazine in presence of DMF were treated to get newly synthesized compound through replacing at 7 th position of chlorine **[27-28]**.

The compounds tested for antibacterial VF 7, VF 10, VF 11 and VF 12 showed promising antibacterial activity. The antifungal studies of synthesized compounds VF 3, VF 6, VF 9, VF 10 and VF 12 showed significant activity at low and high concentration compared to standard, still further studies are requested.

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