SYNTHESIS AND PHARMACOLOGICAL SCREENING OF SOME NEWER BENZOTHIAZOLE DERIVATIVES

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ABSTRACT

A New series of some benzothiazole derivatives were synthesized and the structures of the compounds were established by means of Spectral studies and elemental Analysis. All the compounds were evaluated for anti bacterial, anti fungal, anthelminitic and anti inflammatory activities. Some of the compounds have shown significant anti bacterial, anti fungal, anthelmintic and anti inflammatory activity when compared with the standard drugs.

Key words: Benzothiazole, anti bacterial, anti fungal, anthelminitic and anti inflammatory.

1. INTRODUCTION

The 2-substituted benzothiazoles found to posses broad spectrum of pharmacological activity of clinical importance in the areas of anticancer (Schnur and Rodney, 1992), anti-tubercular(Sheik and Bobade, 1991), carbonic anhydrase inhibitors (Scholewald and Ronald, 1994), local anaesthetics (Costakes and Tsatsasg, 1979), hypoglycemic agents, anti-inflammatory, anti-microbial, cardiovascular drugs, central dopaminergic agents and cholerectic agents.

Imidazolinones exhibit diverse biological properties. These have been reported to posses anti-fungal, anti-tubercular, anti-inflammatory, antiviral (Abhabishnol, 2002) and antihistamine activity.

Based on the above, here we synthesised some fluoro benzothiazole incorporated pyrazoles, imidazoles, thiazolidinones and azetidines starting with fluoro chloro aniline, in hope of getting pharmacological agents with broad spectrum of clinical activity.

2. MATERIALS AND METHODS

Anti Microbial activity

The anti microbial activity of the synthesized compounds were determined by cup-plate method. The organisms selected for anti bacterial activity were Staphylococcus aureus and Escherichia coli. Similarly the anti fungal activity was carried out by using Candida albicans and Aspergillus flavus organisms. The concentrations of the sample and standard compounds were 50mcg/ml and 100mcg/ml. The drugs Procaine pencillin, Streptomycin, and Griseofulvin were used as standard drus against gram+ve, gram-ve, anti fungal activity respectively (IP, 1996).

Anthelminitic Activity

The synthesized compounds are screened for anthelmintic activity by using earth worms. Normal saline was used as control. The concentrations of the sample and standard compounds were 0.1%, 0.2% and 0.5%. Albendazole is used as standard drug for anthelminitic activity (Grover, 1993) .

Anti inflammatory activity

The synthesized compounds were screened for anti inflammatory activity by using inhibition of albumin denaturation technique. Diclofenac sodium is used as standard drug (Rang, 1995).

Experimental

Melting points were determined by open capillar tube method. Elemental analysis of the compounds were determined by using CARLO ERBA-1108 elemental analyzer. Rf values are calculated by using T.L.C. The UV spectrum of the compounds was recorded by using SHIMADZU UV-120-02 Spectrophotometer. IR spectras were recorded on SHIMADZU FTIR-8400S spectrometer by using KBr pellet technique. HNMRspectras of the compounds were recorded by Avance 300 MHZ spectrometer.

The mass spectrum of the some of the compounds was recorded on LCMS-2010A spectrometer (Bellany, 1964; Scoog, 1971).

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SCHEME

Synthesis of 6-fluoro-7-Substituted-2-[(2'-phenyl-4'-benzylidenyl-5'-oxo-imidazolin-1'-yl)-*p*-benzene sulphonamido]-(1,3)-benzothiazoles

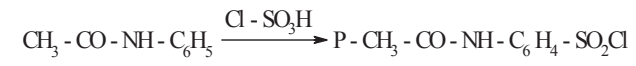
1st Step:

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-(1,3)-benzothiazole.

2nd Step :

- Preparation of *p*-acetamido benzene sulphonyl chloride :

Acetanilide is treated with chlorosulphonic acid to get an oily mixture, upon pouring into crushed ice gives *p*-acetamido benzene sulphonyl chloride.



- 2-amino-6-flouro-7chloro (1,3)-benzothiazole was condensed with *p*-acetamido benzene sulphonyl chloride in presence of pyridine and acetic anhydride to get 6-fluoro-7-chloro-2-(*p*-acetamidebenzene sulphonamido)-(1,3)-benzothiazole.

3rd Step :

6-fluoro-7-chloro-2-(*p*-acetamide benzene sulphonamido)-(1,3)-benzothiazole was treated with various aromatic anilines, morpholines, piperazine, diphenylamine etc in presence of dimethyl formamide (DMF) yield various 6-fluoro-7-substituted-2-[*p*-acetamido benzene sulphonamido]-(1,3)-benzothiazoles.

4th Step :

6-fluoro-7-substituted-2-(*p*-acetamido benzene sulphonamido)-(1,3)-benzo-thiazole were hydrolyzed to 6-fluoro-7-substituted-2-(*p*-amino benzene sulphonamido) (1,3)-benzothiazole in presence of 80% acetic acid.

5th Step :

Preparation of 4-benzylidene-2-phenyl-oxazol-5-one (oxazolone).

Redistilled aldehyde 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-5one upon washing with ice cold alcohol and then with boiling water.

A mixture 6-fluoro-7-substituted-2-(*p*-amino benzene sulphonamido)-(1,3)- benzothiazoles and 2-phenyl-4-benzylidene-5-oxazolinone were refluxed in pyridine and latter excess of pyridine were distilled off; then poured on to crushed ice to get 6-fluoro-7-Substituted-2-[(2'-phenyl-4'-benzylidenyl-5'-oxo-imidazolin-1'-yl)-*p*-benzene sulphonamido]-(1,3)-benzothiazoles.

3. RESULTS AND DISCUSSION

The synthesized compounds were tested for antibacterial, antifungal, anthelmintic, and anti-inflammatory studies.

The compounds tested for antibacterial studies against gram +*ve [staphyloccocus aureus]* and gram-ve. *[Escheria coli]*. Among the compounds tested, VB_3, VB_4, VB_5, VB_{11}, VB_{12}, and VR_{10} showed some significant activity [at low and high concentrations] against gram +ve. And VB_3, VB_4, VB_{11}, VR_2, VR_3, VR_4, and VR_{10} (at low and high conc.) showed some significant activity against gram -*ve* bacteria.

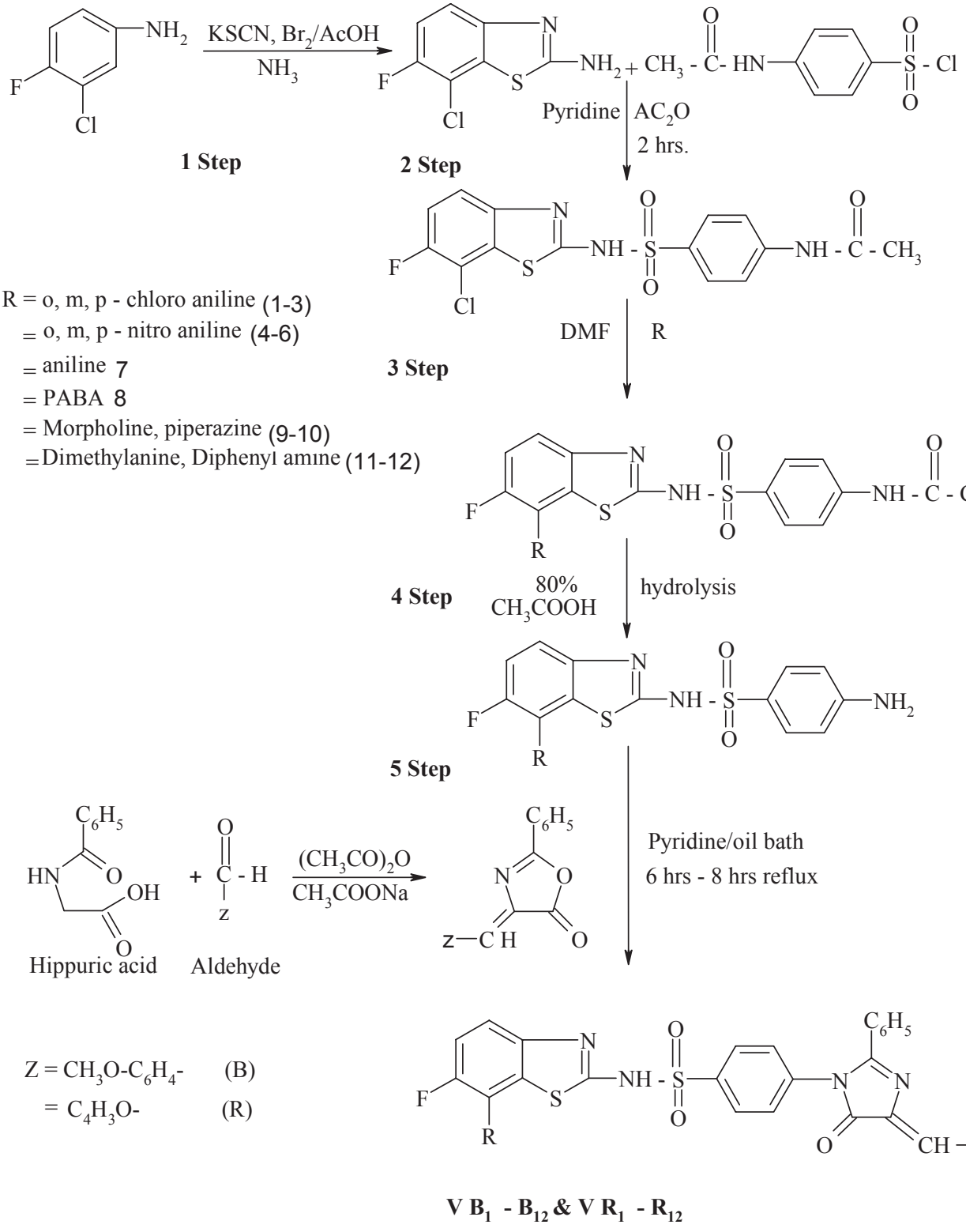
The antifungal studies of synthesized compounds were tested against *Candida albicans* and *Aspergillus flavus*. Among the compounds tested; VB_2, VB_3, VB_4, VB_8, VR_2, VR_3, VR_4, VR_5, VR_7, VR_8, VR_{10}, and VR_{11}, showed activity against both fungus at low and high concentrations compared to standard.

The compounds tested for anthelminitic activity, among VB_3, VB_4, VB_5, VB_9, VB_{11}, VR_7, VR_9, VR_{10}, and VR_{11}, showed significant better paralytic time of earthworms compared to standard albendazole drug.

The compounds were tested for the anti-inflammatory activity by using invitro protein denaturation method. The tested compounds are showing appreciable inhibition of protein denaturation compared to standard. Among the tested compounds VB_3, VB_4, VB_5, VB_9, VB_{11}, VR_7, VR_9, VR_{10}, and VR_{11} showed better anti-inflammatory activity.

The compounds for anti-bacterial, anti-fungal, anthelminitic (paralysis time) and anti-inflammatory requires further studies

SCHEME - I



V B_1 - B_{12} & V R_1 - R_{12}

Table No. 1
Antibacterial activity

Sl. No	Name of the compounds	*Mean zone of inhibition (in mm)*			
		Staphylococcus aureus		*Escherichia coli*	
		50µg	100µg	50µg	100µg
01	Procaine pencillin	20	24	-	-
02	Streptomycin	-	-	19	23
03	V B_1	10	13	12	14
04	V B_2	11	13	12	15
05	V B_3	14	17	13	15
06	V B_4	13	16	13	17
07	V B_5	10	15	12	15
08	V B_6	11	12	12	14
09	V B_7	10	12	11	13
10	V B_8	10	12	11	14
11	V B_9	11	13	11	13
12	V B_{10}	11	13	11	15
13	V B_{11}	14	16	13	15
14	V B_{12}	12	16	13	15
15	VR_1	10	11	11	13
16	VR_2	10	11	16	18
17	VR_3	9	11	15	18
18	VR_4	9	10	14	16
19	VR_5	11	13	11	14
20	VR_6	10	12	10	14
21	VR_7	11	13	11	13
22	VR_8	11	12	12	14
23	VR_9	10	12	11	14
24	VR_{10}	16	19	14	18
25	VR_{11}	11	13	12	14
26	VR_{12}	10	11	12	14

Table No. 2
Antifungal activity

Sl. No	Name of the compounds	Mean zone of inhibition (in mm)			
		Candida albicans		*Aspergillus flavus*	
		50µg	100µg	50µg	100µg
01	Griseofulvin	18	21	19	22
02	V B_1	11	12	12	15
03	V B_2	12	13	12	14
04	V B_3	12	14	13	16
05	V B_4	15	13	12	17
06	V B_5	12	11	12	15
07	V B_6	14	12	11	14
08	V B_7	13	11	11	17
09	V B_8	14	15	12	16
10	V B_9	12	10	13	16
11	V B_{10}	12	12	11	14
12	V B_{11}	11	12	10	13
13	V B_{12}	12	12	11	17
14	VR_1	13	12	11	16
15	VR_2	18	17	14	17
16	VR_3	12	13	12	17
17	VR_4	16	14	13	18
18	VR_5	16	14	13	16
19	VR_6	13	12	14	18
20	VR_7	13	15	15	18
21	VR_8	13	15	15	18
22	VR_9	9	10	13	17
23	VR_{10}	11	14	13	16
24	VR_{11}	15	14	12	15
25	VR_{12}	14	12	12	16

Table No. 3
Anthelminitic Activity

Sl. No.	Name	Concentration	Time in Minutes	
			For Paralysis	For Death
1	**Control**	0.9%	--	--
2	**Albendazole**	0.1%	50	70
		0.2%	45	63
		0.5%	40	55
3	$V B_1$	0.1%	35	150
		0.2%	21	130
		0.5%	19	120
4	$V B_2$	0.1%	38	160
		0.2%	22	152
		0.5%	20	125
5	$V B_3$	0.1%	35	148
		0.2%	20	120
		0.5%	18	110
6	$V B_4$	0.1%	40	175
		0.2%	29	160
		0.5%	21	125
7	$V B_5$	0.1%	32	170
		0.2%	25	145
		0.5%	23	120
8	$V B_6$	0.1%	48	189
		0.2%	35	165
		0.5%	30	130
9	$V B_7$	0.1%	49	192
		0.2%	38	170
		0.5%	32	125
10	$V B_8$	0.1%	59	194
		0.2%	44	170
		0.5%	32	135
11	$V B_9$	0.1%	55	198
		0.2%	39	180
		0.5%	29	120
12	$V B_{10}$	0.1%	75	188
		0.2%	45	145
		0.5%	35	120
13	$V B_{11}$	0.1%	48	150
		0.2%	38	119
		0.5%	30	110

Sl. No.	Name	Concentration	Time in Minutes	
			For Paralysis	For Death
14	$V B_{12}$	0.1%	60	170
		0.2%	40	143
		0.5%	30	120
15	VR_1	0.1%	48	140
		0.2%	35	110
		0.5%	30	98
16	VR_2	0.1%	52	150
		0.2%	39	125
		0.5%	32	110
17	VR_3	0.1%	59	158
		0.2%	45	130
		0.5%	40	110
18	VR_4	0.1%	62	145
		0.2%	42	119
		0.5%	35	112
19	VR_5	0.1%	65	145
		0.2%	48	120
		0.5%	40	109
20	VR_6	0.1%	70	168
		0.2%	56	135
		0.5%	45	118
21	VR_7	0.1%	80	170
		0.2%	64	149
		0.5%	50	125
22	VR_8	0.1%	64	180
		0.2%	49	136
		0.5%	35	101
23	VR_9	0.1%	52	175
		0.2%	39	155
		0.5%	31	110
24	VR_{10}	0.1%	60	185
		0.2%	42	160
		0.5%	32	125
25	VR_{11}	0.1%	70	162
		0.2%	50	140
		0.5%	38	105
26	VR_{12}	0.1%	52	145
		0.2%	39	120
		0.5%	30	98

Table No. 4
Anti-inflammatory activity

Sl No	Name of the compounds	Absorbence value (Mean ± SE)	Inhibition of denaturation (in %)
01	**Control**	0.087 ± 0.001	-
02	V B_1	0.101 ± 0.001	16.09
03	V B_2	0.102 ± 0.002	17.24
04	V B_3	0.147 ± 0.003	68.96
05	V B_4	0.139 ± 0.001	59.77
06	V B_5	0.152 ± 0.002	74.71
07	V B_6	0.099 ± 0.002	13.79
08	V B_7	0.098 ± 0.001	12.64
09	V B_8	0.151 ± 0.001	73.56
10	V B_9	0.102 ± 0.002	17.24
11	V B_{10}	0.145 ± 0.001	66.66
12	V B_{11}	0.095 ± 0.001	9.19
13	V B_{12}	0.097 ± 0.002	11.49
14	VR_1	0.098 ± 0.001	12.64
15	VR_2	0.097 ± 0.003	11.49
16	VR_3	0.147 ± 0.002	68.96
17	VR_4	0.125 ± 0.001	43.67
18	VR_5	0.141 ± 0.001	62.06
19	VR_6	0.142 ± 0.002	63.21
20	VR_7	0.142 ± 0.001	63.21
21	VR_8	0.122 ± 0.001	40.22
22	VR_9	0.133 ± 0.002	52.87
23	VR_{10}	0.134 ± 0.002	54.02
24	VR_{11}	0.127 ± 0.001	45.97
25	VR_{12}	0.152 ± 0.001	74.71
26	Diclofenac sodium	0.161 ± 0.001	85.05

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