Oriental Journal of Chemistry Vol. **24**(2), 475-484 (2008)

Synthesis of fluoro substituted benzothiazoles incorporated with 1,3,4-thiadiazoles for biological and pharmacological screening

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(Received: March 30, 2008; Accepted: May 28, 2008)

ABSTRACT

Various substituted 2[5'-(3-Methyl benzene)-1',3',4-thiadiazol-2'-yl amino)-6-flouro-7substituted (1,3) benzothiazoles and 2[5'-(p-chlorobenzene)-1',3',4'-thiadiazole-2'-yl amino) -6-fluoro-7substituted (1,3) benzothiazole containing different functional groups have been synthesized by condensing hydrazine hydrate with substituted 2-aminobenzothiazole in presence of ammonia, carban disulphide with ethanol and sodium chloroacetate. Further it is treated with various aromatic acid (p-chloro benzoic acid and 3-methyl benzoic acid) in presence of pyridine. The identity of compounds were confirmed on the basis of their spectral (UV, IR, ^{1}H NMR and MASS) data. Further, they have been screened for their antimicrobial, anti-inflammatory and anticonvulsant activities.

Key words: Fluorine, Benzothiazole, Thiadiazole, anti-microbial.

INTRODUCTION

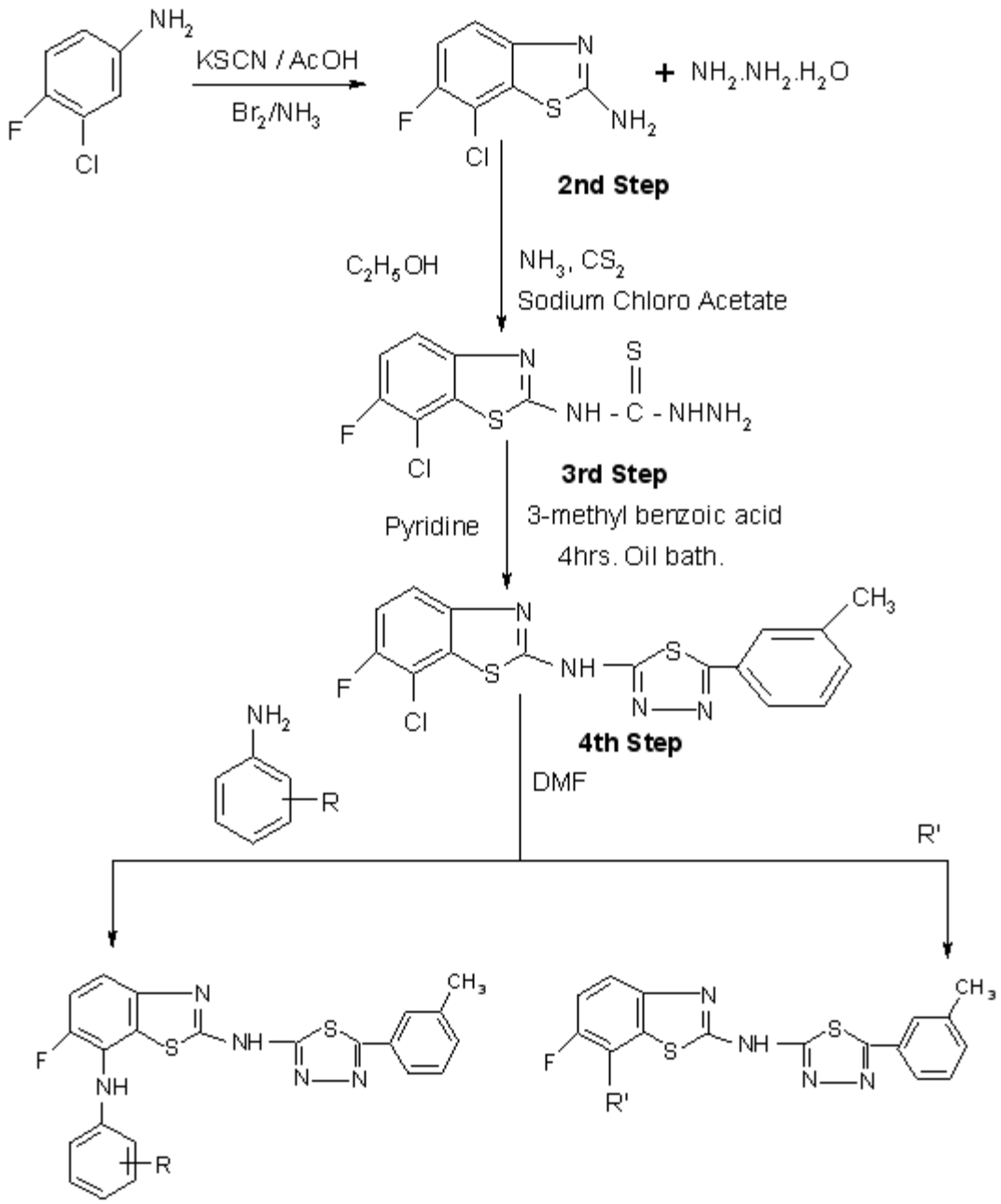
The thiadiazole drugs were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infection in human beings (eg. Sulphamethazole). They are also choice for the drug as diuretic (eg. Acetazol-amide). Benzothiazole with thiadiazole group etc. were reported to possess various pharmacological activity of clinical importance.

Thiadiazole derivatives are well known to have number of biological and antimicrobial activities[1-12], this also having antiinflammatory[13-18], and anticonvulsant activities[19-21].

MATERIAL AND METHODS

Melting point was 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.

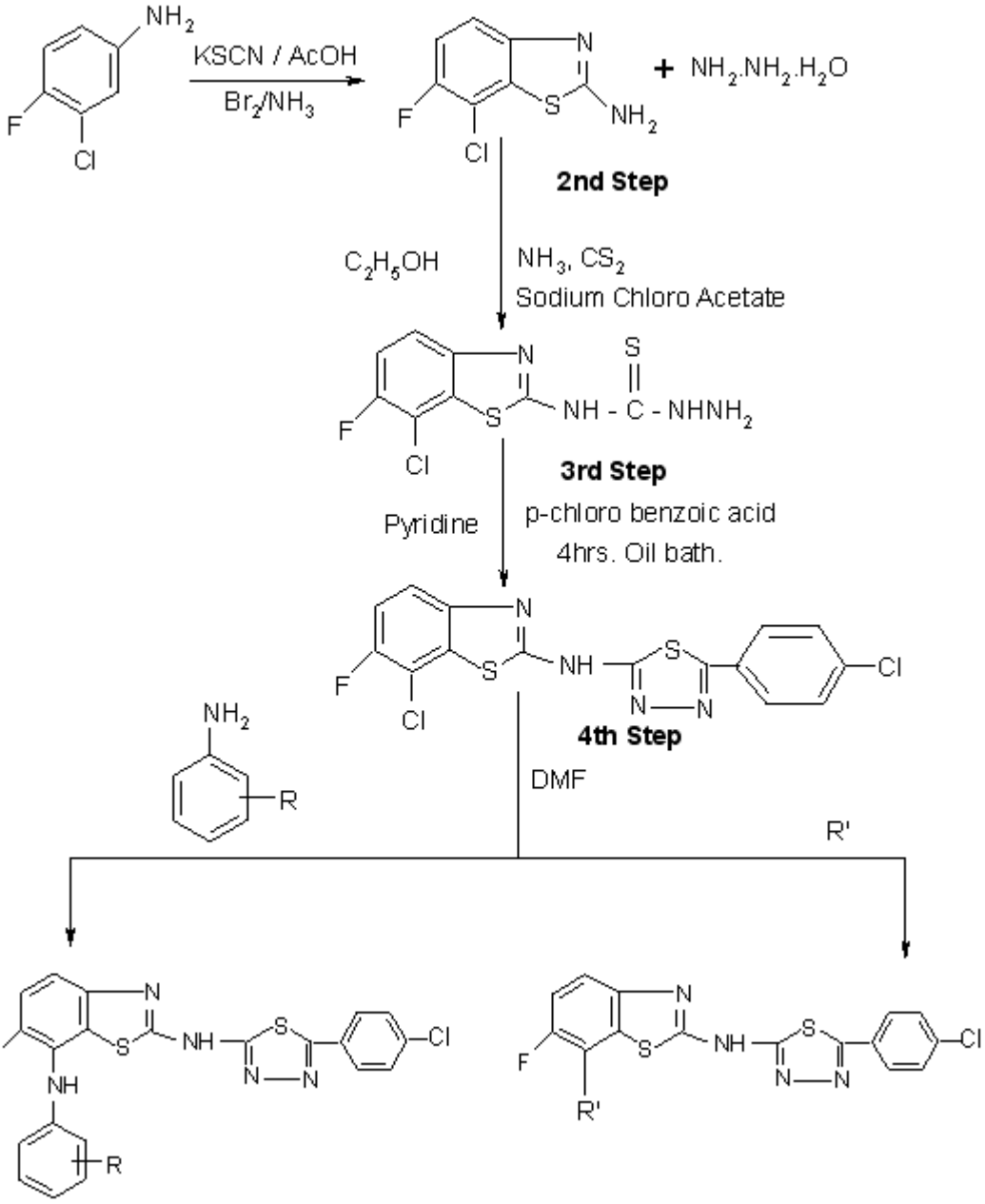
All the compounds synthesized were screened for antibacterial and antifungal activities at two different concentrations (50µg/ml, 100µg/ml) against *Staphylococcus aureus*, *Streptococci, Escherchia coli, Ps. aureus* and *Candida albicans*, *Aspergillus niger* by cup plate method using Procaine Penicillin, Streptomycin and Griseoflavin respectively as standards. The compounds showed considerable activity against all species tested at 50µg/ml, 100µg/ml. Fluoro substituted benzothiazoles series was tested for antibacterial activity. Were calculated which are shown in the table. The compounds showing activity index more than 0.7 were considered to be significantly active.



R = o, m ,p Nitro (M_1-M_3)
= o, m, p Chloro (M_4-M_6)
= PABA M_{10}
= o-Toludine M_{11}
= p-Toludine M_{12}

R' = Morpholine M_7
= Piperazine M_8
= N-Methyl - piperzine M_9

Scheme 1



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Scheme 2

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

2-amino benzothiazole (0.1 mol) 20.25 gm, was dissolved in ethanol (95%) 50 ml and ammonia solution was added to it. The reaction mixture was cooled below 30^{0}C and carbondisulphide (8 ml) was added slowly within 15 minutes with continuous shaking. After complete addition of carbon disulphide the solution was cooled to stand for 1 hour. After that sodium chloroacetate (0.1 mol) 9.4 gm was added to it. The reaction was exothermic. To it 50% hydrazaine hydrate (20 ml) was added. The mixture was warmed gently, filtered and boiled to half of its volume and kept overnight. Next day the product thiosemicarbazide was filtered and recrystalised from ethanol.

Preparation of 6-fluoro-7-chloro-2-[5'-(3-methyl benzene) 1',3',4'-thiadiazol-2'yl] amino (1,3) benzothiazoles

An intimate mixture of 13.9 gm (0.05 mol) of (1,3) benzothiazoles 6-fluoro-7-chloro-2-thiosemicarbazides and 3-methyl benzoic acid (0.05 mol) 6.8 gm and pyridine (100 ml) heated at 170^0-210°C for 4 hours in an oil bath under moister free condition. The fused material after cooling was

Table 1: Analytical data

S No.	Compd. Code	m.p./b.p. (°C)	yield (%)	Molecular formula	M.Wt.	C %	H %	N %
1.	V M1	235-236	80%	$C_{22}H_{15}O_2S_2N_6F$	478	55.23	3.14	17.57
2.	V M2	190-192	82%	$C_{22}H_{15}O_2S_2N_6F$	478	55.23	3.14	17.57
3.	V M3	230-231	65%	$C_{22}H_{15}O_2S_2N_6F$	478	55.23	3.14	17.57
4.	V M4	192-194	72%	$C_{22}H_{15}S_2N_5FCl$	467.5	56.47	3.21	14.97
5.	V M5	205-207	74%	$C_{22}H_{15}S_2N_5FCl$	467.5	56.47	3.21	14.97
6.	V M6	211-213	73%	$C_{22}H_{15}S_2N_5FCl$	467.5	56.47	3.21	14.97
7.	V M7	198-200	76%	$C_{20}H_{18}OS_2N_5F$	427	56.21	4.22	16.39
8.	V M8	203-204	75%	$C_{20}H_{19}S_2N_6F$	426	56.34	4.46	19.72
9.	V M9	225-226	69%	$C_{21}H_{17}S_2N_6F$	440	57.27	3.86	19.09
10.	V M10	214-215	83%	$C_{23}H_{16}O_2S_2N_5F$	477	57.86	3.35	14.68
11.	V M11	188-189	67%	$C_{23}H_{18}S_2N_5F$	447	61.74	4.03	15.66
12.	V M12	240-242	85%	$C_{23}H_{18}S_2N_5F$	447	61.74	4.03	15.66
13.	V C1	236-238	86%	$C_{21}H_{12}O_2S_2N_6FCl$	498.5	50.55	2.41	16.85
14.	V C2	220-221	78%	$C_{21}H_{12}O_2S_2N_6FCl$	498.5	50.55	2.41	16.85
15.	V C3	195-196	80%	$C_{21}H_{12}O_2S_2N_6FCl$	498.5	50.55	2.41	16.85
16.	V C4	232-233	78%	$C_{21}H_{12}S_2N_5FCl_2$	488	51.64	2.46	14.34
17.	V C5	227-228	76%	$C_{21}H_{12}S_2N_5FCl_2$	488	51.64	2.46	14.34
18.	V C6	223-224	72%	$C_{21}H_{12}S_2N_5FCl_2$	488	51.64	2.46	14.34
19.	V C7	211-212	82%	$C_{19}H_{15}OS_2N_5FCl$	445.5	51.18	3.37	15.71
20.	V C8	208-209	83%	$C_{19}H_{16}S_2N_6FCl$	446.5	51.06	3.58	18.81
21.	V C9	205-206	87%	$C_{21}H_{18}S_2N_6FCl$	460.5	54.72	3.91	18.24
22.	V C10	221-222	73%	$C_{22}H_{13}O_2S_2N_5FCl$	497.5	53.07	2.61	14.07
23.	V C11	200-201	74%	$C_{22}H_{15}S_2N_5FCl$	467.5	56.47	3.21	14.97
24.	V C12	203-204	85%	$C_{22}H_{15}S_2N_5FCl$	467.5	56.47	3.21	14.97

treated with cold sodium bicarbonate solution (10%). The resulting solution was filtered wash and recrystalised from methanol.

Preparation of 2[5'-(3-methyl benzene)-1',3',4'-thiadiazol-2'-yl-amino]-6-fluoro-7-substituted (1,3) benzothiazoles

To 0.01 mol of 6-fluoro-7-chloro-2-[5'-(3-methyl benzene) 1',3',4'-thiadiazol-2'yl) amino (1,3) benzothiazole was treated with equimolar quantity (0.01 mol) of various substituted aromatic amines, PABA, morpholine, piperazine, p-toludine, o-toludine 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 absolute alcohol (1:1).

6-fluoro-7-chloro-2[5'-(p-chloro benzene)1',3',4'-thiadiazol-2'-yl amino] (1,3) benzothiazoles

An intimate mixture of 13.9 gm (0.05 mol) of (1,3) benzothiazoles 6-fluoro-7-chloro-2-

Table 2: Characteristics IR absorption bands

S. No.	Spec No.	Comp. Code	Ar-NH_2 cm^{-1}	ArC=C cm^{-1}	Cyclic C=Ncm^{-1}	C-F cm^{-1}	C-Cl cm^{-1}	NO_2 cm^{-1}	CH_3 cm^{-1}	C-N cm^{-1}	C-S-C cm^{-1}
1.	03	CFA	3433	1494	-	1259	762	-	-	-	-
2.	04	2AB	3479	1460	1646	1193	685	-	-	-	-
3.	05	2HB	3476	1450	1632	1194	688	-	-	-	-
4.	06	V M1	3350	1375	1620	1190	-	740	1100	1635	660
5.	07	V M2	3425	1380	1625	1200	-	740	1120	1610	660
6.	08	V M3	3360	1360	1600	1200	-	725	1100	1630	660
7.	09	V M4	3350	1370	1650	1200	725	-	1100	1675	660
8.	10	V M5	3360	1375	1650	1200	725	-	1115	1675	660
9.	11	V M6	3365	1370	1640	1190	720	-	1100	1660	660
10.	12	V M7	3375	1360	1610	1200	-	-	1120	1650	660
11.	13	V M8	3350	1375	1620	1200	-	-	1100	1640	660
12.	14	V M9	3400	1375	1620	1200	-	-	1100	1650	660
13.	15	V M10	3400	1375	1600	1200	-	-	1120	1600	665
14.	16	V M11	3370	1380	1600	1200	-	-	1100	1650	665
15.	17	V M12	3380	1375	1620	1200	-	-	1110	1650	660
16.	18	V C1	3480	1375	1650	1200	725	740	-	1600	1070
17.	19	V C3	3450	1375	1650	1190	725	720	-	1600	1070
18.	20	V C4	3460	1370	1660	1210	725	-	-	1620	1070
19.	21	V C5	3460	1370	1660	1210	725	-	-	1620	1070
20.	22	V C6	3460	1370	1660	1210	725	-	-	1620	1070
21.	23	V C7	3480	1360	1600	1190	725	-	-	1660	1075
22.	24	V C8	3470	1360	1600	1190	725	-	-	1600	1075
23.	25	V C9	3480	1350	1600	1190	725	-	1100	1600	1075
24.	26	V C10	3475	1360	1600	1190	720	-		1600	1075
25.	27	V C11	3480	1360	1600	1190	725	-	1110	1600	1075
26.	28	V C12	3480	1370	1600	1190	720	-	1100	1600	1075

thiosemicarbazides and p-chloro benzoic acid (0.05 mol) 7.8 gm and pyridine (100 ml) heated at 170°-210°C for 4 hours in an oil bath under moister free condition. The fused material after cooling was treated with cold sodium bicarbonate solution (10%). The resulting solution was filtered wash and recrystalised from methanol.

2[5'-(p-chloro benzene) 1',3',4'-thiadiazol (-2'--yl amino) -6-fluoro-7-substituted (1,3) benzothiazoles

The 0.01 mol of 6-fluoro-7-chloro-2[5'-(p-chloro benzene) 1',3',4' thiadiazol (-2'-yl amino) (1,3) benzothiazole was treated with equimolar quantity (0.01 mol) of various substituted aromatic anilines, PABA, morpholine, piperazine, o-toludine, p-toludine, N-methyl piperazine and refluxed for 2 hrs in the presence of DMF (dimethyl formamide) then the mixture was cooled and poured in to crushed ice. The solid separated was filter off, dried and recrystalised from benzene and absolute alcohol (1:1).

RESULTS AND DISCUSSION

Anti-bacterial activity

Synthesis and pharmacological screening of 2-[5'-(3-methyl benzene)-1',3',4'-thiadiazol-2'-yl amino] 6-fluoro-7-substituted (1,3)-benzothiazole and 2[5'-(p-chloro benzene)-1',3',4'--thiadiazol-2'-yl amino]-6-fluoro-7-substituted (1,3) benzothiazole were tested for the antibacterial activity against following bacteria;

- *S. aureus*
- *Streptococci (gram +ve)* and
- *E. coli*
- *Pseudomonas (gram –ve)*.

Table 3: NMR spectral data

S.No	Spectra No.	Compound Code	Hydrogen	δ (ppm)	Multiplity	Solvent
1.	29	VM_1	-10H-Ar-H	7.2-7.5	Multiplet	$CDCl_3$
			-H-NH	5.4	Singlet	
			-H-NH	2.1	Singlet	
2.	30	VM_5	-Ar-H	7.0-7.5	Multiplet	$CDCl_3$
			-1H-NH	2.1	Singlet	
			-Ar-CH_3	2.8	Singlet	
3.	31	VM_7	-Ar-H	6.7-7.4	Multiplet	DMSO
			-1H-NH	2.1	Singlet	
			-Ar-CH_3	2.5	Singlet	
4.	32	VM_8	-10H-Ar-H	6.6-7.4	Multiplet	DMSO
			-1H-NH	2.1	Singlet	
			-Ar-CH_3	2.5	Singlet	
5.	33	VC_1	-Ar-H	7.0-7.5	Multiplet	DMSO
			-1H-NH	2.1	Singlet	
6.	34	VC_5	-Ar-H	7.0-7.5	Multiplet	DMSO
			-1H-NH	2.1	Singlet	
7.	35	VC_7	-Ar-H	7.0-7.6	Multiplet	DMSO
			-1H-NH_2	2.1	Singlet	
8.	36	VC_8	-Ar-H	7.0-7.7	Multiplet	DMSO

The test compounds VC_1, VC_3, VC_6, VC_7, VC_8, VM_{11} and VM_{12} showed better antibacterial activity against *Streptococci* (gram +ve) at lower and higher concentration compounds VC_1, VC_2, VC_8, VC_9, VM_4, VM_5 and VM_7, VM_{10} showed promiting antibacterial activity againsty *Pseudomonas aureus* (gram –ve) at higher and lower concentration.

Compounds VC_3, VC_7, VC_{10}, VM_5, VM_6 and

Table 4: Antibacterial activity

S. No	Name of the compounds	*Mean zone of inhibition (in mm)**			
		Staphylococcus aureus		*Escherichia coli*	
		50µg	**100µg**	**50µg**	**100µg**
1.	Procaine penicillin	20	25	-	-
2.	Streptomycin	-	-	20	23
3.	V M1	14 (0.7)	19 (0.76)	12 (0.6)	15 (0.65)
4.	V M2	13 (0.65)	16 (0.64)	12 (0.65)	15 (0.65)
5.	V M3	14 (0.7)	18 (0.72)	11 (0.55)	14 (0.60)
6.	V M4	15 (0.75)	18 (0.72)	13 (0.65)	16 (0.69)
7.	V M5	15 (0.75)	19 (0.76)	12 (0.55)	15 (0.65)
8.	V M6	15 (0.75)	19 (0.72)	13 (0.65)	15 (0.65)
9.	V M7	17 (0.85)	19 (0.72)	14 (0.7)	17 (0.73)
10.	V M8	14 (0.7)	18 (0.72)	12 (0.55)	15 (0.65)
11.	V M9	11 (0.55)	15 (0.6)	13 (0.65)	15 (0.65)
12.	V M10	12 (0.6)	16 (0.69)	16 (0.8)	20 (0.86)
13.	V M11	10 (0.5)	14 (0.54)	10 (0.5)	14 (0.6)
14.	V M12	10 (0.5)	13 (0.49)	12 (0.6)	14 (0.6)
15.	V C1	14 (0.7)	18 (0.72)	14 (0.7)	17 (0.73)
16.	V C2	14 (0.7)	18 (0.72)	13 (0.65)	17 (0.73)
17.	V C3	15 (0.75)	19 (0.76)	13 (0.65)	16 (0.69)
18.	V C4	15 (0.75)	18 (0.72)	13 (0.65)	16 (0.69)
19.	V C5	14 (0.7)	19 (0.76)	14 (0.7)	18 (0.78)
20.	V C6	14 (0.7)	16 (0.64)	12 (0.6)	16 (0.69)
21.	V C7	15 (0.75)	19 (0.76)	12 (0.6)	17 (0.73)
22.	V C8	14 (0.7)	18 (0.72)	12 (0.6)	17 (0.73)
23.	V C9	15 (0.75)	18 (0.72)	13 (0.65)	15 (0.65)
24.	V C10	15 (0.75)	19 (0.76)	13 (0.65)	16 (0.69)
25.	V C11	14 (0.7)	18 (0.72)	12 (0.6)	15 (0.65)
26.	V C12	14 (0.7)	18 (0.72)	13 (0.65)	16 (0.69)

$$*\text{Activity index} = \frac{\text{Text compound}}{\text{Standard compound}}$$

VM_7 showed promising antibacterial activity against *Strphylococus aureus* (gram +ve).

Compounds VC_1, VC_5, VM_7 and VM_{10} showed moderate antibacterial activity compared to Procaine penicillin (gram +ve) and Streptomycin against *E. coli* (gram –ve).

Anti-fungal activity

The above screened compounds were tested for antifungal activity against *Candida albicans* and *Aspergillus niger*.

Among the compounds tested VC_1, VC_6, VC_9, VM_1, VM_3, VM_9, VM_{10} showed comparatively better antifungal activity against *Aspergellus niger* at both concentration compare to standard Griseofulvin.

Table 5: Antibacterial activity

S. No.	Name of the compounds	Mean zone of inhibition (in mm)*			
		Staphylococcus aureus		*Escherichia coli*	
		50µg	100µg	50µg	100µg
1.	Procaine penicillin	21	25	-	-
2.	Streptomycin	-	-	20	23
3.	V M1	14 (0.66)	19 (0.76)	14 (0.7)	19 (0.82)
4.	V M2	11 (0.51)	20 (0.8)	15 (0.75)	20 (0.86)
5.	V M3	13 (0.61)	19 (0.76)	15 (0.75)	19 (0.82)
6.	V M4	15 (0.71)	18 (0.74)	19 (0.95)	21 (0.91)
7.	V M5	16 (0.76)	17 (0.68)	16 (0.8)	21 (0.91)
8.	V M6	14 (0.66)	16 (0.64)	15 (0.75)	20 (0.86)
9.	V M7	15 (0.71)	17 (0.68)	16 (0.8)	21 (0.91)
10.	V M8	11 (0.51)	16 (0.64)	15 (0.75)	21 (0.91)
11.	V M9	12 (0.56)	17 (0.68)	15 (0.75)	20 (0.86)
12.	V M10	13 (0.61)	18 (0.72)	16 (0.8)	21 (0.91)
13.	V M11	14 (0.66)	19 (0.76)	15 (0.75)	20 (0.86)
14.	V M12	15 (0.71)	20 (0.8)	14 (0.7)	19 (0.82)
15.	V C1	15 (0.71)	19 (0.76)	15 (0.75)	19 (0.82)
16.	V C2	15 (0.71)	18 (0.72)	16 (0.80)	21 (0.91)
17.	V C3	16 (0.76)	17 (0.68)	14 (0.7)	17 (0.73)
18.	V C4	13 (0.61)	16 (0.64)	15 (0.75)	19 (0.82)
19.	V C5	14 (0.66)	17 (0.68)	14 (0.7)	18 (0.78)
20.	V C6	15 (0.71)	19 (0.76)	15 (0.75)	19 (0.82)
21.	V C7	16 (0.76)	18 (0.72)	15 (0.75)	19 (0.82)
22.	V C8	17 (0.81)	17 (0.68)	16 (0.8)	21 (0.91)
23.	V C9	15 (0.71)	16 (0.64)	16 (0.8)	21 (0.91)
24.	V C10	12 (0.56)	16 (0.64)	15 (0.75)	19 (0.82)
25.	V C11	14 (0.66)	17 (0.68)	14 (0.7)	18 (0.78)
26.	V C12	15 (0.71)	18 (0.72)	15 (0.75)	20 (0.86)

$$*\text{Activity index} = \frac{\text{Text compound}}{\text{Standard compound}}$$

Table 6 : Antifungal activity

S. No.	Name of the compounds	Mean zone of inhibition (in mm)* *Staphylococcus aureus*		*Escherichia coli*	
		50µg	100µg	50µg	100µg
1.	Griseofulvin	21	25	21	25
2.	V M1	13 (0.61)	18 (0.74)	14 (0.66)	20 (0.8)
3.	V M2	13 (0.61)	18 (0.72)	12 (0.57)	16 (0.65)
4.	V M3	11 (0.51)	14 (0.56)	14 (0.66)	19 (0.76)
5.	V M4	12 (0.56)	17 (0.68)	12 (0.57)	17 (0.7)
6.	V M5	12 (0.56)	16 (0.64)	13 (0.61)	18 (0.72)
7.	V M6	13 (0.61)	17 (0.68)	14 (0.66)	19 (0.76)
8.	V M7	12 (0.56)	16 (0.64)	14 (0.66)	19 (0.76)
9.	V M8	12 (0.56)	16 (0.64)	12 (0.57)	16 (0.65)
10.	V M9	13 (0.61)	17 (0.68)	14 (0.66)	19 (0.76)
11.	V M10	12 (0.56)	16 (0.64)	14 (0.66)	19 (0.76)
12.	V M11	11 (0.51)	14 (0.56)	12 (0.57)	15 (0.6)
13.	V M12	13 (0.66)	18 (0.72)	14 (0.66)	18 (0.72)
14.	V C1	11 (0.51)	15 (0.60)	14 (0.66)	19 (0.76)
15.	V C2	13 (0.61)	16 (0.64)	14 (0.66)	18 (0.72)
16.	V C3	12 (0.56)	16 (0.64)	13 (0.61)	18 (0.72)
17.	V C4	12 (0.56)	16 (0.64)	12 (0.57)	15 (0.6)
18.	V C5	13 (0.61)	18 (0.72)	13 (0.61)	18 (0.72)
19.	V C6	12 (0.56)	16 (0.64)	14 (0.66)	20 (0.80)
20.	V C7	13 (0.61)	16 (0.64)	13 (0.61)	19 (0.76)
21.	V C8	12 (0.56)	15 (0.6)	14 (0.66)	19 (0.76)
22.	V C9	12 (0.56)	16 (0.64)	15 (0.71)	20 (0.80)
23.	V C10	12 (0.56)	15 (0.6)	14 (0.66)	19 (0.76)
24.	V C11	12 (0.56)	16 (0.64)	12 (0.57)	16 (0.65)
25.	V C12	12 (0.56)	16 (0.64)	14 (0.66)	19 (0.76)

$$*\text{Activity index} = \frac{\text{Text compound}}{\text{Standard compound}}$$

ACKNOWLEDGEMENTS

The authors are thankful to Shri. Sha. Bra. Chandramouleshwara Shivacharya Swamiji, President, Sri. T. M. Chandrashekaraiah M.A. Secretary, T.M.A.E. Society Harapanahalli. for providing necessary facilities through the Principal, S.C.S. college of Pharmacy, Harapanahalli to carryout this work.

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