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Synthesis of bioactive molecule fluoro substituted benzothiazole comprising quinazolinyl imidazole for biological and pharmacological screening

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ABSTRACT

Various substituted 3-{7-substituted-6-1,3 -benzothiazol-2-yl-1-({4-methylphenyl) sulfonyl]20thixo-2,3dihydroquinazolin –4 (1H)-one and 2-[(4Z)-4-benzylidine-2-phenyl-5-oxo-4,5-dihydro-1H-imidazole-1-yl]-N-(7-substituted-6-fluro-1,3-benzothiazole-2-yl) benzamide containing different functional groups have been synthesized by condensing Ethylchloroformate with substituted 2-aminobenzothiazoles in presence dry acetone and K_2CO_3. The identity of compounds were confirmed on the basis of their spectral (UV-Visible, IR, 1H NMR and MASS) data. Further, they have been screened for their antimicrobial, antiinflammatory, anticonvulsant and anthlmentic activities.

Key words: Fluorine, Benzothiazole, sulphonamide, imidazole, quinazolin.

INTRODUCTION

The chemistry and pharmacology of quinazoline have been of great interest because quinazoline derivatives possess various biological activities. This include antimicrobial[1-2], anticonvulsant[3-5], antineoplastic, analgesic and antiinflammatory[6-7] etc.

Therefore in present work we have prepared quinazoline incorporate with fluoro substituted benzothiazole.

Imidazoliones exhibit diverse biological properties. Hence synthesis of new imidazolinones is of considerable interest. In the recent years the chemistry of oxazolones have received much attention due to their use as intermediates for the synthesis of some heterocyclic systems.

Imidazolinones have been reported to posses antifungal[8-9], anti-inflammatory[10], antiviral[11], antitubercular, antihistamine activity.

Recently 1,2,4-trisubstituted-5-imidazolones have been reported to possess monoamino oxidase (MAO) inhibitory and anticonvulsant activity. Benzylidene derivatives are also found to possess MAO inhibitory activity.

The sulfonamide[12-16] drugs were the first effective chemotherapeutic agents to be employed systemically for the prevention and cure of bacterial infectiont in human beings. The introduction of trimethaprim and sulphamethoxazole has resulted in creased use of sulfonamide for the treatment of specific microbial infection. Benzothiazoles with sulphonyl group, imdazolone etc were reported to posses various pharmacological activity of clinical importance.

However, little is known about substituted benzothiazoles having sulphonamido moiety and imidazole with sulphonamido group. Therefore in present work we have sulphonamido group link with benzothiazole ring and imidazolone group to get good biodynamic leads.

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 50µ/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.

Table 1: Analytical data

S. No.	Compd. Code	m.p./b.p. (°C)	Yield (%)	Molecular Formula	M.wt	Calculated% C	H	N
1.	P1	260	78%	$C_{28}H_{18}O_5S_3N_5F$	619	54.28	2.91	11.31
2.	P2	242	82%	$C_{28}H_{18}O_5S_3N_5F$	619	54.28	2.91	11.31
3.	P3	230	75%	$C_{28}H_{18}O_5S_3N_5F$	619	54.28	2.91	11.31
4.	P4	237	72%	$C_{28}H_{18}O_3S_3N_4FCl$	608.5	55.22	2.91	11.31
5.	P5	255	74%	$C_{28}H_{18}O_3S_3N_4FCl$	608.5	55.22	2.91	11.31
6.	P6	225	73%	$C_{28}H_{18}O_3S_3N_4FCl$	608.5	55.22	2.91	11.31
7.	P7	227	76%	$C_{26}H_{21}O_4S_3N_4F$	568	54.93	3.07	9.86
8.	P8	250	65%	$C_{29}H_{19}O_5S_3N_4F$	618	56.31	3.07	9.06
9.	P9	253	69%	$C_{26}H_{22}O_3S_3N_5F$	567	55.02	3.88	12.35
10.	P10	222	83%	$C_{27}H_{24}O_3S_3N_5F$	581	55.77	4.13	12.05
11.	P11	253	77%	$C_{29}H_{21}O_3S_3N_4F$	588	59.18	3.57	9.52
12.	P12	228	85%	$C_{29}H_{21}O_3S_3N_4F$	588	59.18	3.57	9.52
13.	P13	195	86%	$C_{34}H_{23}O_3S_3N_4F$	650	62.77	3.54	8.62
14.	P14	250	78%	$C_{24}H_{19}O_3S_3N_4F$	526	54.75	3.61	10.62
15.	P15	223	80%	$C_{28}H_{17}O_3S_3N_4FCl_2$	643	52.25	2.64	8.71
16.	P16	228	78%	$C_{28}H_{17}O_3S_3N_4FCl_2$	643	52.25	2.64	8.71
17.	P17	241	76%	$C_{29}H_{21}O_4S_3N_4F$	604	57.62	3.48	8.27
18.	P18	225	72%	$C_{28}H_{17}O_3S_3N_4F_2Cl$	626.5	53.63	2.71	8.94
19.	OX1	177-179	82%	$C_{36}H_{23}O_4SN_6F$	654	66.06	3.52	12.84
20.	OX2	180	83%	$C_{36}H_{23}O_4SN_6F$	654	66.06	3.52	12.84
21.	OX3	185	87%	$C_{36}H_{23}O_4SN_6F$	654	66.06	3.52	12.84
22.	OX4	175	73%	$C_{36}H_{23}O_2SN_5FCl$	643.5	67.13	3.57	10.88
23.	OX5	178	74%	$C_{36}H_{23}O_2SN_5FCl$	643.5	67.13	3.57	10.88
24.	OX6	195	85%	$C_{36}H_{23}O_2SN_5FCl$	643.5	67.13	67.13	10.88
25.	OX7	190	79%	$C_{34}H_{26}O_3SN_5FCl$	603	67.66	4.31	11.60
26.	OX8	185	65%	$C_{37}H_{24}O_4SN_5FCl$	653	67.99	3.67	10.72
27.	OX9	142	68%	$C_{34}H_{26}O_3SN_5FCl$	602	67.77	4.49	13.95
28.	OX10	202-203	76%	$C_{37}H_{26}O_3SN_5FCl$	639	69.48	4.07	10.95
29.	OX11	165	72%	$C_{36}H_{26}O_3SN_5F$	639	69.48	4.07	10.95
30.	OX12	150	81%	$C_{36}H_{22}O_2SN_5FCl_2$	678	63.72	3.24	10.32

Table 2: Characteristics IR absorption bands

S. No.	Spec. No.	Com. code	Ar-NH_2 cm^{-1}	ArC=C C=N	Cyclic cm^{-1}	C=F cm^{-1}	C-Cl cm^{-1}	NO_2 cm^{-1}	CH_3 cm^{-1}	C-N cm^{-1}	SO_2 cm^{-1}
1.	03	CFA	3433	1494	-	1259	762	-	-	-	-
2.	04	2AB	3479	1460	1646	1193	685	-	-	-	-
3.	05	ABQ	3450	1455	1612	1186	706	-	-	-	-
4.	06	2HBQ	3478	1452	1635	1190	688	-	-	-	-
5.	07	P0	3450	1520	1650	1010	815	-	1295	-	1330
6.	08	P1	3380	1530	1630	1000	-	650	1280	-	1360
7.	09	P2	3390	1535	1640	990	-	630	1270	-	1390
8.	10	P3	3430	1480	1632	1140	-	625	1275	-	1388
9.	11	P4	3437	1465	1640	1090	798	-	1295	-	1385
10.	12	P5	3445	1468	1648	1012	792	-	1282	-	1375
11.	13	P6	3432	1475	1642	1185	780	-	1285	-	1385
12.	14	P7	3390	1490	1632	1070	-	-	1268	-	1395
13.	15	P8	3485	1510	1612	1060	-	-	1265	-	1405
14.	16	P9	3478	1505	1642	1038	-	-	1267	-	1408
15.	17	P10	3455	1475	1658	1042	-	-	1260	-	1388
16.	18	P11	3462	1520	1662	1042	-	-	1280	-	1385
17.	19	P12	3460	1422	1614	1081	-	-	1275	-	1382
18.	20	P13	3445	1480	1628	1087	-	-	1270	-	1375
19.	21	P14	3435	1484	1688	1087	-	-	1288	-	1391
20.	22	P15	3442	1490	1640	1058	780	-	1290	-	1395
21.	23	P16	3460	1412	1652	1055	792	-	1295	-	1402
22.	24	P17	3479	1500	1648	1050	-	-	1305	-	1408
23.	25	P18	3451	1510	1645	1040	782	-	1285	-	1408
24.	26	OX	3460	1520	1645	1090	760	-	-	1305	-
25.	27	OX1	3420	1488	1648	1020	-	670	-	1310	-
26.	28	OX2	3428	1478	1638	1040	-	680	-	1318	-
27.	29	OX3	3444	1472	1635	1030	-	675	-	1320	-
28.	30	OX4	3448	1481	1676	1032	772	-	-	1315	-
29.	31	OX5	3440	1466	1680	1038	778	-	-	1318	-
30.	32	OX6	3450	1454	1675	1042	765	-	-	1315	-
31.	33	OX7	3480	1455	1650	1011	-	-	-	1335	-
32.	34	OX8	3459	1478	1652	1018	-	-	-	1317	-
33.	35	OX9	3479	1488	1642	1028	-	-	-	1307	-
34.	36	OX10	3488	1490	1618	1037	-	-	-	1305	-
35.	37	OX11	3460	1451	1622	1049	-	-	-	1318	-
36.	38	OX12	3458	1442	1624	1079	788	-	-	1315	-

Synthesis of 2-amino-N-(2-benzothiazol 6-fluoro-7-chloro)benzamide

Anthranilic acid (4.0 g, 0.029 mol) and 2-amino-benzothiazole (5.22 g, 0.026 mol), were dissolved in dry pyridine (20 ml, 0.25 mol). The solution was refluxed for 8 hr. The solution was cooled and poured in water. The separated mass was filtered, washed with water and dried. The product was recrystallized using ethanol.

Synthesis of 2-thione-3-(2-benzothiazol 6-fluoro-7-chloro)-4-(3H)-quinanzoliones

To an ice cold solution of potassium hydroxide (0.1 g, 0.02 mol) in dry ethanol (50 ml), 2-amino-N-(2'-benzothiazolyl 6'-fluoro-7'-chloro) benzamide (2.6 g, 0.008 mol) and carbon disulphide (6.0 ml, 0.078 mol) was added with stirring. The solution was refluxed for 10 hr and cooled. The quantity of solvents was reduced by distillation. The separated solid was filtered, washed with dry ether and dried. The product was recrystallized from ethanol.

synthesis of 3-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)-1-[(4-methyl phenyl) sulfonyl]-2-thioxo-2,3-dihydroquinazoline-4(1H)-one

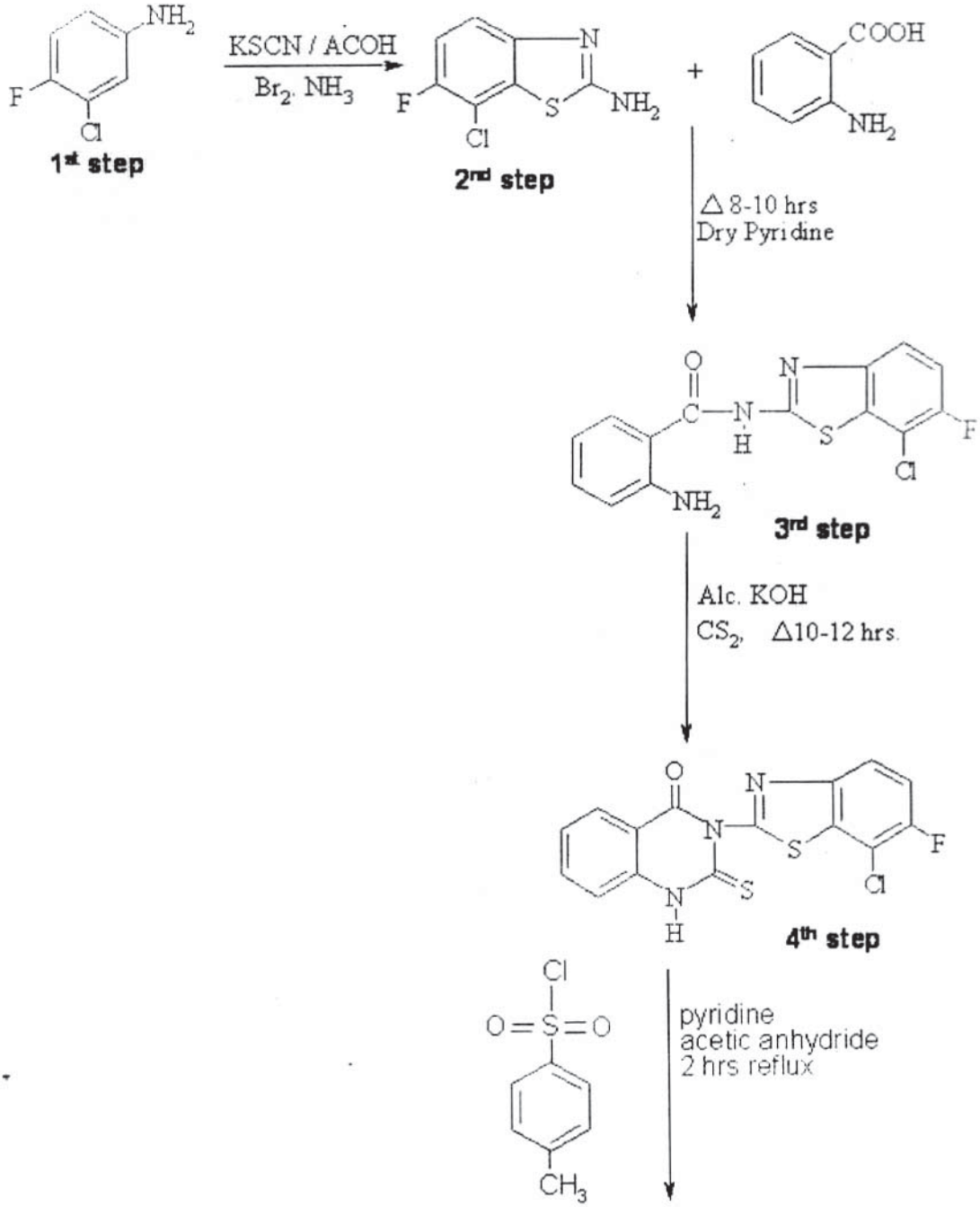
The (0.013 mol, 4.72gm) of 3(7-chloro-6-fluro-1,3-benothiazole-2yl)-1-[(4-methyl phenyl) sulfonyl]-2-thioxo-2,3-dihydroquinazoline-4(1H)-one was taken in pyridine (4ml) and acetic anhydride (20ml) and p-toluene sulphonyl chloride (0.01mol, 1.71 gm) were added and the mixture was kept in oild bath for refluxed about 2hrs. The mixture was cooled and poured into the ice water. The product was recrystalized using ethanol.

Synthesis of 3(7-substituted-6-fluoro-1,3-benzothiazole-2yl-1-[(4-methyl phenyl) sulfonyl] 2-thioxo-2,3-dihydroquinazoline-4(1H)-one

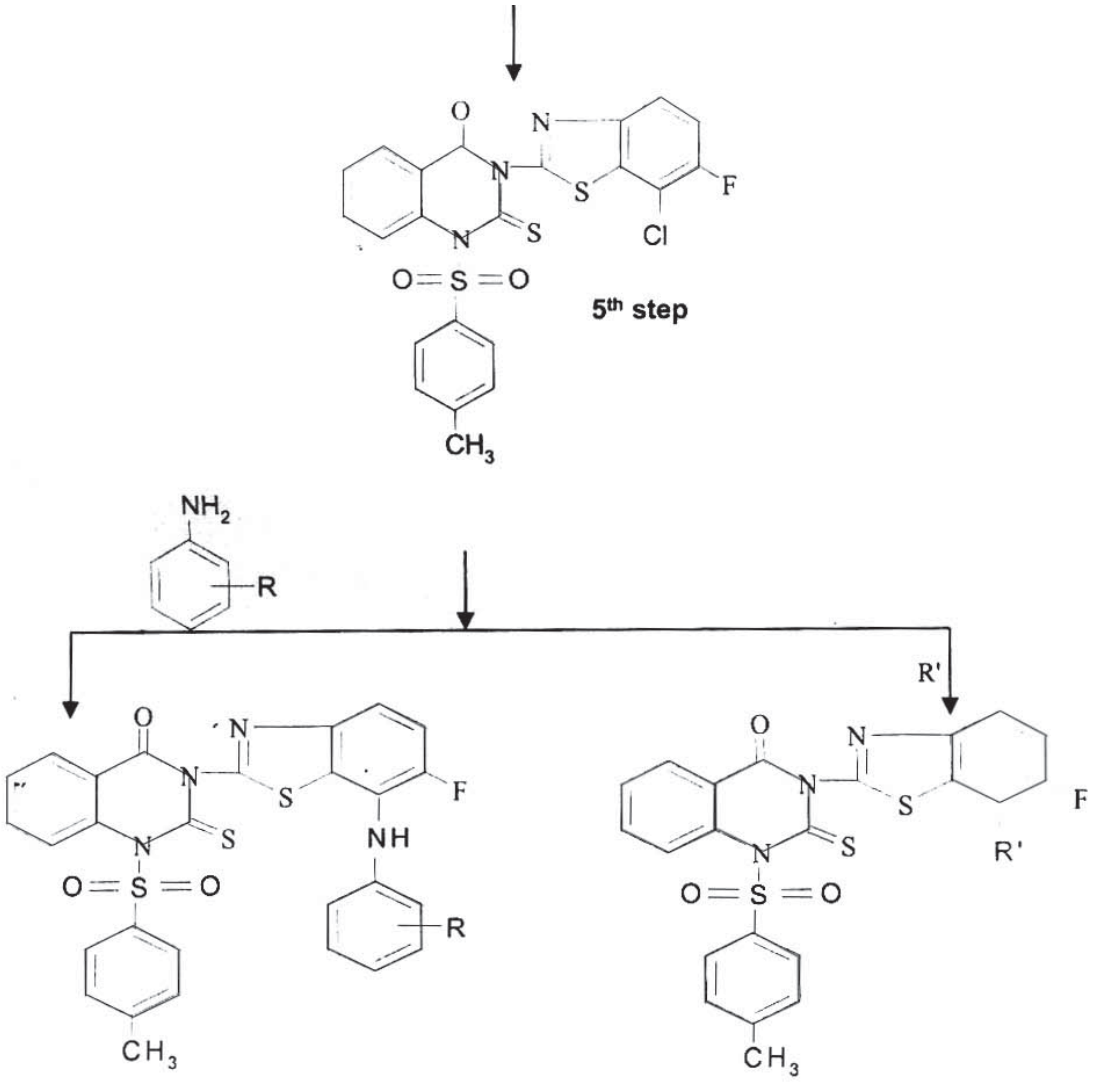
To 0.01 mol of 3(7-chloro-6-fluro-1,3-benothiazole-2yl)-1-[(4-methyl phenyl) sulfonyl] thioxo-2,3-dihydroquinazoline-4(1H)-one was treated with equimolar quantity (0.01mol).

Table 3: NMR spectral data

S No.	Spectra no.	Compound code	Hydrogen	δ (ppm)	Multiplity	Solvent
1	39	P_1	Ar-H	7.1-7.5	Multiplet	DMSO
			$-CH_3$	2.7	Singlet	
2	40	P_5	Ar-H	7.2-7.7	Multiplet	DMSO
			$-CH_3$	2.2	Singlet	
3	41	P_7	Ar-H	7.2-7.7	Multiplet	DMSO
			$-CH_3$	2.2	Singlet	
4	42	P_9	Ar-H	7.2-7.7	Multiplet	DMSO
			$-CH_3$	2.2	Singlet	
5	43	OX_1	-Ar-H	6.6-7.9	Multiplet	DMSO
			-Ar-CH-	6.2	Singlet	
			-1H-NH-	8.5	Singlet	
6	44	OX_5	-Ar-H-	6.6-8.1	Multiplet	DMSO
			-Ar-CH-	6.2	Singlet	
			-1H-NH-	8.8	Singlet	
7	45	OX_7	-Ar-H-	7.0-7.5	Multiplet	DMSO
			-Ar-CH-	6.7	Singlet	
8	46	OX_9	-Ar-H-	6.9-7.5	Multiplet	DMSO
			-Ar-CH-	6.9	Singlet	
			-1H-NH-	7.9	Singlet	


NH2
F
Cl
1st step
KSCN / ACOH
Br2, NH3
N
S
NH2
F
Cl
2nd step
+
COOH
NH2
△ 8-10 hrs
Dry Pyridine
O
C
N
H
N
S
F
Cl
NH2
3rd step
Alc. KOH
CS2, △10-12 hrs.
O
N
N
S
F
Cl
N
H
S
4th step
Cl
O=S=O
CH3
pyridine
acetic anhydride
2 hrs reflux

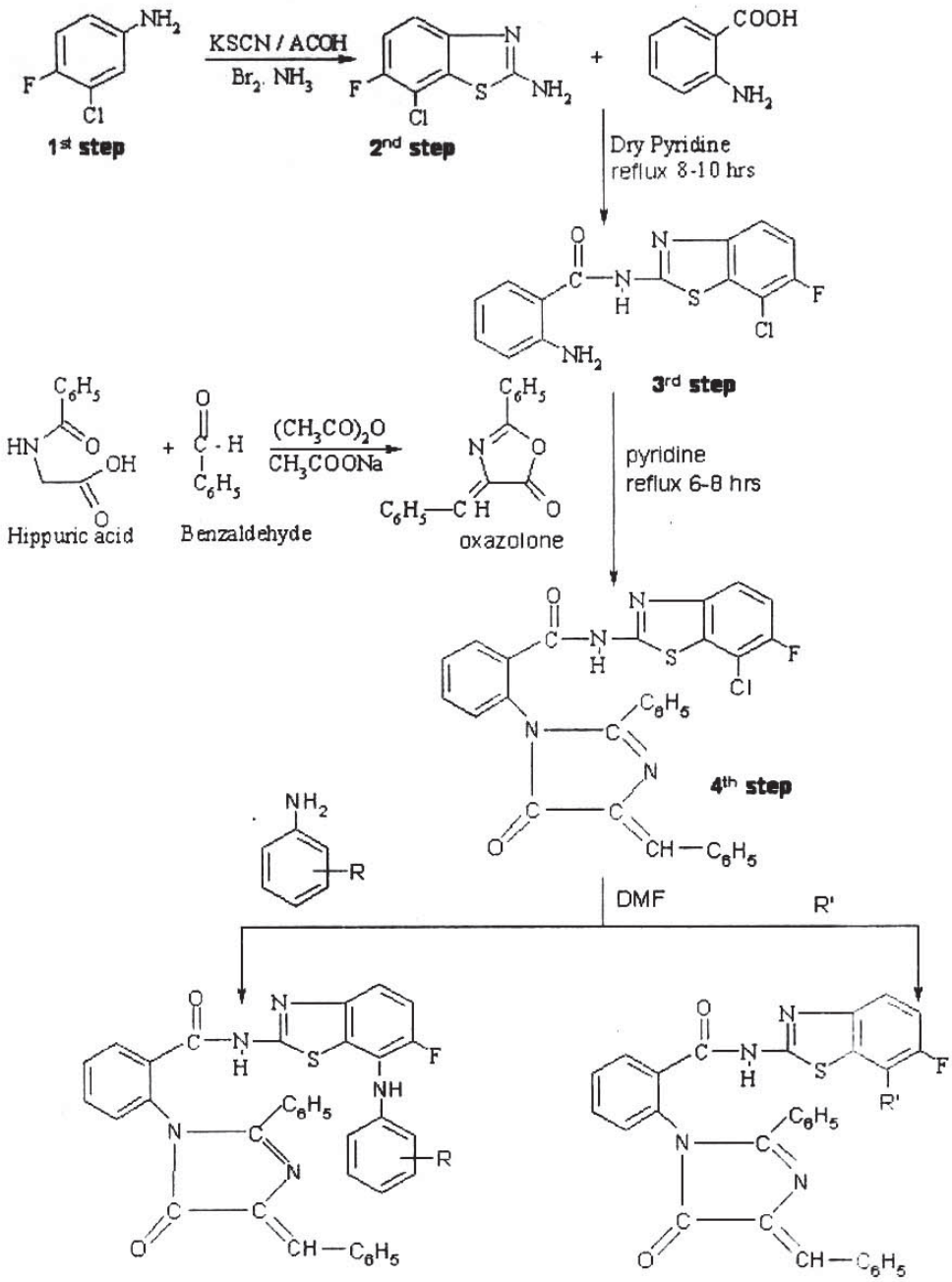
Scheme 1



R = o, m, p- nitro aniline (P_1 - P_3)
= o, m, p- chloro aniline (P_4 – P_6)
= PABA (P_8)
= Diphenyl (P_{13})
= Dimethyl (P_{14})
= 2,3-dichloro (P_{15})
= 3,4-dichloro (P_{16})
= Fluoro chloro (P_{18})
= O- toludine (P_{11})
= P- toludine (P_{12})
= O- anisidine(P_{17})

R' = morpholine, (P_7)
= piperazine (P_9)
=N-methyl piperazine(P_{10})

Scheme 1 Contn.



R = o, m, p- nitro aniline ($OX_1 - 0X_3$)
= o, m, p- chloro aniline ($0X_4 - 0X_6$)
= PABA (OX_8)
= 2,3-dichloro (OX_{12})
= O-anisidine (OX_{10})
= P-anisidine (OX_{11})

R' = morpholine, (OX_7)
= piperazine (OX_9)

Scheme 1

Table 4: Antibacterial activity

S. No.	Name of the compounds	Mean zone of inhibition (in mm)*			
		Staphylococcus aureus		*Escherichia coli*	
		50mg	100mg	50mg	100mg
1.	Procaine penicillin	20	24	-	-
2.	Streptomycin	-	-	18	24
3.	P_1	12	14	12	13
4.	P_2	10	13	10	12
5.	P_3	13	15	11	12
6.	P_4	12	15	9	11
7.	P_5	10	11	9	12
8.	P_6	11	14	12	11
9.	P_7	9	13	9	11
10.	P_8	10	14	12	12
11.	P_9	10	10	10	12
12.	P_{10}	10	12	9	10
13.	P_{11}	11	13	11	13
14.	P_{12}	11	14	9	12
15.	P_{13}	12	13	10	12
16.	P_{14}	11	15	9	11
17.	P_{15}	9	13	11	10
18.	P_{16}	10	15	9	12
19.	P_{17}	12	13	9	10
20.	P_{18}	12	14	9	11
21.	OX_1	10	14	11	12
22.	OX_2	12	14	10	12
23.	OX_3	13	15	11	11
24.	OX_4	13	14	9	10
25.	OX_5	10	11	10	12
26.	OX_6	12	12	10	11
27.	OX_7	12	14	9	10
28.	OX_8	10	13	11	11
29.	OX_9	9	12	9	11
30.	OX_{10}	9	10	11	12
31.	OX_{11}	10	13	12	13
32.	OX_{12}	11	14	9	12

Table 4: Antibacterial activity

S. No.	Name of the compounds	Mean zone of inhibition (in mm)*			
		Staphylococcus aureus		*Escherichia coli*	
		50mg	100mg	50mg	100mg
1.	Procaine penicillin	19	23	-	-
2.	Streptomycin	-	-	18	21
3.	P_1	10	13	10	12
4.	P_2	11	14	11	14
5.	P_3	11	13	9	11
6.	P_4	9	12	9	10
7.	P_5	10	14	10	10
8.	P_6	12	14	10	12
9.	P_7	12	15	12	13
10.	P_8	13	16	11	13
11.	P_9	12	13	9	11
12.	P_{10}	10	14	11	11
13.	P_{11}	10	15	11	13
14.	P_{12}	12	13	10	11
15.	P_{13}	10	12	11	13
16.	P_{14}	10	13	9	12
17.	P_{15}	10	13	10	12
18.	P_{16}	9	11	11	12
19.	P_{17}	10	12	10	13
20.	P_{18}	11	12	9	10
21.	OX_1	12	13	10	12
22.	OX_2	10	12	10	13
23.	OX_3	10	13	9	12
24.	OX_4	12	13	10	10
25.	OX_5	9	10	10	12
26.	OX_6	10	13	11	12
27.	OX_7	10	14	9	11
28.	OX_8	11	14	11	13
29.	OX_9	12	15	12	14
30.	OX_{10}	9	12	9	12
31.	OX_{11}	10	14	9	11
32.	OX_{12}	11	14	12	13

Of various substituted aromatic amines, PABA, morpholine amine, piperazine, N-methyl piperazine, O-toludine, P-toludine, O-anisidine, dipphenyl amine, dimethyl amine, 2,3-dichloro aniline,3,4-dichloro aniline and fluro chloro aniline refluxed for 2hrs. In the present of DMF. Then mixture was cooled and poured in the crushed ice. The solid separated was filtered off, dried and recrystalized from benzene, acetone and absolute alcohol.

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

A mixture of 27g (26ml, 0.25ml) or redistilled benzaldeyde, 45g (0.25 mol) of benzoylglycine 77g (71.5ml, 0.75mol) of acetic anhydride and 20.5 gm (0.25mol) of anhydrous sodium acetate was placed in a 500ml conical flask and heated on an eletric hot plate with constant shaking. As soon as the mixture has liquified completely, the flask was transferred to water bath

Table 5: Antifungal activity

S. No.	Name of the compounds	Mean zone of inhibition (in mm)*			
		Candida albicans		*Aspergillus niger*	
		50mg	100mg	50mg	100mg
1.	Streptomycin	19	24	19	23
2.	P_1	11	13	10	12
3.	P_2	09	11	10	13
4.	P_3	10	13	09	11
5.	P_4	10	15	11	14
6.	P_5	11	13	10	13
7.	P_6	10	14	09	13
8.	P_7	12	14	09	13
9.	P_8	9	13	10	13
10.	P_9	10	13	11	14
11.	P_{10}	12	13	11	13
12.	P_{11}	11	13	12	14
13.	P_{12}	10	14	10	12
14.	P_{13}	10	13	10	13
15.	P_{14}	09	11	09	12
16.	P_{15}	12	14	09	11
17.	P_{16}	10	14	12	15
18.	P_{17}	09	14	13	15
19.	P_{18}	09	11	12	14
20.	OX_1	09	12	10	13
21.	OX_2	10	13	11	13
22.	OX_3	10	14	10	12
23.	OX_4	11	14	09	12
24.	OX_5	10	13	12	15
25.	OX_6	10	12	12	14
26.	OX_7	10	11	10	13
27.	OX_8	09	11	9	10
28.	OX_9	10	14	10	12
29.	OX_{10}	09	11	09	11
30.	OX_{11}	09	12	09	12
31.	OX_{12}	11	15	09	12

and refluxed for 2hrs. 100ml of ethanol was added slowly to the contents of the flask. The mixture was allowed to stand overnight. The crystalline product obtained was filtered by suction. It was washed with two 25ml portions of boiling water and dried at 100°C.

The yield of pure oxazolone is 40g (64%) m.p. 165-166°C. Recrystallisation from benzene raised the m.p. to 167-168°C

Synthesis of 2-[(4Z)-4-benylidine-2-phenyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl]-N-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)benzamide

2-amino-N(2-benzothiazolyl-6-fluoro-7-chloro) benzamide (0.01mol, 3.215gm) and oxazolone (0.01mol, 2.49gm) was refluxed in pyridne was distilled off and resulting mass poured into crushed ice and neutralized from dilute hydrochloric acid. The product was recrystalised using ethanol.

Synthesis of 2-[(4Z)-4-benylidine-2-phenyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl]-N-(7-substituted-6-fluoro-1,3,-benzothiazol-2-yl)benzamide

0.005 mol of 2-[(4Z)-4-benylidine-2-phenyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl]-N-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)benzamide was treated with eqimolar quantity (0.005mol) of various substituted amines, morpholine, piperazine, PABA, O-anisidine, P-anisidine ad 2,3-dichloro aniline refluxed for 2 hrs in the presence of DMF. Then the mixture was cooled and pured into the crushed ice. Solid separated was filtered off, dried and recrystalised from benzene, acetone and absolute alcohol.

RESULTS AND DISCUSSION

Anti-bacterial activity

Synthesis and Pharmacological screening of 3-{7-substituted6-fluoro-1,3-benzothiazol -2-yl}-1-[(4-methyl phenyl) sulfonyl]-2-thioxo-2,3-dihydroquinazolin-4(1H)-one and 2-[(4Z)-4-benzylidine-2-phenyl-5-oxo-4,5-dihydro-1H-imidazole-1-yl]-N-(7-substituted-6-fluror-1,3-benzothiaozl-2-yl) benzamide were tested for the antibacterial activity against following bacteri;

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

The test compounds P_2,P_3 and OX_3 showed moderate antibacterial activity against *S.aureus* (gram +ve) compare to standard drug Procaine Penicillin.

Compounds P_1,P_6 and OX_{11} showed promising antibacterial activity against, *E. coli* (gram-ve) compared to standard drugs and streptomycin.

Compounds P_6,P_7, P_8, P_{12} and OX_{12} showed promising antibacterial activity against, gram +ve (*Streptococci*) at both lower and higher concentration (50µ/ml).

Compound P_7 and OX_2, OX_{12} showed moderate activity against gm -ve (*Pseudomonas*) at both lower and higher concentration compare to standard drug Streptomycin.

Anti-fungal activity

Synthesis and Pharmacological screening of 3-{7-substituted6-fluoro-1,3-benzothiazol -2-yl}-1-[(4-methyl phenyl) sulfonyl]-2-thioxo-2,3-dihydroquinazolin-4(1H)-one and 2-[(4Z)-4-benzylidine-2-phenyl-5-oxo-4,5-dihydro-1H-imidazole-1-yl]-N-(7-substituted-6-fluror-1,3-benzothiaozl-2-yl) benzamide were tested for antifungal activity against *Candida albicans* and *Aspergillus niger.*

Among the compounds tested, P_4, P_7 and OX_3, OX_4, OX_9, OX_{15} showed good activity against *Candida albicans* at both concentration compare to standard Griseoflavin.

P_{11}, P_{16}, P_{17} and OX_5, OX_6 showed significant activity agasint *Aspergillus niger* compare to standard Griseoflavin.

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