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SYNTHESIS OF SOME FLUORO SUBSTITUTED SULPHONAMIDE BENZOTHIAZOLE COMPRISING THIAZOLE FOR ANTI-MICROBIAL SCREENING.

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ABSTRACT

Some novel 3-[6'Fluoro-7'-substituted-(1',3')benzothiazol-2'-yl]p-benzene sulphonamido-2-o-nitrobenzene (1,3) thiazolidin-4-one have been synthesized and screened for anti-microbial activity. Literature revealed that vast majority of benzothiazoles and sulphonamide compounds are known to possess pharmacologically proven therapeutic potentials. The wide range of biodynamic properties shown by fluorobenzenes 2-substituted benzothiazoles prompted us to synthesize novel compounds in hope of getting potent biodynamic agents. In the present study benzothiazole were prepared from 3-chloro-4fluoro aniline. The ortho, meta, para, nitroanilines, ortho, meta, para, chloroanilines, morpholine, piperazine, PABA, dimethyl amine, diphenyl amine derivatives of fluorobenzothiazole comprising Sulfonamido thiazole, were chosen for synthesis and pharmacological evaluation. The compounds were characterized by means of physical constants, solubility tests, TLC and by UV,IR spectral studies. This is followed by biological and pharmacological evaluation especially anti-microbial activities.

KEYWORDS

Fluorobenzothiazole, Thiazolidinone, Sulfonamido, anti-microbial activity.

INTRODUCTION

The sulfonamide[1-5] drugs were the first effective chemotherapeutic agents to be employed systemically for the prevention and cure of bacterial infection in human beings. The introduction of trimethoprim and sulphamethoxazole has resulted in increased use of sulfonamide for the treatment of specific microbial infection. The wide range of biodynamic properties shown by fluorobenzenes 2-substituted benzothiazoles[6-10]. Benzothiazoles with sulphonyl group and pyrazolone etc were reported to posses various pharmacological activity of clinical importance. However, little is known about substituted benzothiazoles having sulphonamido moiety and thiazole. Therefore in present work we have sulphonamido group

incorporated with benzothiazole ring with thiazolone group to get good biodynamic leads. Thiazoles are well known to have number of biological activities[11-16]. This includes anti-inflammatory, anti-bacterial, anti-neoplastic and anti-allergic activity. Therefore in present work we have prepared thiazoles incorporated with substituted Benzothiazole ring. This is followed by biological and pharmacological evaluation especially anti-microbial activities[17-20].

MATERIALS AND METHODS

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. The anti-microbial activity was tested against Gram positive and Gram negative bacteria and antifungal activity against various fungal strains. Synthesized compounds were screened for their in vitro antimicrobial activity against the standard strains S. aureus, B. subtilis, E. coli, and the yeasts C. albicans, A. flavus and A. niger . To evaluate the activity of synthesized compounds against bacteria minimum inhibitory concentrations (MICs) were determined. Procaine penicillin and Streptomycin (the reference antibacterial drug) and Griseofulvin (the reference antifungal drug) were used as positive control. The results are described in the table no. 3.

EXPERIMENTAL

Condensation of 2-amino-6-fluoro-7-chloro-(1,3)benzothiazole and p-acetamido benzene sulphonyl chloride (2)

2-amino-6-fluoro-7-chloro (1,3) benzothiazole (0.013 mol) was taken in pyridine (4 ml) and acetic anhydride (20 ml), to this p-acetamido benzene sulphonyl chloride (0.01 mol) were added and the mixture was kept in water bath for 2 hrs. The reaction mixture then poured in to 20 ml of ice cold water. The solid obtained was filtered and recrystalised from dil ethanol (80%) to get pure compound 6-fluoro-7-chloro-2-(p-acetamido benzene sulphonamido) (1,3)-benzothiazole.

Synthesis of 6-fluoro-7-chloro-2-(p-amino benzene sulphonamido) (1,3) benzothiazole (3)

The derivatives obtained were then hydrolyzed by boiling them in 50 ml of 80% acetic acid for 4 to 5 hrs and the contents were poured onto crushed ice. The obtained hydrolyzed derivatives were filtered at suction and dried.

Synthesis of 6-fluoro-7-chloro-2-[p-(m-nitro benzylidine) amino benzene sulphonamido] (1,3) benzothiazole (4)

0.01 mol of 6-fluoro-7-chloro-2-(p-amino benzene sulphonamido) (1,3) with 0.015 mol solution of m-nitro benzaldehyde, added 20 ml ethanol and 3-4 drops of HCl and refluxed for 2-3 Hrs. Solution cooled and poured into crushed ice. Recrystalised with benzene and ethanol.

Synthesis of 3-[6'Fluoro-7'-Chloro-(1',3')benzothiazol-2'-yl]p-benzene sulphonamido-2-m-nitrobenzene (1,3) thiazolidin-4-one (5)

A mixture of Schiff's base (0.01 mol) and 0.025 mol of 2-thioglycolic acid heated on oil-bath at 115º-120 º c for 12 Hrs. After reflux cool and triturated with 10% sodium bicarbonate solution. Crystallized from water.

Synthesis of 3-[6'Fluoro-7'-substituted-(1',3')benzothiazol-2'-yl]p-benzene sulphonamido-2-m-nitrobenzene (1,3) thiazolidin-4-one (A_1-A_{12})

3-[6'Fluoro-7'-Chloro-(1',3')benzothiazol-2'-yl]p-benzene sulphonamido-2-m-nitrobenzene (1,3) thiazolidin-4-one were treated with equimolar quantities of various aromatic amines, refluxed for 2 hours in presence of DMF, recrystalised from alcohol and benzene.

Table No. 1
Analytical Data of the Compounds (A_1-A_{12})

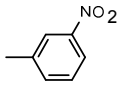
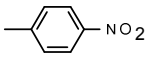
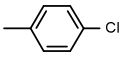
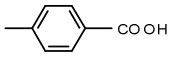
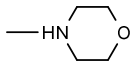
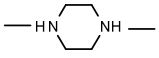
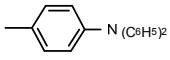
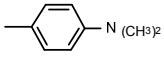
Compds	R	M.P (ºC)	Yield (%)	Molecular Formula	Molecular Wt.	Elemental Analysis Data (Calculated in %)		
						C	H	N
A1		180	72	C28H18N6O7S3F	665	50.52	2.70	12.63
A2		132	78	C28H18N6O7S3F	665	50.52	2.70	12.63
A3		97	83	C28H18N6O7S3F	665	50.52	2.70	12.63
A4		170	88	C28H18N6O5S3FCl	655	51.29	2.74	12.82
A5		125	70	C28H18N6O5S3FCl	655	51.29	2.74	12.82
A6		82	80	C28H18N6O5S3FCl	655	51.29	2.74	12.82
A7		90	89	C28H19N5O5S3F	620	54.19	3.06	11.29
A8		80	72	C29H19N5O7S3F	664	52.40	2.86	10.54
A9		145	67	C26H17N5O6S3F	610	51.14	2.78	11.47
A10		110	72	C26H18N6O5S3F	609	51.23	2.95	13.79
A11		280	68	C34H23N5O5S3F	696	58.62	3.30	10.05
A12		101	74	C24H19N5O5S3F	572	50.34	3.32	12.23

Table2.
IR spectral assignments of synthesized compounds (A_1-A_{12})

Compounds	*Characteristic absorption bonds (in cm^{-1})*									
	Ar-NH_2 Str.	S=O Str.	Aro.C=C Str.	C-F Str.	C-Cl Str.	NO_2	SO_2-NH Str.	3º-Nitrogen	CH_3 Str.	*C-S-C*
A1	3385	1815	1450	1190	---	720	1380	3080	1300	*1193*
A2	3400	1830	1435	1200	---	725	1385	3100	1295	*1280*
A3	3390	1830	1440	1210	---	718	1390	3090	1285	*1195*
A4	3128	1825	1607	1282	1197	---	1356	3369	1290	*1182*
A5	3228	1820	1555,1699	1296	1195	---	1385	3315	1295	*1184*
A6	3201	1825	1512,1690	1397	1172	---	1390	3452	1300	*1297*
A7	3200	1820	1550	1195	---	---	1380	3110	1310	*1184*
A8	3370	1825	1600	1249	---	---	1380	3100	1295	*1170*
A9	3350	1835	1597	1295	---	---	1395	3095	1300	*1280*
A10	3400	1820	1540	1195	---	---	1385	3080	1295	*1170*
A11	3101	1823	1616	1249	---	---	1390	3406	1290	*1170*
A12	*3395*	*1810*	*1445*	*1200*	---	---	*1385*	*3085*	*1300*	*1197*

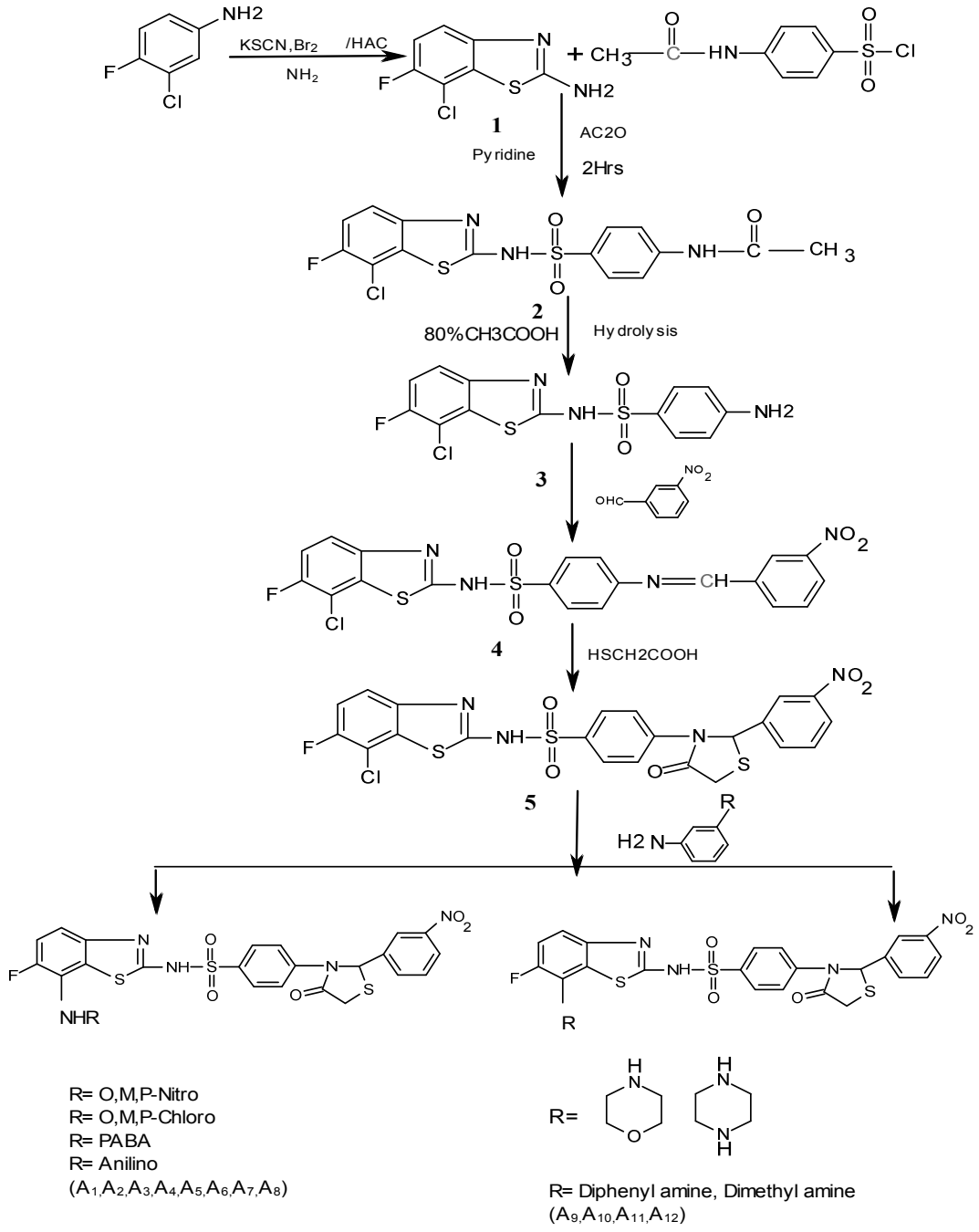
Screening for Anti-microbial Activity (In-vitro method)

The antibacterial activity was tested against various Gram positive and Gram negative bacteria and anti fungal activity against various fungal strains. Synthesized compounds were screened for their in vitro antimicrobial activity against the standard strains: S. aureus (ATCC 25923), B. subtilis (ATCC 6633), E. coli (ATCC 25922) and the yeasts C. albicans (ATCC 10231), A. flavus and A. niger (AIIMS). To evaluate the activity of synthesized compounds against bacteria minimum inhibitory concentrations (MICs) were determined. Procaine penicillin and Streptomycin (the reference antibacterial drug) and Griseofulvin (the reference antifungal drug) were used as standard. The results are de-scribed in the table 3.

Table3
Anti-microbial activity of synthesized compounds (A_1-A_{12})

Compounds	Mean Zone of Inhibition (in mm)					
	Bacteria			Fungi		
	S.aureus	B.subtillis	E.coli	C.albicans	A.flavus	A.niger
Procaine penicillin	20	24	25	---	---	---
Streptomycin	17	23	23	---	---	---
Griseofulvin	---	---	---	20	18	24
A1	15	16	16	14	15	11
A2	13	17	14	12	13	14
A3	12	18	19	13	16	16
A4	16	17	14	10	13	13
A5	11	16	13	10	15	12
A6	09	16	13	10	12	18
A7	18	20	14	11	18	23
A8	19	21	13	11	17	17
A9	18	19	20	12	15	17
A10	10	18	14	11	14	16
A11	14	21	17	12	18	15
A12	10	22	14	13	16	22

SCHEME


KSCN,Br2 /HAC
NH2
1
Pyridine
AC2O
2Hrs
2
80%CH3COOH
Hydrolysis
3
4
HSCH2COOH
5
H2 N
NHR
R
R= O,M,P-Nitro
R= O,M,P-Chloro
R= PABA
R= Anilino
(A1,A2,A3,A4,A5,A6,A7,A8)
R=
R= Diphenyl amine, Dimethyl amine
(A9,A10,A11,A12)

RESULT AND DISCUSSION

In present investigation synthesis of several novel 3-[6'Fluoro-7'-substituted-(1',3') benzothiazol-2'-yl] p-benzene sulphonamido-2-substituted (1,3) thiazolidin-4-one (**A_1-A_{12}**) is reported. All the synthesized compounds exhibited good to moderate anti-microbial activity. In conclusion, this class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress.

REFERENCES

1. Bhusari K.P., Khedekar P.B. Indian J.Heterocycl Chem., 9: 213-16, (2000).
2. Pattan S.R., Narendra S.N., Jayashri Indian J Heterocycl Chem., 11: 333-34, (2002).
3. Bhusare S.R., Pawar R.P., Vibhute Y.B. Indian J.Heterocycl Chem., 11:78-80,(2001).
4. Chandra Shekar B., Roy K. De AU. Indian J.Heterocycl Chem., 10:237-38, (2001).
5. Bahar Ahmed., Siddiqui A.A. Indian J. Heterocycl Chem., 8:129-32, (1998).
6. Shieke V.G., Bodade A.S. Chem Abstr, 11423845r, (1991).
7. Sidoova E. Chem Abstr, 106: 32907z, (1987).
8. Mouysset, Genevieve, Desagnil Sannes Gilbet., Younus Saloma, Chem Abstr; 104: 122136 s, (1991).
9. Chernykh V.P., Sidorenko O.F. Chem Abstr, 98: 89233 x, (1983).
10. Costakes E, Tsatsas G. Chem Abstr, 90: 203935q, (1979).
11. Newbould B.B., Br.J.Pharmacol, 24:632, (1965).
12. Patel D.R., Satpanthi P.S., Patel P.B., Trivedi J.J., Inst. Chem.,48:305, (1976).
13. Fujikawa F., Hirai K., Hirayama T., Yoshikawa T., Nakagawa T., Naito M., Tsukama S., Kamada M., Ohta Y., Zasshi Y., Chem. Abstr.,72:3420j, (1970).
14. Mcgruire W.C., O'Neil R.C., Brody G., J. Parasitol.,52:528, (1966).
15. Akerblom E.B., J. Med. Chem., 17:609, (1974).
16. Rao R.P., Curr. Sci.,35:541, (1966).
17. Jayachandran E., Naragund L.V.G., Shivkumar B., Bhatia Kamal, Ori J Chem 19(1): 139-142, (2003).
18. Gurupadaiah B.M., Jayachandran E., Shivakumar B., Nagappa A.N., Nargund L.V.G. Ind J Heterocycl Chem, 7: 213, (1998).
19. Murthy V.S., Nagappa A.N., Nargund L.V.G., Ind J Heterocyclic Chem, 8: 23, (1998).
20. Biological assay, Indian Pharmacopoeia, Govt of India Publisher, 2:A-88, (1996).