International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.2, No.2, pp 1209-1213, April-June 2010

2-Substituted Hydrazino-6-Fluoro-1,3-Benzothiazole: Synthesis and Characterization of new Novel AntimicrobiaL Agents

Priyanka Yadav[1]*, Deepa Chauhan[2], Neeraj K Sharma[1], Sachin Singhal[1]

[1]Department of Pharmacy, Teerthanker Maheveer University, Delhi Road, Bagarpur, Moradabad-244001, U.P.,India

[2]I.T.S. Paramedical (pharmacy) college, Muradnagar, Ghaziabad, U.P., India

*Corres author: priya_its@rediffmail.com
Phone: +919451011349*

ABSTRACT: A series of novel 2-substituted hydrazino-6-fluoro-1,3-benzothiazole derivatives were synthesized by synthesizing the 2-hydrazino-6-fluorobenzothiazole and refluxing of this with different substituted acetophenones. The synthesized compounds were evaluated for their possible antimicrobial activity. The structures of few representative compounds were elucidated by IR and NMR. For present work efficacy of compounds was determined against *S.aureus*, *S.epidermidis*, *E. coli*, *P. aeruginosa* for their microbiological activities.
KEYWORDS: Fluorobenzothiazole, Antimicrobial, Acetophenones

INTRODUCTION

The development of new and different antimicrobial agents has been a very important step and much of the research program efforts are directed toward to the design of new and available drugs, because of the unsatisfactory status of treatments of microorganisms, drug side effects, and the acquisition by the infecting organisms of resistance to the available drugs[1].

A review of the literature revealed that many effective antimicrobial agents have a heterocyclic system in their molecule[2]. Recent observation suggests that several analogs of benzimidazole ring system such as benzoxazole and benzothiazole derivatives also indicate potential activity with lower toxicity in the antimicrobial therapeutic approach in man[3-7].

Benzothiazole derivatives have attracted a great deal of interest due to their biological and commercial importance. They have been found to have antiviral[8], antibacterial[9], antimicrobial[10], and fungicidal activities[11]. They are also useful as antiallergic[12], antidiabetic[13], antitumor[14], anti-inflammatory[15], anthelmintic[16], and anti HIV agents[17]. The present study is aiming at the synthesis of heterocyclic systems containing the substituted benzothiazole moiety that would be expected to have antimicrobial activity.

In the present study 6-fluoro-1, 3-benzothiazol-2-Amine was synthesized from 4-fluoro aniline. This has been condensed with hydrazine hydrate to form 2-hydrazino-6-fluorobenzothiazole. Then the derivatives (D1-D4) were synthesized by condensation of 2-hydrazino-6-fluorobenzothiazole with different substituted acetophenones. Chromatographic analysis (TLC) of these compounds, used to check the completion of reaction. The structures of the compounds were stabilized on the basis of their IR and ^{1}H-NMR data. In IR spectra some significant stretching bands due to C=N between a range of 1600-1750 cm^{-1}, N-H at 3400-3100 cm^{-1}, C-F~ 1100 cm^{-1}, C-H Ar~3080 cm^{-1}, C-N~1281 cm^{-1}, thiazole~1441 cm^{-1}were found.

In the ^{1}H-NMR spectra, the signal due to NH proton were observed at 9.0-11.0 ppm as broad peak,

while the signals due to aromatic protons were observed at 6.5-7.5ppm.

All the synthesized compounds were screened for their antimicrobial activity using the Ampicillin as reference standard.

EXPERIMENTAL

All melting points were determined in open capillaries and are uncorrected. The progress of the reaction and the purity of compounds were checked by TLC on percolated silica gel plates using chloroform-ethyl acetate mixture (7:3). Detection of compounds was made by treatment with iodine vapours.

IR spectra of compounds were recorded on FT/IR 4100 typeA spectrophotometer and HNMR spectra (DMSO) on Bruker FTAC spectrometer with TMS as internal standard.

6-FLUORO-1, 3-BENZOTHIAZOL-2-AMINE (S1)

Glacial acetic acid (20 ml) was cooled to 5^0C and added to a mixture of potassium thiocyanate (8 gm) and 4-substituted aniline (0.01 mol). To this, bromine solution was added (1.6 ml bromine in 6 ml glacial acetic acid) drop wise during the stirring. The solution was stirred for 2 hrs. at 0-10^0C, then at room temperature for 10 hrs. and then allowed to stand for overnight at room temperature. To this 10 ml of water was added and the mixture was heated on water bath and filtered while hot. Treated the filtrate with glacial acetic acid 10 ml and heated again on water bath and filtered. Combined and cooled the hot filtrate and neutralized with conc. ammonia to pH 6. The resulting ppt. was dried and crystallized with absolute ethanol.

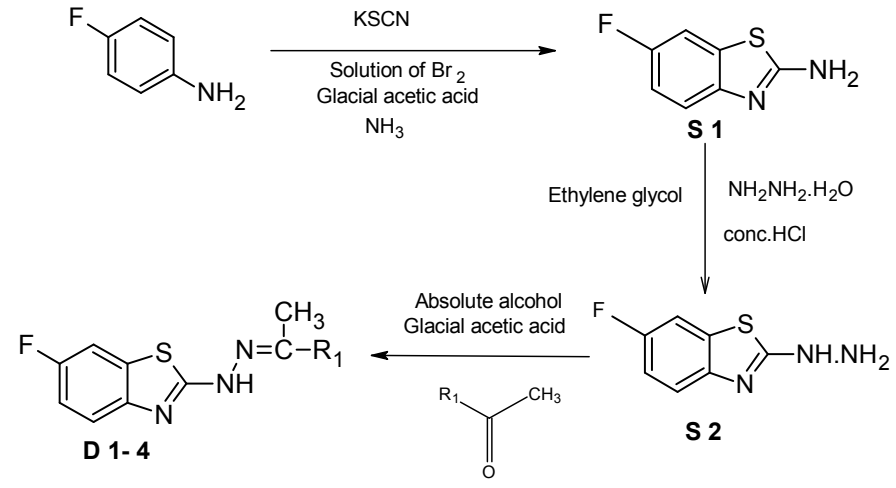
2-HYDRAZINO-6-FLUOROBENZOTHIAZOLE (S2)

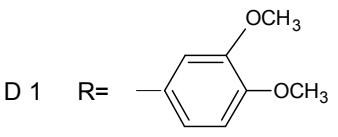
Conc. HCl (6 ml) was added drop wise with stirring to hydrazine hydrate (6 ml) at 5-10^0C. To it ethylene glycol (24 ml) and Benzothiazolamine (0.03 mol) were added and refluxed for 3 hours. On cooling solid separated out which was filtered, washed with water and recrystallized from ethanol.

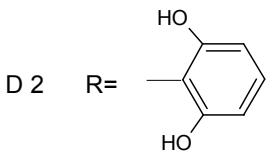
GENERAL PROCEDURE FOR SYNTHESIS OF DERIVATIVES (D1-D4)

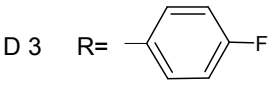
2-hydrazino-6-fluorobenzothiazole (1.5 mmol) and appropriate substituted acetophenone (2.2 mmol) and glacial acetic acid (2-3 drops) were taken in absolute ethanol (20 ml) and refluxed on water bath for 10-14 hours, till a different spot on TLC may appear. On cooling solid separated out which was filtered, washed with little water and recrystallized from ethanol. The characterization data of synthesized compounds (D1-D4) are summarized in table no. 1.

REACTION SCHEME









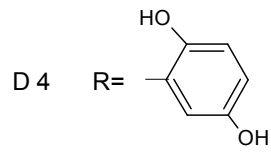


Table No. 1- Characterization data of compounds

Compd	M. P. (^{0}C)	Yield (%)	Mol. formula	Mol. Wt.	IR (cm^{-1})	^{1}H-NMR (δ)
S 1	205	90	$C_7H_5N_2SF$	168	3452 (1^0 N-H), 3080 & 813 (C-H Ar), 1281 (C-N), 1630 (C=N), 1529 (C=CAr), 1441 (thiazole), 712 (C-F)	6.9 (S, 2H, NH), 7.0-7.5 (m, 3H, Ar-H)
S 2	192	91	$C_7H_6N_3SF$	183	3200 & 1595(1^0 & 2^0 N-H), 3060 & 857 (C-H Ar), 1262 (C-N), 1645 (C=N), 1550 (C=C Ar), 1451 (thiazole), 1046 (C-F)	9.0 (S, NH).7.0-7.5(S, Ar- H)
D 1	210	94	$C_{17}H_{16}N_3O_2SF$	345	3080 AND 1519 (1^0 and 2^0NH), 2841 AND 802 (C-H Ar), 1272 (C-N), 1605 (C=N), 1519 (C=C Ar), 1022 (C-F), (1253) R-OCH_3, (1340) C-CH_3	Ar-H(6.9-7.7), CH_3(2.3-3.3), OCH_3 (3.7), 11.5 (1S, 1H, NH)
D 2	197	92	$C_{15}H_{12}N_3O_2SF$	317	3461 AND 1566 (1^0 and 2^0NH), 825 (C-H Ar), 1222 (C-N), 1613 (C=N), 1454 (C=C Ar), 1042 (C-F),1326 (C-OH), 1368 (C-OH), 1253 (C-CH_3)	Ar-H (7.0-7.6),CH_3 (2.4-3.3), OCH_3 (3.3), (1S,1H,NH) 11.7
D 3	200	90	$C_{15}H_{11}N_3SF_2$	303	3346 AND 1509 (1^0 and 2^0NH), 832 (C-H Ar), 1232 (C-N), 1573 (C=N), 1459 (C=C Ar), 1342 (C-CH_3), 1459 (Thiazole), 1071 (C-F), 1157 (C-F)	(1S,3H,CH_3) 2.3-3.3, (1S,1H,NH) 11.7, 7.1-7.8 (Ar-H)
D 4	198	94	$C_{15}H_{12}N_3O_2SF$	317	3267 AND 1567 (1^0 and 2^0NH), 842 (C-H Ar), 1239 (C-N), 1517 (C=N), 1464 (Thiazole), 1106 (C-F), 1376 (Alkane), 1567 (C=C Ar), 1288 (C-OH) , 1348 (C-OH)	Ar-OH (2.4-3.3), Ar-H (6.8-7.9), CH_3 (3.3), 1S,2H,NH (10.1), 1S, 2H, NH (10.3)

BIOLOGICAL ACTIVITY

2-substituted hydrazino-6-fluoro-1,3-benzothiazole derivatives(D1-D4) were evaluated *in-vitro* for antimicrobial activity against *S. aureus, P. aeruginosa, S. epidermidis and E. coli.* using DMF as solvent by cup-plate method[18]. Preparation of nutrient broth, sub-cultures, base layer medium, agar medium and peptone water was done as per the standard procedure. 5 mg of each test compound was dissolved in 5 ml of dimethylformamide (1000 µg/ml), which was used as sample solution.

The cups were made by scooping out agar medium in a Petri dish, which were previously inoculated with the microorganisms. The solution of each test compound (0.1 ml) was added in the cups and petri dishes were incubated at 37^{0}C for 24 hrs. Ampicillin was used as reference drug and DMF as control. Zone of inhibition was measured in mm.

The comparable zone of inhibition and antimicrobial activities with known chosen drug are reported in table no. 2 and 3. The graph of comparative study of the compounds against all strains is shown in fig.no.1.

Table No. 2: Zone of inhibition of compounds

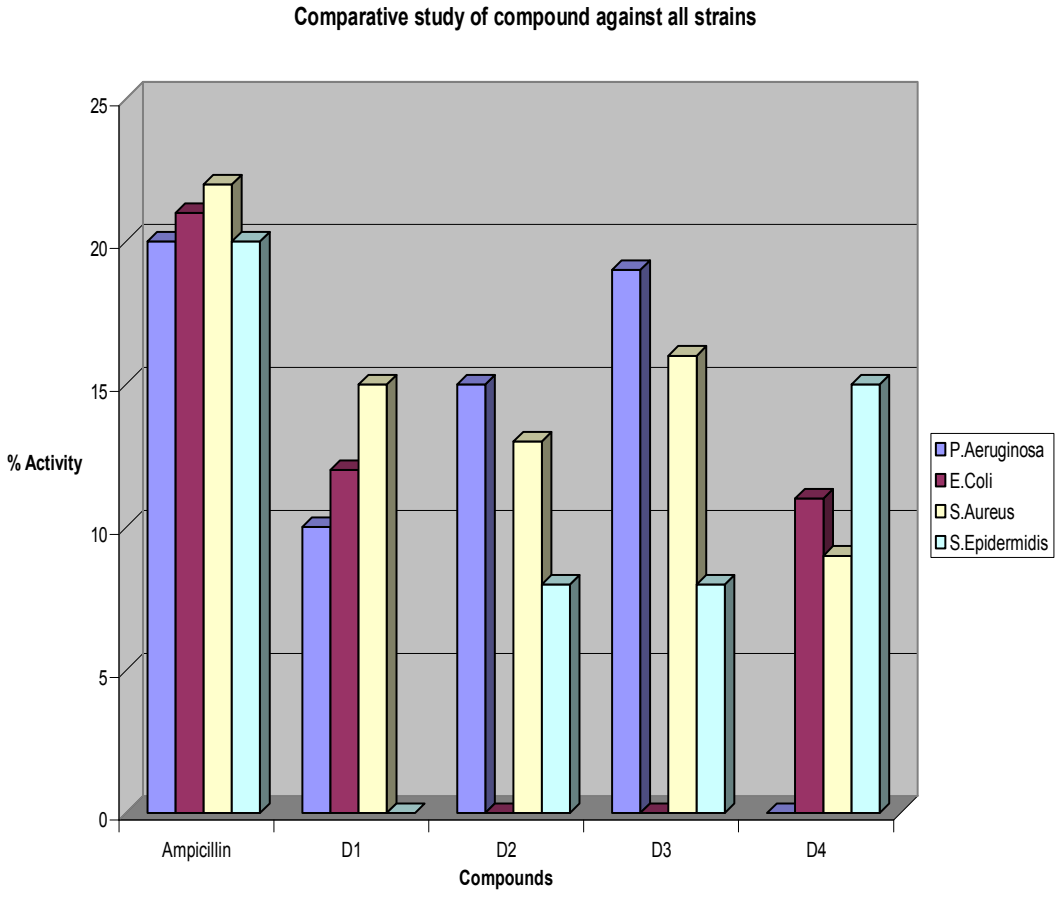
Compounds	Anti-bacterial activity			
	S.aureus	*S.epidermidis*	*P.aeruginosa*	*Ecoli*
Ampicillin(std)	+++	+++	+++	+++
D 1	++	-	+	++
D 4	+	++	-	+
D 2	++	+	++	-
D 3	++	+	+++	-

+++ Diameter of zone of inhibition between 17-22 mm.
++ Diameter of zone of inhibition between 12-16 mm.
+ Diameter of zone of inhibition between 8-11 mm.
- No zone of inhibition observed

Table No.3- Antimicrobial activity screening

Compounds	Antimicrobial activity			
	S.aureus	*S.epidermidis*	*P.aeruginosa*	*Ecoli*
Ampicillin(std)	22 mm	20 mm	20 mm	21 mm
D 1	15 mm (68%)	-	10 mm (50%)	12 mm (57%)
D 4	9 mm(41%)	15mm(68%)	-	11mm(50%)
D 2	13 mm (59%)	8 mm (40%)	15 mm (75%)	-
D 3	16 mm (72%)	8 mm (40%)	19 mm (95%)	-

Fig. 1 Comparative study of compounds against all strains



RESULTS AND DISCUSSION

All the 6-fluoro-1,3-benzothiazole derivatives were obtained in good yield and has the melting points in the range of 192-210 ^{0}C. In IR spectra some significant stretching bands due to C=N between a range of 1600-1750 cm^{-1}, N-H~3400-3100 cm^{-1}, C-F~ 1100 cm^{-1}, C-H Ar~3080 cm^{-1}, C-N~1281 cm^{-1}, thiazole~1441 cm^{-1} were observed. In the ^{1}H-NMR spectra, the signal due to NH proton were observed at 9.0-11.0 ppm as broad peak, while the signals due to aromatic protons were observed at 6.5-7.5ppm.

All the newly synthesized compounds showed good antimicrobial activity against *S.aureus* (D1-D4), *S.epidermidis* (D2-D4), *P.aeruginosa* (D1-D3) *and E.coli* (D1 & D4).

The results show that the compound D3 has better antimicrobial activity against *Staphylococcus aureus* than other compounds. Compound D4 showed better activity against *Staphylococcus epidermidis* and Compound D2 showed better activity against *Pseudomonas aeruginosa* whereas compound D1 shows potent activity against *Escherichia coli*.

REFERENCES

1. Javetz E., Melnick J.L., Adelberg E.A., *In: Review of Medical Microbiology*, 1984, Lange, California, 122.
2. Daidone G., Maggio B., Schillaci D., *Pharmazie,,1990,45,441.*
3. Geigy Chemical Corporation, US Patent Office, 1971, 3, 586, 670.
4. Brown D.J., Dunlap W.C., Grigg G.W., Danckwerts L., *Aust J Chem,* 1978, 31, 447.
5. Philips M.K., Kell D.B., *FEMS Microbiology Letters,* 1981, 11, 111.
6. Hauwitz R.D., Angel R.G., Jacobs G.A., Maurer B.V., Narayanan V.L., Cruthers L.R., Szanto J., *J Med Chem* 1982, 25, 969.
7. Hisano T., Ichikawa M., Tsumoto K., Tasaki M., *Chem Pharm Bull*, 1982, 30, 2996.
8. Akihama S., Okhude M., Mizno A., *Meiji Yakka Diagakn Kenkyu Kiyo,* 1966, 1 [*Chem. Abstr.,* 1968, 68, 10369 v.]
9. Russo F., Santagati M., *Farmaco Ed Sci,* 1976, 31, 41.
10. Ghoneim K.M., El-Basil S., Osman A.N., Said M.M., Megahed S.A., *Rev Roum Chim,* 1991, *36*, 1355.
11. Singh S.P., Seghal S., *Indian J Chem,* 1988, 27 *B*, 94.
12. Musser J.H., Brown R.E., Love B., Baily K., Jones H., Kahen R., Huang F., Khandwala A., Leibowitz M., *J Med Chem,* 1984, 27, 121.
13. Pattan S.R., Suresh C., Pujar V.D., Reddy V.V.K., Rasal V.P., Kotti B.C., *Indian J Chem,* 2005, 4B, 2404.
14. Yoshida M., Hayakawa I., Hyashi N., Agatsuma T., Oda Y., Tanzawa F., Iwasaki S., Koyama K., Furukawa H., Kurakata S., Sugano Y., *Bioorg Med Chem Letters,* 2005, 15*,* 3328.
15. Sawhney S.N., Bansal O.P., *Indian J Chem,* 1977, 15B, 121.
16. Brown H.D., U S Pat., 1966, 3, 278, 547, *Chem Abstr, 65,* 18593.
17. Getman D.P., Decreescenzo G.A., Fresko J.N., Vazquez M.L., Sikorski J.A., Devadas B., Nagarajan S., US, 1998, 5, 705, 500.
18. Barry A.L., *The antimicrobial susceptibility test, Principle and Practices,* 1976, 180.

*****