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Synthesis And Biological Activities Of Fluoro Substituted Benzothiazole Derivatives

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Some new fluorine substituted Benzo[d]thiazole derivatives have been synthesized and their characterization was done by IR, NMR and mass spectral data. The antibacterial activities of these synthesized compounds are done by agar well diffusion method at two different concentrations in DMF against some Gram positive and Gram negative bacteria. The antifungal activity of these synthesized compounds is also studied. It is observed that the synthesized compounds could inhibit both Gram positive bacteria only at higher concentrations and morpholine substitution is most effective. Against Gram positive bacteria *P. mirabilis*, only two compounds are found to be effective at higher concentrations and piperadine had no effect against this bacterium. All the compounds exhibited inhibition against fungal strain *A. niger* and morpholine substituent is most effective.

Keyword: Benzothiazole derivatives, Morpholine, Piperadine, N-phenylpiperadine, N,N-dimethylformamide , Antibacterial activity, Antifungal activity etc.

1. Introduction

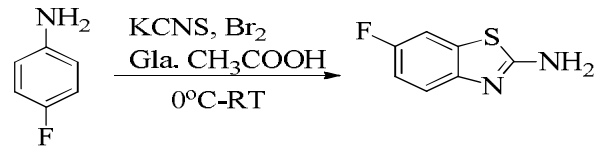
The chemistry and biological study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. Benzothiazole derivatives are an important class of compounds, which is becoming increasingly important due to their broad spectrum of biological activities [1-5]. Literature survey shows that many Benzothiazole derivatives are known to exhibit pharmacological activities such as antitumor and antiviral [6-8], anti proliferative [9], anticancer [10-11], antimicrobial [12], antibacterial [13], anthelmintic [14], as Cholinesterase inhibitors [15], antidiabetic [16], anti-Inflammatory [17-18], antimalarial [19], antifungal [20] etc. Hence, syntheses of such compounds are of considerable interest. It is well known that the introduction of fluorine atom into an organic molecule causes dramatic changes in its biological profile, mainly due to high electro negativity of fluorine causes increase lipid solubility. Hence, In the present study, some new derivatives of 2-chloro-N-(6-flourobenzo[d]thiazol-2-yl)acetamide with morpholine, piperadine, and N-phenyl piperazine have been synthesized. Their characterization was done by spectroscopic methods. Further, antibacterial and antifungal activities of these derivatives have been studied in DMF.

2. Experimental

Reagent grade chemicals were used without further purification. All the melting points were taken in open capillaries and are uncorrected. The purity of the synthesized compounds was checked by Thin Layer Chromatography.

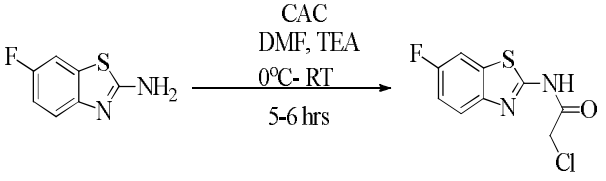
2.1 Synthesis of 6-Substituted-1,3-benzothiazol-2-amine:

To an ice cooled equimolar mixture of substituted aniline and potassium thiocyanate in glacial acetic acid, bromine (1 equivalent) was added drop wise with continuous stirring in such a rate that the temperature does not rise beyond 5 ºC. The solution was stirred for 2 hrs at 0 ºC and then at room temperature (RT) for 10-12 hours. It was then allowed to settle overnight so that orange colored precipitate was settled at the bottom. To this, hot water was added and the mixture was heated at 85 ºC on steam bath. It was then filtered while hot and washed with hot glacial acetic acid. The filtrate was cooled and neutralized with concentrated ammonia solution up to pH 6. The solid obtained was filtered and recrystallined with methanol.



2.2 Synthesis of 6-fluoro-1,3-benzothiazole-2-carbonyl chloride:

To equimolar mixture of 6-fiuoro-1,3-benzothiazole-2-amine and triethylamine (TEA) in DMF, chloro acetyl chloride (CAC) was added drop wise with constant stirring at 0^0 to 5 ^{0}C. The stirring was continued for about 2-3 hrs in the same cooling condition and then for 2 hrs at room temperature (RT). After completion of reaction, the reaction mixture was poured in to cold water and neutralized by sodium bicarbonate with constant stirring. The resulted precipitate was filtrated, dried and recrystallized using methanol.



2.2 Synthesis of N-(6-fluorobenzo[d] thiazole-2-yl)-2-morpholinoacetamide (RT-1):

To an equimolar solution of 6-fiuoro-1,3-benzothiazole-2-amine and secondary amine in N,N-dimethylformamide, triethylamine was added and the reaction mixture was refluxed on oil/water bath at about 85º-90ºC with constant stirring for 4-5 hours. After completion of reaction, the reaction mixture was poured in cold water and neutralized by sodium bicarbonate with constant stirring. The precipitate is filtered, dried and recrystallized with methanol.

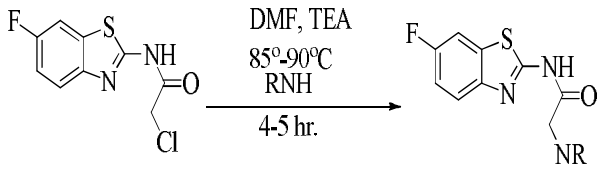


Table 1: Physical data of synthesized compounds

Code	-NR	M. P. (ºC)	Rf* Value	Yield (%)
RT-1	$-NC_4H_8O$	91-92	0.22	61
RT-2	$-NC_4H_8NC_6H_5$	161-162	0.85	58
RT-3	$-NC_5H_{10}$	89-90	0.31	67

*Hexane: Ethyl acetate; 8:2

2.3 Spectroscopic study:

The characterization of synthesized compounds was done by IR, NMR and mass spectral data. IR spectra were scanned on SHIMADZU FTIR-8400 Spectrophotometer in frequency range of 4000-400 cm^{-1} by KBr–DRS Method. ^{1}H NMR spectral was recorded in DMSO with tetramethylsilane (TMS) as the internal standard at 400 MHz on a BRUKER AVANCE II - 400 spectrophotometer. The chemical shifts are reported as parts per million (ppm). The mass spectra of synthesized compounds were recorded by GCMS-SHIMADZU-QP2010.

N-(6-fluorobenzo[d]thiazol-2-yl)-2-morphol inoacetamide (RT-1):

IR (KBr) (υ, cm^{-1}); 1608.69 & 3402.54(N-H), 3064.99 & 1456.23 (ArC-H), 1286.56 (C-N), 1608.35 (C=O), 1566.25(ArC=C)

^{1}H NMR (DMSO-d_6, 400 MHz); δ(ppm), 3.69-3.71 (t, 4H, $-CH_2-$), 2.59-2.61 (t, 4H, $-CH_2-$), 3.33 (s, 2H, -

CH_2-), 9.15 (s,1H,-NH-), 7.66-7.69 (q,1H, Ar-H), 7.61-7.64 (dd, 1H, Ar-H), 7.13-7.18 (m, 1H, Ar-H)
Mass, m/z; 295 (M^+).

N-(6-fluoro-1,3-benzothiazol-2-yl)-2-(4-phenylpiperazine-4-yl)acetamide (RT-2):
IR (KBr) (υ, cm^{-1}); 3252.09 & 1600.97 (N-H), 3064.99 & 1452.45 (ArC-H), 1249.91 (C-N), 1631.83 (C=O), 1535.39 (ArC=C)
^{1}H NMR (DMSO-d_6, 400 MHz), δ(ppm): 3.24-3.26 (t, 4H, -CH_2-), 2.77-2.83 (t, 4H, -CH_2-), 3.41 (s, 2H, -CH_2-), 11.77 (s,1H,-NH-), 7.67-7.71 (q,1H, Ar-H), 7.50-7.62 (dd, 1H, Ar-H), 7.13-7.18, (m, 1H, Ar-H), 6.70-6.82 (t,1H,Ar-H), 7.23-7.24(t,2H,Ar-H), 6.92-6.95 (d,2H,Ar-H)
Mass, m/z; 370 (M^+)

N-(6-fluoro-1,3-benzothiazol-2-yl)-2-(piperidine-1-yl) Acetamide [RT-3]:
IR (KBr) (υ, cm^{-1}); 1608.69 (N-H), 827.49 & 1454.38 (ArC-H), 1305.85 (C-N), 1681.98 & 1668.48 (C=O), 1562.39 (ArC=C)
^{1}H NMR (DMSO-d_6, 400 MHz), δ(ppm): 3.20-3.36 (t, 4H, -CH_2-), 2.87-2.89 (t, 4H, -CH_2-), 3.37 (s, 2H, -CH_2-),3.11- 3.26 (m, 2H, -CH_2-), 11.65 (s,1H,-NH-), 7.61-7.79 (q,1H, Ar-H), 7.58-7.72 (dd, 1H, Ar-H), 7.11-7.28, (m, 1H, Ar-H), 6.60-6.87 (t,1H,Ar-H), 7.25-7.28(t,2H,Ar-H), 6.95-6.98 (d,2H,Ar-H)
Mass, m/z; 293(M^+)

3. Biological Activity:

All the synthesized compounds have been screened for in-vitro antibacterial activity against two gram positive bacteria *Staphylococcus aureus* ATCC 25923, *Bacillus megaterium* ATCC 9885, and two Gram negative bacteria viz. *Escherichina coli* ATCC 8739 and *Proteus mirabilis* NCIM 2241 by using Agar well diffusion method. The antifungal activity was determined against *Aspergillus niger* ATCC 16404 fungal strain.

3.1 Preparation of solutions:

All the synthesized compounds were recrystallized from methanol prior to use. The DMF used for antimicrobial study was also purified before use by standard method [21]. For all the compounds, solutions of two different concentrations were prepared.

3.2 Agar well Diffusion Method:

The antimicrobial evaluation was done by agar well diffusion method using Mueller Hinton Agar No.2 as the nutrient medium. The agar well diffusion method was preferred to be used in this study since it was found to be better than the disc diffusion method as suggested Parekh et al [22]. The bacterial strains were activated by inoculating a loop full of test strain in 25 ml of N-broth and the same was incubated for 24 hrs in an incubator at 37 °C.
0.2 ml of the activated strain was inoculated in Mueller Hinton Agar kept at 45 °C. It was then poured in the Petri dishes and allowed to solidify. After solidification of the media, 0.85 cm well was made in the plates using a sterile cork borer. Each well was filled with 0.1 ml of the test solution. The plates were incubated for 24 hrs at 37 °C.The mean value obtained for the two wells was used to calculate the zone of growth inhibition of each sample. The controls were maintained for each bacterial strain, where pure solvent (DMF) was inoculated into the well. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antimicrobial activities of the synthetic compounds.

4. Results and Discussion:

Table 1 shows the physical properties and substituted group of synthesized compounds.
Figure 1 shows the inhibition zones of the synthesized compounds against the Gram positive and Gram negative bacterial strains. It is observed from Figure 1[A] that all the synthesized compounds show the significant activity against both Gram positive bacteria and inhibition is maximum against *B. magaterium*.
Against Gram negative bacteria (Figure 1[B]), for 80 evg, only RT-1 and RT-3 showed inhibition against *E. coli* RT-2 exhibited no inhibition at all. However, for 80 evg, all the three compounds showed inhibition and RT-1 and RT-3 exhibited maximum inhibition. Against *P. mirabilis*, only RT-1 and RT-2 are found to be effective only at 80 evg.

Table 2: Antibacterial and antifungal activity of synthesized compounds against gram positive and gram negative bacteria in DMF.

Sample Code	Antibacterial activity Zone of inhibition in mm								Antifungal activity Zone of inhibition (mm) *A. niger* 50 evg
	B. megaterium		*S. aureus*		*E. coil*		*P. mirabilis*		
	20 evg	80 evg	20 evg	80 evg	20 evg	80 evg	20 evg	80 evg	
RT-1	-	21	-	16	11	17	-	16	14
RT-2	-	14	-	14	-	15	-	15	10
RT-3	-	14	-	10	11	17	-	-	09

Table 3: Antibacterial and antifungal activity of Standard Drugs against in DMF.

Name of Drug	Antibacterial activity Zone of inhibition in mm								Antifungal activity Zone of inhibition (mm) *A. niger* 50 evg
	B. megaterium		*S. aureus*		*E. coil*		*P. mirabilis*		
	20 evg	80 evg	20 evg	80 evg	20 evg	80 evg	20 evg	80 evg	
Chloro-amphanicol	-	20	-	17	12	20	20	26	-
Ampicilim	12	21	18	18	11	16	-	14	-
Greseofulum	-	-	-	-	-	-	-	-	11
DMF	-	12	-	17	11	16	-	14	11

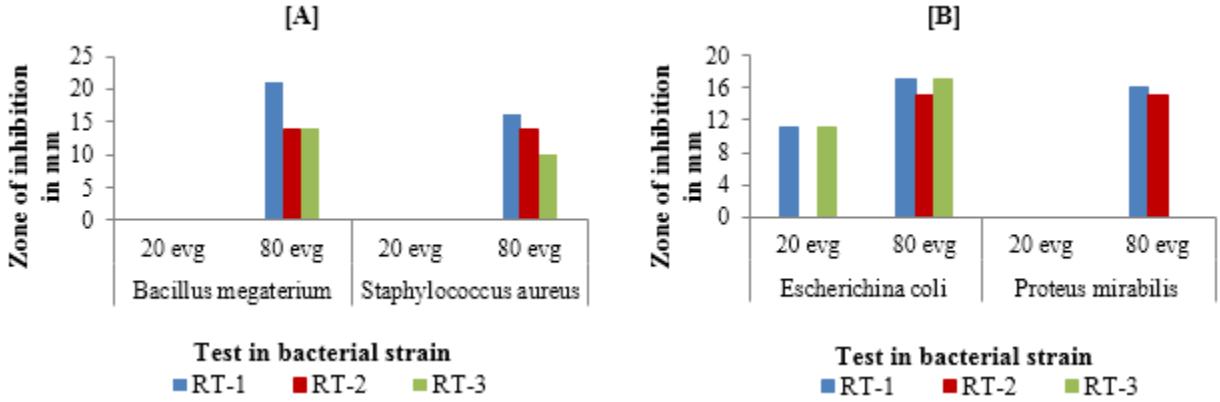


Fig 1: Antibacterial activity of Benzothiazole derivatives against [A] Gram-positive bacteria and [B] Gram-negative bacteria in DMF

RT-1 compound shows higher bacteriostatics effect against both the bacteria. The inhibition depends on the substitution. The presence of morpholine substitution is thus more effective against studied Gram positive bacteria.

Thus, at lower concentration, N-phenyl piperazine is not effective at all whereas other two substitutions morpholine and piperidine are effective against *E. coli*. However, for *P. mirabilis*, only at 80 evg, morpholine and N-phenyl piperazine are found to be effective. Piperadine had no effect against this bacterium. Against fungal strain *A. niger*, all the three compounds exhibited inhibition and inhibition is maximum for RT-1. So, against this fungal strain, morpholine substituent is most effective.

Thus, it is concluded that the synthesized compounds are effective against studied bacterial and fungal strains. *E. coli* is most resistant bacteria

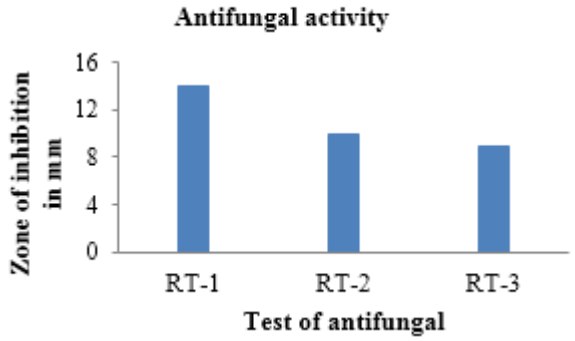


Fig 2: Antifungal activity of Benzothiazole derivatives in DMF.

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