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Synthesis and Antimicrobial Evaluations of Sulfur Inserted Fluoro-Benzimidazoles

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A new series of fluorinated sulfur inserted benzimidazole analogues $\mathbf{Z}_{a\text{-}i}$ were synthesized and characterized. The new compounds were screened for their antimicrobial and antioxidant potential. The synthesized compounds were obtained by multiple step synthesis, initiating from the synthesis of 5-(difluoromethoxy)-1*H*-benzimidazole-2-thiol **X**. The compounds $\mathbf{Y}_{a\text{-}i}$ prepared by reacting differently substituted anilines with chloroacetylchloride and triethylamine in DMF. Finally, the compound **X** was reacted with different derivatives of 2-chloro-*N*-phenylacetamide resulting in formation of titled compounds $\mathbf{Z}_{a\text{-}i}$. The synthesized compounds ($\mathbf{Z}_a$-$\mathbf{Z}_i$) were characterized by spectral analysis *viz.* ^{1}H & ^{13}C NMR, mass spectra, elemental analysis and IR. The *in vitro* antimicrobial potential against Gram-positive (*S. aureus* and *E. faecalis*) and Gram-negative bacterial (*E. coli* and *P.aeruginosa*) strains as well as fungi (*A. niger* and *C. albicans*) was recorded for the obtained compounds. Some of the compounds exhibited encouraging results (in MIC) against Gram-positive and Gram-negative bacterial strains. These studies thus suggest that the designed sulfur inserted fluoro-benzimidazoles scaffold may serve as new promising template for further amplification as antimicrobial agents.

Keywords: Benzimidazole, Fluorinated sulfur, Antimicrobial, Antibacterial, Antifungal.

INTRODUCTION

Among the most promising category of bioactive heterocycles, the benzimidazole and their analogs are claimed to possess potent anticancer [1-4], antimicrobial [5-9], antiparasitic [10], analgesic [11], antiprotozoal [12] and molluscicidal [13] properties. It is observed that benzimidazole derivatives possess anti-HIV [14], anthelmintic [15], antimalarial [16], antimycobacterial [17], antidiabetic [18] and antioxidant properties [19]. This promising class of bioactive scaffolds also exhibit other diverse varieties of biological activities such as antiallergic [20], analgesic [21] and anti-hypertensive properties [22].

Benzimidazole is an important privileged sub-structure in medicinal chemistry with structural analogy to nucleotides detected in human body. A variety of marketed drugs such as nocodazole (anticancer), thiabendazole and flubendazole (anthelmintic), astmizole (antihistaminic), lansoprazole and omeprazole (antiulcerative) possess this vital pharmacophore (Fig. 1). The drugs rabeprazole and pantoprazole have been developed after the synthesis and evaluation of different substituted benzimidazole analogs. Literature survey also reveals that the molecules obtained by changing the groups on the core structure of benzimidazole ring are potent antibacterial and antifungal agents [23,24]. Other biological activities like inhibition of CK2 proteins and Rho-kinase (ROCK) make them useful against neoplastic growth [25] and glaucoma [26], respectively. The importance of some fused heterocyclic benzimidazole derivatives are used as eukaryotic topisomerase II inhibitors has been demonstrated [27]. The substituted benzimidazoles showed potent activity against a wide variety of virus including HIV and several molecules with benzimidazole skeleton were investigated and found to be capable of ceasing the replication of adenovirus [28]. In addition to this, butyrylcholinesterase and acetylcholinesterase inhibitor activity have been demonstrated for benzimidazole derivatives using tacrine as standard drug [29].

It has been established that synthetic modifications of various existing drugs may results in increased activity against the targets [30]. It is further revealed that the derivatives results from changes in the important heterocyclic pharmacophore

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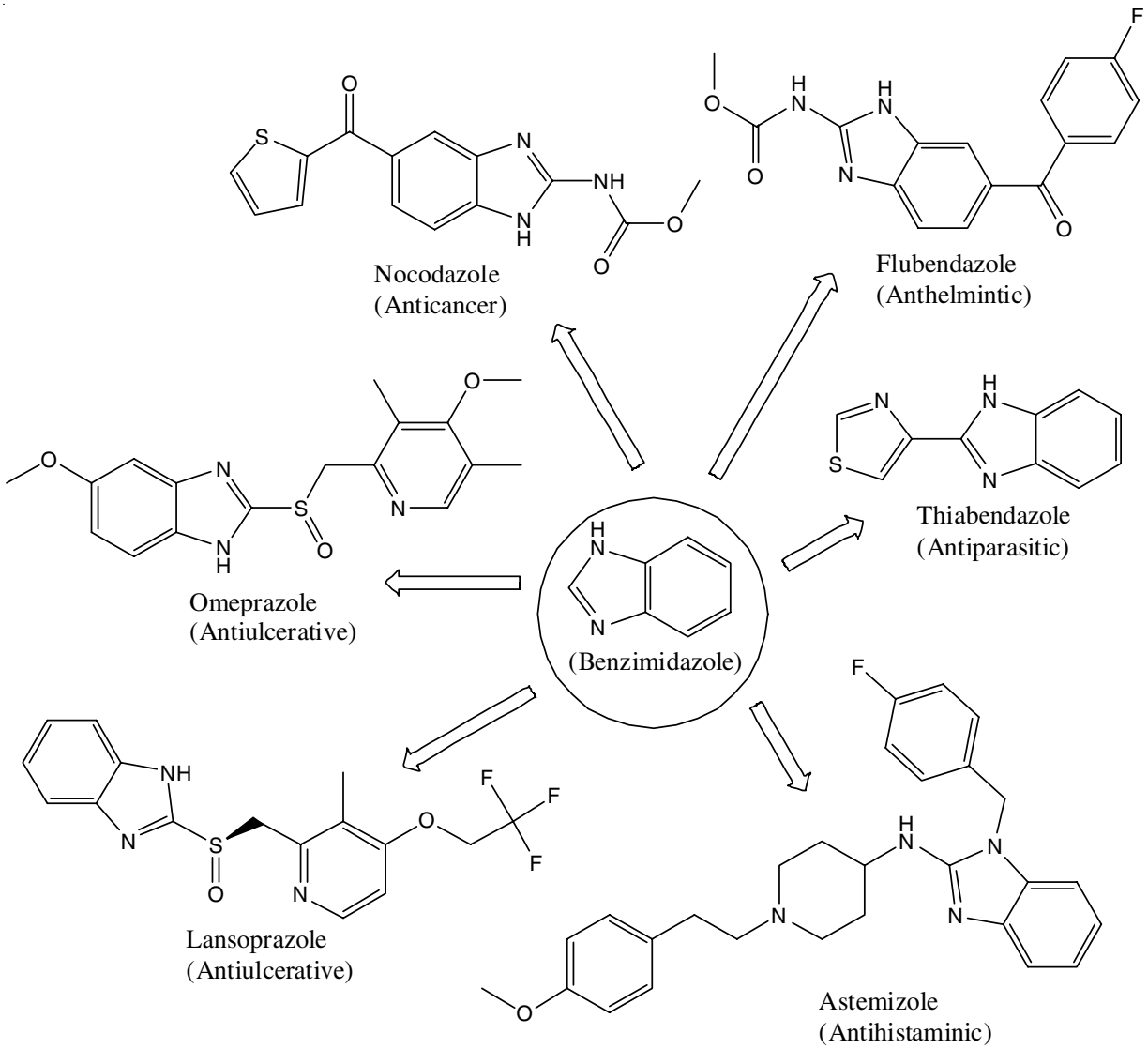


Fig. 1. Some benzimidazole scaffold containing drugs

such as benzimidazole are active against new targets [31]. To understand the versatility of benzimidazole and its promising activity as a therapeutic agent the literature survey is highly useful [32-35], which also prompted us to synthesize the titled compounds $\mathbf{Z}_{a\text{-}i}$ possessing benzimidazole nucleus. In continuation with our earlier works of synthesizing heterocyclic bioactive molecules [30,31], we have tried to synthesize a series of potent antimicrobial and antioxidant heterocyclic compounds bearing benzimidazole nucleus as the centre.

EXPERIMENTAL

All the chemicals and solvents required for the synthesis of titled derivatives and corresponding intermediates were purchased from Merck Ltd., s.d. Fine Chemicals, LOBA Chemie and HIMEDIA. Melting points were obtained using open end capillary method and are uncorrected. TLC plates (TLC Silica gel 60 F_{254}) used for monitoring the completion of reaction were purchased from Merck. The IR spectral data were measured by using Bruker FT-IR alpha-t (ATR). The ^{1}H & ^{13}C NMR were obtained using Bruker Spectrophotometer-400MHz and 100 MHz, respectively, where DMSO-d_6 was used as solvent and TMS as reference. The mass spectral analysis was conducted on Shimadzu mass analyzer. The elemental analysis was carried out on Perkin-Elmer 2400 CHN analyzer.

Synthesis of 5-(difluoromethoxy)-1*H*-benzo[*d*]imidazole-2-thiol (X): The titled compound was obtained by literature procedure [36]. Solid white; Yield: 52%; m.p.: 242 ºC; IR (ATR, cm^{-1}): 1180 (-C-F *str*. -$OCHF_2$), 1588 (-C=N *str*., benzimidazole nucleus), 3001 (-CH *str*. -$OCHF_2$), 3404 (-NH *str.* 2º-amine); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.25 (1H, s, -$OCHF_2$), 6.83-7.96 (3H, m, Ar-H), 11.12 (1H, s, -NH); MS (*m/z*): 217; Anal. calcd. (found) % $C_8H_6ON_2SF_2$: C, 44.44 (44.43); H, 2.80 (2.81); N, 12.96 (12.98).

General procedure for the synthesis of 2-chloro-*N*-(aryl)-acetamide derivatives ($Y_{a\text{-}i}$): Various substituted amines (0.01 mol) were added to a solution of DMF (35 mL) containing triethylamine (3-4 drops). After stirring of the mixture for 10 min at room temperature, chloroacetyl chloride (0.015 mol, 1.19 mL) was added to this. The temperature was maintained

between 0 to 5 ºC. The obtained solution was then stirred at room temperature for 4-6 h. The completion of reaction was monitored with TLC using toluene: acetone (8:2) as mobile phase. The solution was then added onto crushed ice and the separated precipitates were filtered and dried. Crystallized was done from methanol.

General method for the synthesis of final derivatives Z_{a-i}: 5-(Difluoromethoxy)-1*H*-benzo[*d*]imidazole-2-thiol (**X**) (0.01 mol, 1.8 g) was made soluble in acetone. To this stirred solution different acetamide derivatives Y_{a-i} (0.01 mol) were added to the above solution. Now K_2CO_3 (0.02 mol, 2.76 g) was added to this solution. The mixture was allowed to stir for 4 h at room temperature. The completion of reaction was monitored using TLC plate with mobile phase ethyl acetate:*n*-hexane (6:4). The final products thus obtained were poured into ice cold water and stirred for 0.5 h. The precipitates were filtered and washed occasionally. The crystallization of final products Z_{a-i} was done from alcohol.

***N*-(2,5-Dichlorophenyl)-2-(5-difluoromethoxy-1*H*-benzoimidazol-2-ylsulfanyl)acetamide (Z_a):** Yield: 87%; m.p.: 151 ºC; IR (ATR, cm^{-1}): 1161 (-C-F *str*. -$OCHF_2$), 1579 (-C=N *str*. benzimidazole nucleus), 1686 (-C=O *str*.), 2830 (-CH_2 *str*. methylene), 2983 (-CH *str*. -$OCHF_2$), 3097 (-CH *str*. aromatic ring), 3388 (-NH *str*. 2º-amine); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.28 (2H, s, -C<u>H</u>$_2$), 7.18 (1H, s, -$OCHF_2$), 6.74-8.02 (6H, m ,Ar-<u>H</u>), 9.74 (1H, s, -N<u>H</u>), 12.24 (1H, s, benzimidazole-N<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 40.2, 103.1, 107.2, 114.5, 117.1, 122.5, 127.9, 130.6, 131.1, 135.2, 140.1, 141.6, 143.7, 148.2, 155.8, 167.1; MS (*m/z*): 416 (M^+). Anal. calcd. (found) % $C_{16}H_{11}N_3O_2SCl_2F_2$: C, 45.95 (45.87); H, 2.65 (2.73); N, 10.05 (10.12); S, 7.67 (7.61).

***N*-(2,6-Dichlorophenyl)-2-(5-difluoromethoxy-1*H*-benzoimidazol-2-ylsulfanyl)-acetamide (Z_b):** Yield: 89%; m.p.: 149 ºC; IR (ATR, cm^{-1}): 1163 (-C-F *str*. -$OCHF_2$), 1577 (-C=N *str*. benzimidazole nucleus), 1682 (-C=O *str*.), 2837 (-CH_2 *str*. methylene), 2979 (-CH *str*. -$OCHF_2$), 3089 (-CH *str*. aromatic ring), 3380 (-NH *str*. 2º-amine); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.12 (2H, s, -C<u>H</u>$_2$), 7.21 (1H, s, -$OCHF_2$), 6.78-7.94 (6H, m ,Ar-<u>H</u>), 9.64 (1H, s, -N<u>H</u>), 12.11 (1H, s, benzimidazole-N<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 39.8, 103.6, 106.8, 113.9, 117.5, 121.7, 128.1, 130.4, 131.8, 135.6, 139.9, 141.4, 143.2, 147.5, 155.4, 167.3; MS (*m/z*): 416 (M^+). Anal. calcd. (found) % $C_{16}H_{11}N_3O_2SCl_2F_2$: C, 45.95 (45.82); H, 2.65 (2.71); N, 10.05 (10.08); S, 7.67 (7.64).

***N*-(3,4-Dichlorophenyl)-2-(5-difluoromethoxy-1*H*-benzoimidazol-2-ylsulfanyl)acetamide (Z_c):** Yield: 86%; m.p.:152 ºC; IR (ATR, cm^{-1}): 1167 (-C-F *str*. -$OCHF_2$), 1567 (-C=N *str*. benzimidazole nucleus), 1689 (-C=O *str*.), 2830 (-CH_2 *str*. methylene), 2966 (-CH *str*. -$OCHF_2$), 3084 (-CH *str*. aromatic ring), 3383 (-NH *str*. 2º-amine); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.96 (2H, s, -C<u>H</u>$_2$), 7.18 (1H, s, -$OCHF_2$), 6.73-7.68 (6H, m, Ar-<u>H</u>), 9.68 (1H, s, -N<u>H</u>), 12.20 (1H, s, benzimidazole-N<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 40.4, 103.8, 107.2, 114.7, 118.1, 120.9, 128.8, 131.2, 132.5, 134.9, 139.8, 142.1, 143.3, 147.1, 156.2, 167.6; MS (*m/z*): 416 (M^+). Anal. calcd. (found) % $C_{16}H_{11}N_3O_2SCl_2F_2$: C, 45.95 (45.63); H, 2.65 (2.78); N, 10.05 (10.19); S, 7.67 (7.62).

***N*-(2,3-Dichlorophenyl)-2-(5-difluoromethoxy-1*H*-benzoimidazol-2-ylsulfanyl)acetamide (Z_d):** Yield: 90%; m.p.:154 ºC; IR (ATR, cm^{-1}): 1162 (-C-F *str*. -$OCHF_2$), 1570 (-C=N *str*. benzimidazole nucleus), 1684 (-C=O *str*.), 2835 (-CH_2 *str*. methylene), 2974 (-CH *str*. -$OCHF_2$), 3088 (-CH *str*. aromatic ring), 3389 (-NH *str*. 2º-amine); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.15 (2H, s, -C<u>H</u>$_2$), 7.24 (1H, s, -$OCHF_2$), 6.77-7.79 (6H, m ,Ar-<u>H</u>), 10.12 (1H, s, -N<u>H</u>), 12.26 (1H, s, benzimidazole-N<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 40.1, 102.9, 107.6, 115.1, 117.7, 121.2, 128.6, 130.8, 132.4, 135.1, 139.4, 142.6, 143.2, 146.7, 156.5, 167.7; MS (*m/z*): 416 (M^+). Anal. calcd. (found) % $C_{16}H_{11}N_3O_2SCl_2F_2$: C, 45.95 (45.66); H, 2.65 (2.73); N, 10.05 (10.15); S, 7.67 (7.64).

***N*-(2,4-Dichlorophenyl)-2-(5-difluoromethoxy-1*H*-benzoimidazol-2-ylsulfanyl)-acetamide (Z_e):** Yield: 85%; m.p.:150 ºC; IR (ATR, cm^{-1}): 1165 (-C-F *str*. -$OCHF_2$), 1562 (-C=N *str*. benzimidazole nucleus), 1689 (-C=O *str*.), 2840 (-CH_2 *str*. methylene), 2983 (-CH *str*. -$OCHF_2$), 3092 (-CH *str*. aromatic ring), 3385 (-NH *str*. 2º-amine); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.94 (2H, s, -C<u>H</u>$_2$), 7.31 (1H, s, -$OCHF_2$), 6.70-7.94 (6H, m ,Ar-<u>H</u>), 10.11 (1H, s, -N<u>H</u>), 12.13 (1H, s, benzimidazole-N<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 40.4, 103.5, 108.1, 115.7, 118.2, 122.1, 128.7, 131.3, 132.9, 135.5, 140.2, 141.9, 143.6, 146.9, 156.1, 168.1; MS (*m/z*): 416 (M^+). Anal. calcd. (found) % $C_{16}H_{11}N_3O_2SCl_2F_2$: C, 45.95 (45.77); H, 2.65 (2.70); N, 10.05 (10.08); S, 7.67 (7.63).

2-(5-Difluoromethoxy-1*H*-benzoimidazol-2-ylsulfanyl)-*N*-(2,4-dimethyl-phenyl)acetamide (Z_f): Yield: 91%; m.p.: 192 ºC; IR (ATR, cm^{-1}): 1170 (-C-F *str*. -$OCHF_2$), 1569 (-C=N *str*. benzimidazole nucleus), 1671 (-C=O *str*.), 2842 (-CH_2 *str*. methylene), 3005 (-CH *str*. -$OCHF_2$), 3088 (-CH *str*. aromatic ring), 3402 (-NH *str*. 2º-amine); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.41(3H, s, -CH_3), 2.56 (3H, s, -CH_3), 4.31 (2H, s, -C<u>H</u>$_2$), 6.84 (1H, s, -$OCHF_2$), 6.51-8.12 (6H, m ,Ar-<u>H</u>), 10.98 (1H, s, -N<u>H</u>), 12.37 (1H, s, benzimidazole-N<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 20.1, 24.6, 40.2, 104.1, 108.6, 114.9, 118.7, 122.3, 129.2, 131.8, 133.1, 135.4, 140.5, 142.3, 143.7, 147.2, 156.8, 168.5; MS (*m/z*): 377 (M^+). Anal. calcd. (found) % $C_{18}H_{17}N_3O_2SF_2$: C, 57.28 (57.23); H, 4.54 (4.48); N, 11.13 (11.22); S, 8.50 (8.54).

2-(5-Difluoromethoxy-1*H*-benzoimidazol-2-ylsulfanyl)-*N*-(2,6-dimethyl-phenyl)acetamide (Z_g): Yield: 93%; m.p.: 194 ºC; IR (ATR, cm^{-1}): 1172 (-C-F *str*. -$OCHF_2$), 1573 (-C=N *str*. benzimidazole nucleus), 1675 (-C=O *str*.), 2851 (-CH_2 *str*. methylene), 3007 (-CH *str*. -$OCHF_2$), 3091 (-CH *str*. aromatic ring), 3405 (-NH *str*. 2º-amine); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.63 (3H, s, -CH_3), 2.75 (3H, s, -CH_3), 4.34 (2H, s, -C<u>H</u>$_2$), 6.81 (1H, s, -$OCHF_2$), 6.54-8.11 (6H, m ,Ar-<u>H</u>), 11.14 (1H, s, -N<u>H</u>), 12.43 (1H, s, benzimidazole-N<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 18.2, 22.4, 40.5, 104.6, 108.7, 115.3, 118.2, 122.5, 130.5, 131.9, 133.8, 135.2, 141.2, 142.4, 143.3, 147.7, 157.4, 168.6; MS (*m/z*): 377 (M^+). Anal. calcd. (found) % $C_{18}H_{17}N_3O_2SF_2$: C, 57.28 (57.25); H, 4.54 (4.51); N, 11.13 (11.18); S, 8.50 (8.52).

***N*-(2-Chloro-4-nitrophenyl)-2-(5-difluoromethoxy-1*H*-benzoimidazol-2-ylsulfanyl)acetamide (Z_h):** Yield: 87%; m.p.: 195 ºC; IR (ATR, cm^{-1}): 1177 (-C-F *str*. -$OCHF_2$), 1588

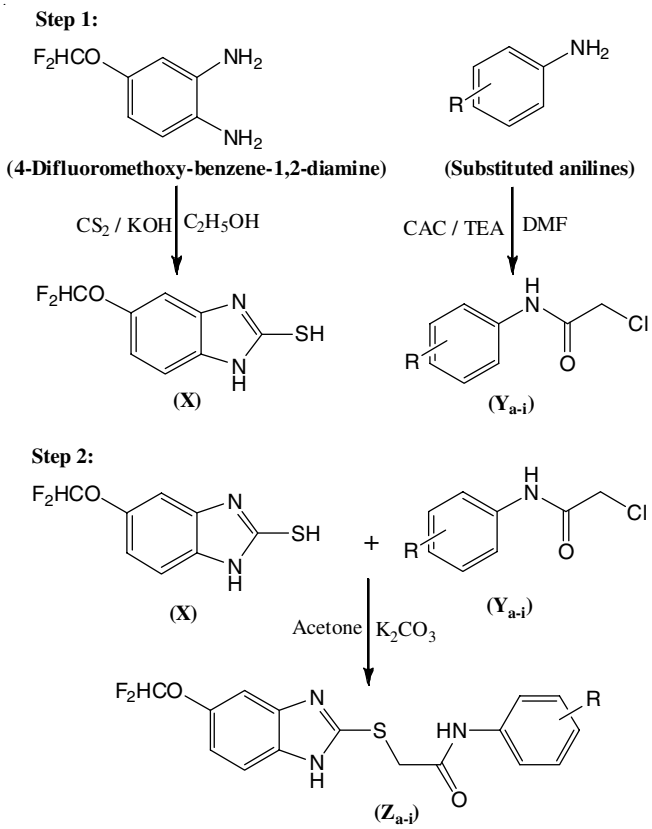
(-C=N *str.* benzimidazole nucleus), 1681 (-C=O *str*.), 2836 (-CH_2 *str.* methylene), 3001 (-CH *str*. -$OCHF_2$), 3093 (-CH *str*. aromatic ring), 3405 (-NH *str.* 2º-amine); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.24 (2H, s, -C<u>H</u>$_2$), 6.97 (1H, s, -$OCHF_2$), 6.54-8.02 (6H, m, Ar-<u>H</u>), 10.91 (1H, s, -N<u>H</u>), 12.42 (1H, s, benzimidazole-N<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 40.7, 103.6, 108.4, 114.9, 117.8, 122.5, 128.2, 130.8, 132.7, 135.6, 141.1, 142.2, 143.5, 146.4, 156.3, 168.2; MS (*m/z*): 428 (M^+). Anal. calcd. (found) % $C_{16}H_{11}N_4O_4SClF_2$: C, 44.82 (44.78); H, 2.59 (2.55); N, 13.07 (13.11); S, 7.48 (7.45).

***N*-(4-Chloro-2-nitrophenyl)-2-(5-difluoromethoxy-1*H*-benzoimidazol-2-ylsulfanyl)acetamide (Z_i):** Yield: 89%; m.p.: 193 ºC; IR (ATR, cm^{-1}): 1172 (-C-F *str*. -$OCHF_2$), 1591 (-C=N *str*. benzimidazole nucleus), 1688 (-C=O *str*.), 2842 (-CH_2 *str*. methylene), 3007 (-CH *str*. -$OCHF_2$), 3095 (-CH *str*. aromatic ring), 3409 (-NH *str*. 2º-amine); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.27 (2H, s, -C<u>H</u>$_2$), 7.13 (1H, s, -$OCHF_2$), 6.65-8.12 (6H, m, Ar-<u>H</u>), 10.97 (1H, s, -N<u>H</u>), 12.45 (1H, s, benzimidazole-N<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 40.5, 104.1, 108.2, 115.1, 118.2, 122.7, 128.6, 131.2, 132.8, 134.9, 141.4, 142.8, 143.6, 146.9, 156.4, 168.8; MS (*m/z*): 428 (M^+). Anal. calcd. (found) % $C_{16}H_{11}N_4O_4SClF_2$: C, 44.82 (44.81); H, 2.59 (2.52); N, 13.07 (13.14); S, 7.48 (7.46).

RESULTS AND DISCUSSION

The titled compounds $\mathbf{Z}_{a\text{-}i}$ were prepared by the procedure as shown in **Scheme-I**. In step 1, simultaneously two reactions were undertaken; 4-(difluoromethoxy)benzene-1,2-diamine was reacted with carbon disulphide (CS_2) and KOH in presence of ethanol, resulting in the formation of 5-(difluoromethoxy)-1H-benzo[*d*]imidazole-2-thiol (**X**) and differently substituted anilines were reacted with chloroacetylchloride (CAC) and triethylamine (TEA) in presence of DMF, which resulted in the formation of 2-chloro-*N*-acetamide derivatives $\mathbf{Y}_{a\text{-}i}$. In step 2, two intermediates thus obtained were condensed in presence of potassium carbonate (K_2CO_3) to yield the desired derivatives $\mathbf{Z}_{a\text{-}i}$ in high yield. The spectral data obtained for the final derivatives $\mathbf{Z}_{a\text{-}i}$ has helped to confirm their formation.

Antimicrobial activity: The synthesized compounds $\mathbf{Z}_{a\text{-}i}$ were screened for their antibacterial and antifungal properties against a broad panel of Gram-positive bacteria, Gram-negative bacteria and fungi. The derivatives were screened for their biological activity by standard protocols like micro dilution-broth titer method. A few derivatives were found to be active against the Gram-positive bacterial strains *S. aureus* and *E. faecalis*. Compounds $\mathbf{Z}_h$ and $\mathbf{Z}_i$ exhibited equivalent activity as that of the standard ciprofloxacin against *S. aureus* (62.5 µg/mL) as well as *E. faecalis* (125 µg/mL). The other derivatives demonstrated poor activity against the Gram-positive bacterial strains. The synthesized compounds ($\mathbf{Z}_{a\text{-}i}$) when tested against Gram-negative bacteria *E. coli* and *P. aeruginosa* were found to exhibit much better activity than that shown against Gram-positive strains (Table-1). Compound $\mathbf{Z}_i$ showed excellent activity (62.5 µg/mL), than the standard (125 µg/mL) against *E. coli*. Compound $\mathbf{Z}_h$ also possessed activity (125 µg/mL) equivalent to that of standard drug ciprofloxacin when tested against *E. coli*. Also compounds $\mathbf{Z}_b$, $\mathbf{Z}_d$ and $\mathbf{Z}_e$ were found to exhibit the significant activity (125 µg/mL) against *E. coli* (Table-1). The complete series of synthesized derivatives were found to exhibit good results against the Gram-negative strain *P. aeruginosa* as compared to the standard. The derivatives $\mathbf{Z}_{a\text{-}i}$ when tested against the fungal strains *C. albicans* and *A. niger*; it was found that none of the compounds showed promising activity even equivalent to that of the standard drug fluconazole. Hence, it was concluded that synthesized derivatives are good antibacterial but none of them could be used as antifungal due to their poor MIC values as compared to the standard.



Scheme-I: Synthesis of fluoro-benzimidazole derivatives

Conclusion

From the antimicrobial data, it can be concluded that the derivatives bearing fluoro-substituted benzimidazole nucleus proved to be potent antibacterial agents. The compounds substituted with nitro groups exhibited significant or equivalent antibacterial activity against the used strains. Further optimization will be undertaken in the structure to enhance the antifungal potential of the derivatives reported.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

TABLE-1
ANTIMICROBIAL DATA OF THE SYNTHESIZED DERIVATIVES (Z_{a-i})

Compd.	-R (derivatives)	Minimum inhibitory concentration (MIC, µg/mL)					
		Gram-positive bacteria		Gram-negative bacteria		Fungi	
		S. aureus	*E. faecalis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
Z_a	2,5-Dichloro-	125	250	250	125	250	125
Z_b	2,6-Dichloro-	125	250	125	125	250	125
Z_c	3,4-Dichloro-	125	250	250	125	250	125
Z_d	2,3-Dichloro-	125	250	125	125	250	125
Z_e	2,4-Dichloro-	125	250	125	125	250	125
Z_f	2,4-dimethyl-	125	500	250	250	250	125
Z_g	2,6-dimethyl-	250	500	500	250	250	125
Z_h	2-Chloro-4-nitro-	62.5	125	125	125	250	125
Z_i	4-Chloro-2-nitro-	62.5	125	62.5	125	250	125
	Fluconazole	–	–	–	–	125	62.5
	Ciprofloxacin	62.5	125	125	125	–	–

Std.: Standard drug fluconazole for antifungal and ciprofloxacin for antibacterial tests

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