Synthesis of New conjugative derivatives of 2-{2-butyl-1-[2-(3`,4`-substituted benzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}-N,N-dimethylacetamides and their antimicrobial activities

P Krishna Kumari and Prof. B. Syama Sundar*

Acharya Nagarjuna University, Guntur-522510, Andhra Pradesh, India
Department of Chemistry

ABSTRACT

A series of benzimidazole derivatives were synthesized using simple approachfrom2-(2-butyl-1,6-dihydro-4-methyl-6-oxopyrimidin-5-yl)-N,N-dimethyl acetamide with various 2-(3,4-substituted benzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl chlorides in presence ofsodium hydride in N,N-dimethyl formamide for 18 to 36 hours at room temperature with good yield.All the compounds were screened for their antimicrobial activities on selected pathogens. The synthesized derivatives (**3a-j**) showed good antibacterial activity against *B. subtilis* with the highest zone of inhibition and also good against *E.coli* and *P.aeruginosa*. Moreover, the compounds also possess good antifungal activity against *C. albicans*.

Keywords:-2-(2-butyl-1,6-dihydro-4-methyl-6-oxopyrimidin-5-yl)-N,N-dimethylacetamide, 2-(3,4-substituted benzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl chlorides,antibacterialactivity, antifungal activity.

1.INTRODUCTION

Benzimidazole [1]is an important class of heterocyclic compounds, that have several applications in pharmaceutical chemistry and drug development. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12 [2].

The incorporation of benzimidazole nucleus, a biologically accepted pharmacophore in medicinal compounds, has made it a versatile heterocyclic moiety possessing wide spectrum of biological activities in a number of fields: analgesic[3-5]anti-inflammatory[4-7], antibacterial [8], antifungal [9], antiviral[10,11], anti-helmenthic [12], anticonvulsant [13,14], anticancer [15,16], antiulcer [17] and antihypertensive [18].There are many drugs based on benzimidazoles currently in the market such as rabeprazole (anti-ulcer), pimozide (antipsychotic), telmisartan (antihypertension), omeprazole (proton pump inhibitor), pimobendan (ionodilator), and mebendazole (antihelmintic) (**Fig. 1**).

Pyrimidine heterocyclic core has a great value in medicinal chemistry since it comprises the base for thiamine, uracil and cytosine nitrogen bases which are the building blocks of the nucleic acids [19,20]. Furthermore, pyrimidine derivatives have registered their importance in the development of various pharmaceuticals of broad spectra of therapeutical activities such as: anti-microbial [21], anti-viral, anti- HIV,anticancer [22,23], anti-tubercular [24], anti-malarial [25], analgesic, anti-inflammatory [26], diuretic [27], cardiovascular [28], hypnotic for the nervous system [29,30], and antioxidantactivities [31].

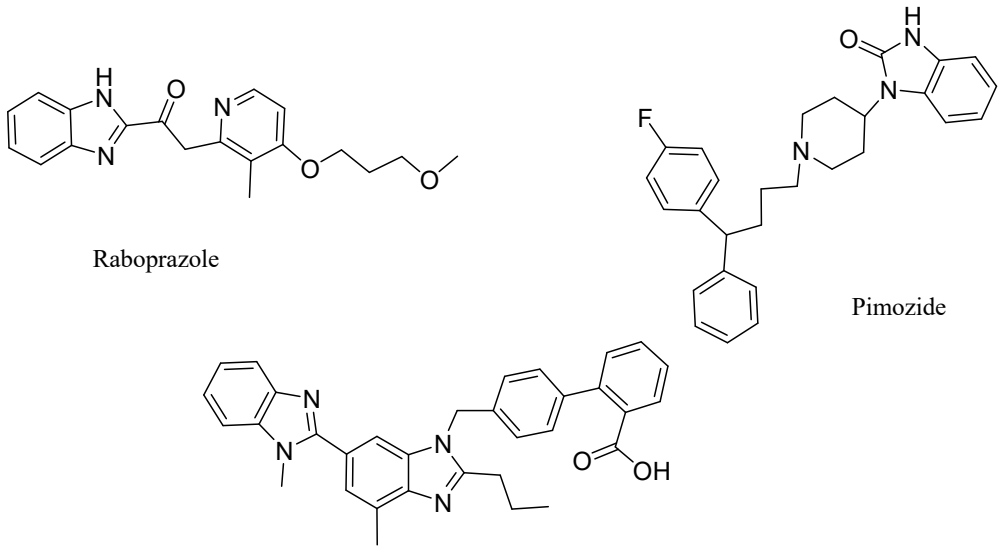


Fig.1. Some of the biologically active Benzimidazolecompounds.

The aim of the present study was to synthesizenew conjugative derivatives of 2-{2-butyl-1-[2-(3`4`-substitutedbenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}-N,N-dimethylacetamides (**3a-j**) by the reaction of 2-(2-butyl-1,6-dihydro-4-methyl-6-oxopyrimidin-5-yl)-N,N-dimethylacetamide(**1**) with 2-(3`,4`-substitutedbenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl chlorides(**2a-j)**and their biological activities as antimicrobial activity.

2.EXPERIMENRAL

Materials

All the chemicals and solvents obtained from Merck Chemical Co. India. All the melting points are uncorrected. The purity was checked by TLC with silica gel 60 GF254 R. Merck pre-coated plates (0.25 mm) was visualized usingUV and characterized by spectral studies. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AM-400 NMR spectrometers in chloroform-*d6* and DMSO-$d_6$solvents. The chemical shifts are reported in δ (ppm) relative to tetramethylsilane as internal standard. Mass spectra analyses performed with an Agilent 6400 series equipped with an electro spray ionization source (capillary voltage at 4000V, nebulizing gas temperature at 300 °C, nebulizing gas flow at 12 L/ min).

General experimental procedure

2-(2-Butyl-1,6-dihydro-4-methyl-6-oxopyrimidin-5yl)-N,N-dimethylacetamide(0.01moles) was dissolved in 15 mL of dryN, N-dimethylformamide and cool the mixture to 0-5^{o}C. Add sodium hydride (0.5 m.eq) in to the reaction mixture at 0-5^{o}C. Dissolve 2-(3`,4`-substitutedbenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl chloride (0.9m.eq) in N, N-dimethylformamide(10 mL) in a separate flask and add this solution to the reaction mixture at 0-5^{o}C slowly for 30minutes. Once addition is completed raise thetemperature of the mixture to 25-30^{o}C. Stir the reaction mixture at 25-30^{o}C 18 to 36 hours. Quench the reaction mixture with water (30 mL) and extract product with ethylacetate (3x60mL). Dry the organic layer over anhydrous sodium sulfate and concentrate to give crude residue of 2-{2-butyl-1-[2-(3`,4`-substitutedbenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-

dihydropyrimidin-5-yl}-N,N-dimethylacetamide. Purify the crude material with flash chromatography(**Scheme 1**).

Spectral data

2-[2-butyl-(1-(2-benzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)-N,N-dimethylacetamide(3a)

^{1}HNMR (CDCl$_3$-d6, 400 MHz,δ ppm): 0.92-0.96 (t,3H, -CH_3), 1.21-1.48 (m,6H, -CH_2), 1.83 (s, 3H, -CH_3), 2.81 (s, 2H,-CH_2), 2.95 (s,6H,2x-CH_3), 3.71 (s,3H,-CH_3), 4.03 (s,2H,-CH_2), 6.89-7.29 (m,5H, -Ar-H), 7.50-7.68 (dd, 2H, -Ar-H), 8.38 (s, 1H, -Ar-H).

^{13}CNMR(DMSO-d6, 100 MHz, δ ppm):13.8, 21.0, 21.6, 22.6, 23.7, 25.8, 31.8, 33.1, 38.6, 115.4, 116.4, 122.9, 123.6, 125.9, 127.8, 128.5, 129.3, 136.5, 139.1, 139.4, 153.5, 153.8, 156.6, 164.6, 166.3,

FAB Mass: m/z 500.26 [M+1].

CHN Analysis: Found: C (69.78%), H (6.68%), N (14.01%),Calc: C (69.72%), H (6.66%), N (14.02%).

2-[2-butyl-1-(2-(3-chlorobenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)-N,N-dimethylacetamide (3b)

^{1}H NMR (CDCl$_3$-d6, 400 MHz, δ ppm): 0.92-0.96 (t,3H, -CH_3), 1.39-1.46 (m,2H, -CH_2), 1.53-1.59 (m,2H, -CH_2), 2.30-2.33 (t,2H, -CH_2), 2.87 (s,2H, -CH_2), 2.99 (s, 6H,-CH_3), 3.25 (s,3H, -CH_3), 3.76 (s,3H, -CH_3), 4.02 (s, 2H,-CH_2), 7.13 (d,1H, -Ar-H), 7.28-7.36 (m,3H, -Ar-H), 7.65-7.68 (d,1H, -Ar-H), 7.72-7.75 (d,1H, -Ar-H), 8.24 (s,1H, -Ar-H).

^{13}CNMR(DMSO-d6, 100 MHz, δ ppm):13.8, 20.9, 21.9, 22.5, 23.5, 25.7, 31.7, 32, 38.3, 115.3, 116.2, 122.8, 123.5, 125.8, 127.9, 128.8, 130, 134.2, 137.6, 139, 139.3, 153.7, 153.8, 156.4, 164.6, 166.1, 170.

FAB Mass: m/z 534.22 [M+1].

CHN Analysis: Found: C (65.20%), H (6.01%), N (13.16%),Calc: C (65.22%), H (6.04%), N (13.11%).

2-[2-butyl-(1-(2-(3-bromobenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)-N,N-dimethylacetamide (3c)

^{1}H NMR (CDCl$_3$-d6, 400 MHz, δ ppm): 0.92-0.95 (t,3H, -CH_3), 1.37-1.43 (m,2H, -CH_2), 1.52-1.58 (m,2H, -CH_2), 2.31-2.34 (t,2H, -CH_2), 2.84 (s,2H, -CH_2), 2.97 (s,6H, -CH_3), 3.21 (s, 3H, -CH_3), 3.73 (s, 3H,-CH_3), 4.03 (s, 2H,-CH_2), 7.18-7.24 (m,2H, -Ar-H), 7.35 (s,1H, -Ar-H), 7.49-7.51 (d,1H, -Ar-H), 7.63-7.66 (d, 1H, -Ar-H), 7.73 (s,1H, -Ar-H), 8.23 (s,1H, -Ar-H)

^{13}CNMR(DMSO-d6, 100 MHz, δ ppm):13.7, 20.3, 21.7, 22.3, 23.6, 25.8, 31.4, 32.2, 38.3, 115.5, 116.7, 122.7, 123.2, 123.5, 127.8, 128.2, 128.5, 129.9, 133.7, 138.3, 139.1, 139.3, 153.8, 153.9, 156.6, 164.7, 166.4, 170.3.

FAB Mass: m/z 578.17 [M+1].

CHN Analysis: Found: C (60.19%), H (5.55%), N (12.15%), Calc: C (60.21%), H (5.58%), N (12.11%).

2-[2-butyl-(1-(2-(4-bromo-3-chlorobenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)-N,N-dimethylacetamide (3d)

^{1}H NMR (CDCl$_3$-d6, 400 MHz, δ ppm): 0.92-0.95 (t,3H, -CH_3), 1.37-1.43 (m, 2H, -CH_2), 1.52-1.59 (m,2H, -CH_2), 2.32-2.35 (t,2H, -CH_2), 2.84 (s, 2H,-CH_2), 2.97 (s, 6H, -CH_3), 3.21 (s, 3H, -CH_3), 3.76 (s, 3H, -CH_3), 4.05 (s, 2H,-CH_2), 6.94-6.96 (d, 1H,-Ar-H), 7.27 (s,1H, -Ar-H), 7.45-7.48 (d, 1H, -Ar-H), 7.63-7.66 (d, 1H,-Ar-H), 7.72-7.75 (d, 1H, -Ar-H), 8.24 (s,1H, -Ar-H).

^{13}CNMR(DMSO-d6, 100 MHz, δ ppm): 13.7, 20.7, 21.5, 22.6, 23.3, 25.8, 31.4, 32.1, 38.4, 115.1, 115.3, 116.4, 122.9, 123.4, 127.3, 130.4, 131.2, 131.8, 132.7, 136.5, 139.2, 139.5, 153.3, 153.7, 156.5, 164.7, 166.3, 170.2.

FAB Mass: m/z 612.13 [M+1].
CHN Analysis: Found: C (56.80%), H (5.12%), N (11.41%),Calc: C (56.83%), H (5.10%), N (11.43%).

2-[2-butyl-1-(2-(3-methylbenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)-N,N-dimethylacetamide (3e)

^{1}H NMR ($CDCl_3$-d6, 400 MHz, δ ppm):0.92-0.95 (t,3H, -CH_3), 1.37-1.42 (m,2H, -CH_2), 1.56-1.62 (m, 2H, -CH_2), 2.30-2.35 (m,5H, -CH_2, -CH_3), 2.87 (s,2H, -CH_2), 2.96 (s,6H, -CH_3), 3.23 (s,3H, -CH_3), 3.76 (s, 3H, -CH_3), 4.02 (s, 2H,-CH_2), 6.95-6.98 (d,1H, -Ar-H), 7.09-7.14 (m,2H, -Ar-H), 7.46-7.49 (d,1H, -Ar-H), 7.63-7.66 (d, 1H,-Ar-H), 7.70-7.72 (d,1H, -Ar-H), 8.25 (s, 1H, -Ar-H).

^{13}CNMR(DMSO-d6, 100 MHz, δ ppm): 13.6, 20.5, 21.3, 21.9, 22.2, 23.8, 25.4, 32.1, 32.4, 38.3, 115.4, 116.1, 122.4, 123.6,126, 127.4, 128.7, 130.2, 136.3, 138.7, 134, 139.6, 153.2, 153.5, 156.3, 164.7, 166.2, 170.2.

FAB Mass: m/z 514.27 [M+1].
CHN Analysis: Found: C (70.11%), H (6.86%), N (13.60%),Calc: C (70.15%), H (6.87%), N (13.63%).

2-[2-butyl-1-(2-(3-fluorobenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)-N,N-dimethylacetamide (3f)

^{1}H NMR ($CDCl_3$-d6, 400 MHz, δ ppm): 0.91-0.94 (t,3H, -CH_3), 1.37-1.41 (m,2H, -CH_2), 1.53-1.58 (m, 2H, -CH_2), 2.31-2.36 (m, 2H, -CH_2), 2.83 (s, 2H, -CH_2), 2.94 (s,6H, -CH_3), 3.21 (s, 3H, -CH_3), 3.71 (s, 3H, -CH_3), 4.03 (s, 2H,-CH_2), 7.14-7.20 (m, 4H, -Ar-H), 7.63-7.66 (d,1H, -Ar-H), 7.72-7.75 (d,1H, -Ar-H), 8.25-8.28 (d, 1H, -Ar-H).

^{13}CNMR(DMSO-d6, 100 MHz, δ ppm):13.7, 20.2, 21.5, 22.4, 23.2, 25.8, 32.2, 32.3, 38.4, 115.2, 115.4, 115.8, 116.3, 122.7, 123.4, 127.5, 130.3, 131.5, 139.2, 139.6, 153.4, 153.8, 156.3, 159.8, 164.3, 166.5, 170.1.

FAB Mass: m/z 518.25 [M+1].
CHN Analysis: Found: C (67.82%), H (6.20%), N (13.55%), Calc: C (67.89%), H (6.23%), N (13.53%).

2-[2-butyl-1-(2-(4-methoxybenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)-N,N-dimethylacetamide (3g)

^{1}H NMR ($CDCl_3$-d6, 400 MHz, δ ppm):0.92-0.95 (t, 3H, -CH_3), 1.37-1.43 (m,2H, -CH_2), 1.52-1.58 (m, 2H,-CH_2), 2.31-2.36 (m, 2H, -CH_2, -CH_3), 2.84 (s,2H, -CH_2), 2.97 (s, 6H,-CH_3), 3.27 (s,3H, -CH_3), 3.72 (s,3H, -CH_3), 3.80 (s,3H, -OCH_3), 4.03 (s,2H, -CH_2), 6.83-6.88 (dd, 2H, -Ar-H), 7.08-7.14 (dd, 2H,-Ar-H), 7.65-7.67 (d, 1H, -Ar-H), 7.83-7.85 (d,1H, -Ar-H), 8.12 (s, 1H, -Ar-H).

^{13}CNMR(DMSO-d6, 100 MHz, δ ppm):13.6, 20.7, 21.5, 22.8, 23.3, 25.6, 32.1, 32.3, 38.6, 55.7, 114.3, 115.7, 116.5, 122.4, 123.4, 127.9, 128.2, 130.1, 139.3, 139.5, 153.5, 153.8, 156.2, 157.8, 164.7, 166.3, 170.2.

FAB Mass: m/z 530.27 [M+1]
CHN Analysis: Found: C (68.06%), H (6.64%), N (13.25%),Calc: C (68.03%), H (6.66%), N (13.22%).

2-[2-butyl-1-(2-(3,4-dichlorobenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)-N,N-dimethylacetamide (3h)

^{1}H NMR ($CDCl_3$-d6, 400 MHz, δ ppm): 0.92-0.95 (t,3H, -CH_3), 1.37-1.42 (m,2H, -CH_2), 1.53-1.58 (m, 2H, -CH_2), 2.31-2.34 (t,2H, -CH_2), 2.86 (s, 2H, -CH_2), 2.97 (s,6H, -CH_3), 3.20 (s,3H, -CH_3), 3.75 (s,3H, -CH_3), 4.05 (s, 2H,-CH_2),7.03-7.05 (d,1H, -Ar-H), 7.6 (s,1H, -Ar-H), 7.64-7.70 (m,2H, -Ar-H), 7.73-7.75 (d,1H, -Ar-H), 8.27 (s,1H, -Ar-H).

^{13}CNMR(DMSO-d6, 100 MHz, δ ppm):13.7, 20.8, 21.4, 22.3, 23.8, 25.2, 31.6, 32.4, 38.9, 115.1, 116.5, 122.5, 123.4, 127.7, 130.1, 130.3, 130.4, 130.7, 131.2, 139.5, 139.8, 153.4, 153.8, 156.6, 164.4, 166.2, 170.2.

FAB Mass: m/z 568.18 (M+1]
CHN Analysis: Found: C (61.27%), H (5.53%), N (12.34%),Calc: C (61.27%), H (5.50%), N (12.32%).

2-[2-butyl-1-(2-(4-methyl benzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)-N,N-dimethylacetamide (3i)

^{1}H NMR ($CDCl_3$-d6, 400 MHz, δ ppm): 0.91-0.93 (t,3H, $-CH_3$), 1.38-1.44 (m, 2H, $-CH_2$), 1.53-1.59 (m,2H, $-CH_2$), 2.17 (s,3H, $-CH_3$), 2.31-2.36 (m, 2H, $-CH_2$, $-CH_3$), 2.86 (s, 2H, $-CH_2$), 2.97 (s, 6H, $-CH_3$), 3.23 (s,3H, $-CH_3$), 3.76 (s,3H, $-CH_3$), 4.03 (s,2H, $-CH_2$), 7.06-7.10 (dd, 2H, -Ar-H), 7.12-7.16 (dd, 2H,-Ar-H), 7.63-7.65 (d,1H, -Ar-H), 7.71-7.73 (d,2H, -Ar-H), 8.21 (s, 1H,-Ar-H).

^{13}CNMR(DMSO-d6, 100 MHz, δ ppm):13.6, 20.7, 21.5, 21.6, 22.3, 23.1, 25.8, 32.1, 32.5, 38.6, 115.8, 116.3, 122.7, 123.5, 127.7, 128.5, 129.6, 133.1, 135.3, 139.2, 139.5, 153.6, 153.4, 156.8, 164.7, 166.3, 170.2.

FAB Mass: m/z 514.27 [M+1]
CHN Analysis: Found: C (70.11%), H (6.86%), N (13.60%) Calc: C (70.15%), H (6.87%), N (13.63%).

2-[2-butyl-1-(2-(3-methoxybenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)-N,N-dimethylacetamide (3j)

^{1}H NMR ($CDCl_3$-d6, 400 MHz, δ ppm): 0.92-0.95 (t,3H, $-CH_3$), 1.37-1.43 (m, 2H, $-CH_2$), 1.55-1.61 (m, 2H, $-CH_2$), 2.30-2.35 (m,2H, $-CH_2$), 2.83 (s, 2H,$-CH_2$), 2.97 (s,6H, $-CH_3$), 3.21 (s,3H, $-CH_3$), 3.73 (s, 3H, $-OCH_3$), 3.74 (s, 3H, $-CH_3$), 4.03 (s,2H, $-CH_2$), 6.83-6.90 (m,3H, -Ar-H), 7.26-7.28 (d, 1H,-Ar-H), 7.63-7.65 (d,1H, -Ar-H), 7.81-7.83 (d,1H, -Ar-H), 8.12 (s,1H, -Ar-H).

^{13}CNMR(DMSO-d6, 100 MHz, δ ppm):13.6, 20.7, 21.5, 22.3, 23.2, 25.6, 32.1, 32.6, 38.7, 55.3, 111.2, 115.4, 115.8, 116.1, 121.6, 122.7, 123.6, 127.7, 129.5, 137.3, 139.1, 139.4, 153.6, 153.9, 156.2, 160.1, 164.5, 166.3, 170.2.

FAB Mass: m/z 530.27 [M+1]
CHN Analysis: Found: C (68.00%), H (6.68%), N (13.22%), Calc: C (68.03%), H (6.66%), N (13.22%).

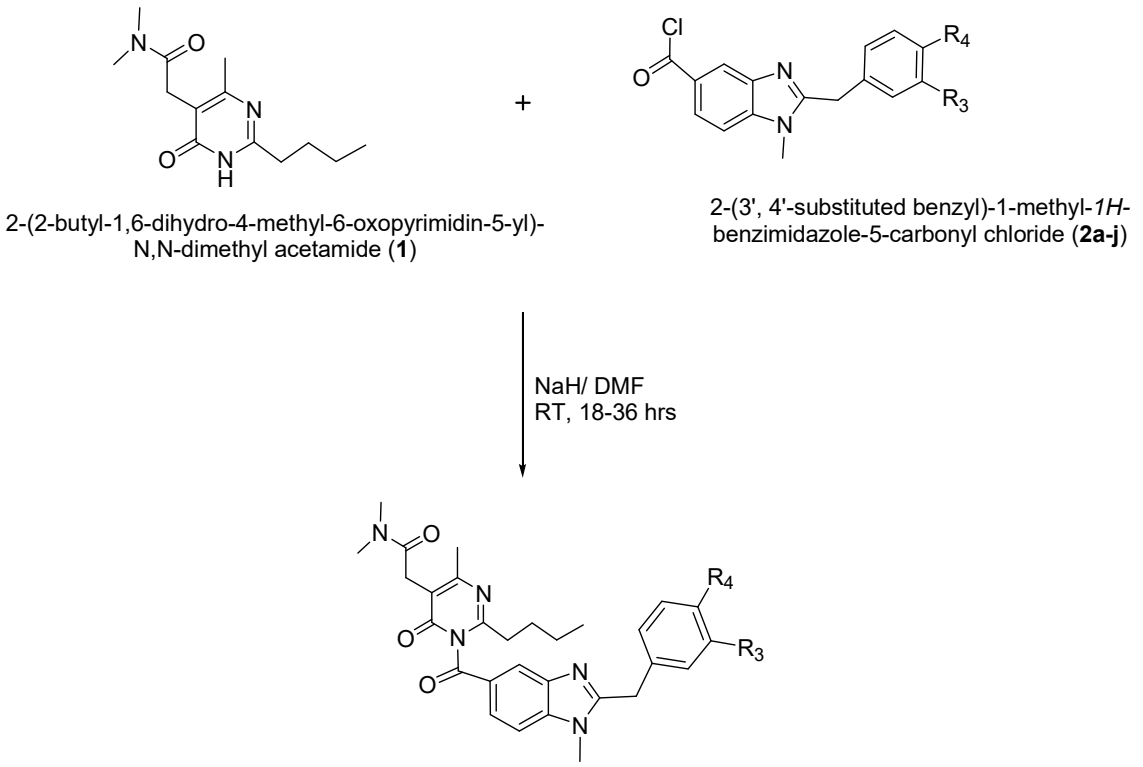
Antimicrobial Activity

The antimicrobial activity of the synthesized compounds was evaluated by disk diffusion method[32] against selected pathogens such as*Staphylococcus aureus* (*S.aureus*)*Bacillus subtilis*(*B.subtilis*),*Escherichia coli* (*E.Coli*) and *Pseudomonas aeruginosa* (*P.aeruginosa*). The synthesized compounds were used at the concentration of 250 µg/mL using DMSO as a solventand comparedwith that of standard Ciprofloxacin. A similar procedure was carried out for studying the antifungal activity the synthesized compounds against *Candida albicans*(*C.albicans*).[33]

3. RESULTS AND DISCUSSION

Synthesis

In the present study, the synthesis of benzimidazole derivatives as a 2-{2-butyl-1-[2-(3`,4`-substitutedbenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}-N,N-dimethylacetamides (**3a-j**) as shown in **Scheme1**. Initially, 2-(2-butyl-1,6-dihydro-4-methyl-6-oxopyrimidin-5-yl)-N,N-dimethylacetamide (**1**) with various 2-(3`,4`-substituted benzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl chlorides (**2a-j**)inpresenceofsodium hydride in N,N-dimethylformamidefor 18 to 36 hours at room temperature.The yields of the products obtained were good and the details of benzimidazole derivatives are provided in **Table 1**.



2-(2-butyl-1,6-dihydro-4-methyl-6-oxopyrimidin-5-yl)-N,N-dimethyl acetamide (**1**)

2-(3', 4'-substituted benzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl chloride (**2a-j**)

2-{2-butyl-1-[2-(3',4'-substituted benzy)l-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}-N,N-dimethyl acetamide (**3a-j**)

Scheme1. Synthesis of 2-{2-butyl-1-[2-(3`,4`-substitutedbenzyl)-1-methyl-*1H*-benzimidazole-5-carbonyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}-N,N-dimethylacetamides (**3a-j**).

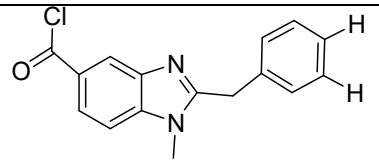
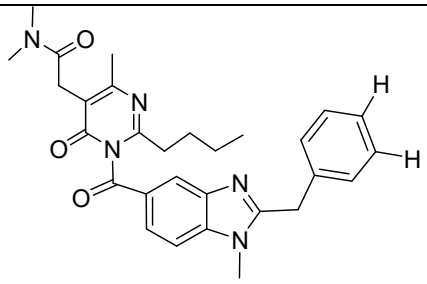
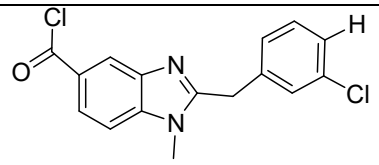
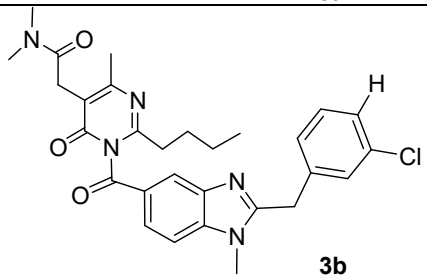
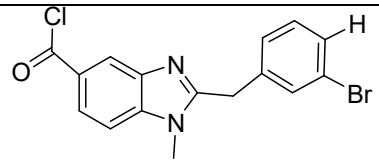
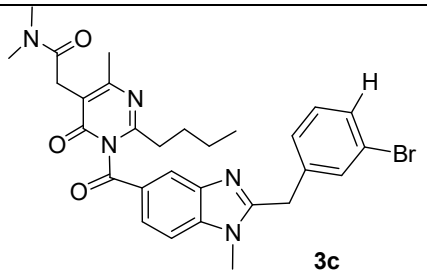
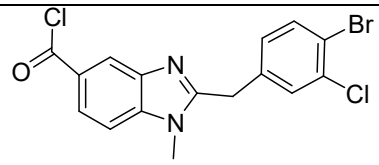
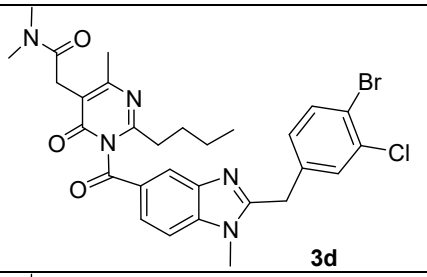
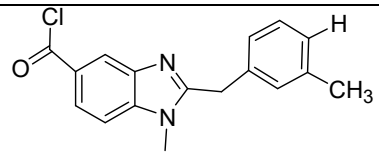
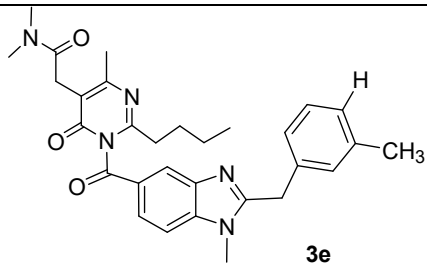
Antimicrobial Activity

The antimicrobial activity of ten benzimidazole derivatives against four selected pathogens and antifungal activity against onefungal species were evaluated by using disc diffusion method at 250 µg/mL and the results are presented in **Table 2.**

Among the tested compounds, all the compounds (**3a-j**) showed highest zone of inhibition against *B. subtilis* with high zone of inhibition. The compounds **3c**, **3d**and **3h** showed good zone of inhibition against *P. aeruginosa* and *E. coli* with a zone of inhibition of 19.5, 20.0, 18.0 mm. Further, the compounds **3a-j**alsofound to good activity with zone of inhibition of 8.0 to 9.00 mm against *S. aureus*.

The antifungal activity of benzimidazole derivatives (**3a-j**) against *C. albicans* is at 250 µg/mL concentration (**Table 2**) in DMSO using *Fluconazole* as a standard. From these results, among the tested compounds **3d** to 3**h** showed good activity against selected strain at 250 µg/mL concentration as compared to *Fluconazole* as a standard. Further, the remaining compounds are good antifungal activity against *C.albicans.* Hence, from these results the synthesized substituted benzimidazole derivatives to be active against various antimicrobial strains.

Table 1. Details of thebenzimidazole derivatives **3a-j**.

S. No	3',4'-substituted Benzimidazole carbonyl chloride	Product	Yield (%)	Melting point (^{o}C)
1	 **2a**	 **3a**	35	191-193
2	 **2b**	 **3b**	33	165-167
3	 **2c**	 **3c**	39	131-132
4	 **2d**	 **3d**	49	177-179
5	 **2e**	 **3e**	41	177-179

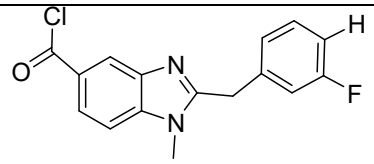
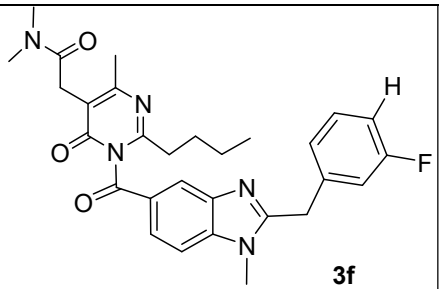
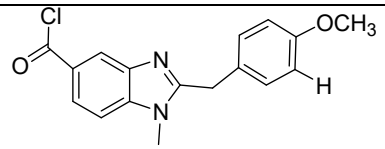
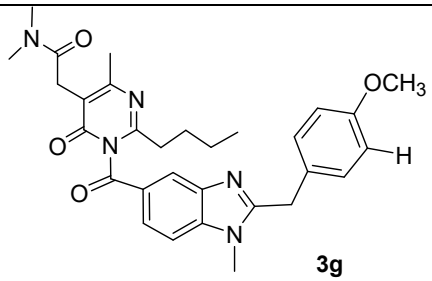
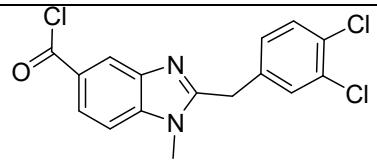
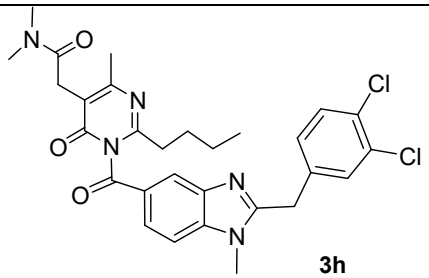
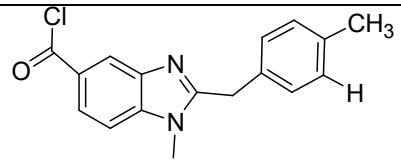
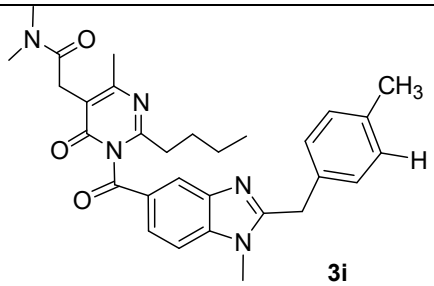
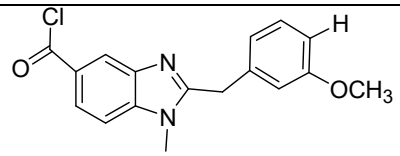
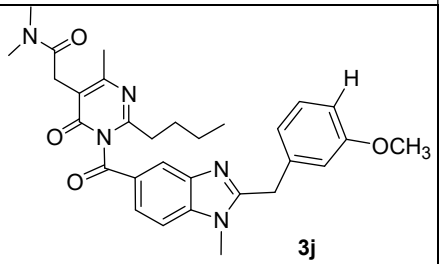
6	 **2f**	 **3f**	49	132-134
7	 **2g**	 **3g**	39	158-160
8	 **2h**	 **3h**	42	185-187
9	 **2i**	 **3i**	49	163-165
10	 **2j**	 **3j**	37	169-171

Table 2: Antimicrobial activity of benzimidazole derivatives at 250 μg/mL (**3a-3j**).

Sample Code	Antibacterial activity (Zone of inhibition in mm)				Antifungal activity (Zone of inhibition in mm)
	B. subtills	***S. aureus***	***E. coli***	***P. aeruginosa***	***C.albicans***
3a	20.0	8.9	15.0	15.5	8.6
3b	18.2	8.0	17.0	17.0	7.2
3c	17.0	8.5	19.0	19.5	8.5
3d	17.5	8.2	20.0	20.0	9.2
3e	18.0	9.0	15.4	14.0	9.2
3f	19.5	9.0	14.0	14.2	9.0
3g	20.8	9.0	15.9	16.2	8.9
3h	16.5	8.0	18.0	18.0	9.0
3i	19.3	8.5	16.0	15.0	7.2
3j	21.0	8.0	16.0	14.1	8.0
Ciprofloxacin	24.0	10.5	24.0	20.5	
Fluconazole					12.0

4. CONCLUTION

In conclusion, the ten benzimidazole derivatives were synthesized using simple approach. All the compounds were screened for antimicrobial activities. The synthesized derivatives (**3a-j**)showed good antibacterial activity against *B. subtilis* with highest zone of inhibition and other also. Moreover, the compounds also possess good antifungal activity against *C.albicans*.From these results, the synthesized benzimidazole derivatives are superior against various antimicrobial strains.

5. REFERENCES

1. F. Hoebrecker Ber., 5 (1872), pp. 920-926.
2. BarkerHA, SmythRD,WeissbachH, TooheyJI, LaddJN,VolcaniBE. Isolation and properties of crystalline cobamidecoenzymes containing benzimidazole or 5,6-dimethylbenzimidazole.J Biolog. Chem., 1960;235(2): 480-488.
3. Shukla A. Synthesis and biological screening of benzimidazole derivatives. Int. J. Pharm. Sci. Res., 2012; 3(3): 922-927.
4. Tupe AP, Pawar PY, Mane BY, Magar SD. Synthesis analgesic and anti-inflammatory activity of some 2-substituted 3-acetic acid benzimidazole derivatives. Res. J. Pharm. Biol. Chem. Sci.,2013; 4(2): 928-935.
5. Sanahanbi N, Sivakumar T. Synthesis of some schiff's bases of 2-methyl benzimidazole derivatives and screening of analgesic and anti-inflammatory activities. CODEN(USA):

AJBPAD, 2013; 4(2).
6. Marriappan G, Bhuyan NR, Pradeep Kumar, Deepak Kumar, Murali K. Synthesis and evaluation of Mannich bases of benzimidazole derivatives. Indian J. Chem., 2011; 50B(09): 1216-1219.
7. Waghulde SO, Lonsane GU, Borwandkar V, Laddha S. Synthesis and anti-inflammatory activity of novel 2-(Substituted alkyl or aryl pyridynyl) benzimidazole derivatives. 16th Int. Electronic Conference on synthetic Organic Chemistry, 2012. doi:10.3390/ecsoc-16-01060.
8. Ansari KF, Lal C. Synthesis and biological activity of some heterocyclic compounds containing benzimidazole and beta-lactam moiety. J. Chem. Sci., 2009; 121(6): 1017-1025.
9. Hamdan S. Al-Ebaisat. Synthesis and biological activities of some benzimidazoles derivatives. J. Appl. Sci. Environ. Manage., 2011; 15(3): 451-454.
10.Chimirri A, Grasso S, Monforte P, Rao A, Zappala M, Monforte AM, Pannecouque C, Witvrouw M, Balzarini J, De Clercq E. Synthesis and biological activity of novel 1H, 3H-thiazolo[3,4-a]benzimidazoles: non-nucleoside human immunodeficiency virus type 1 reverse transcriptase inhibitors. Antivir. Chem. Chemother., 1999; 10(4): 211-217.
11.Shingare MS, Mane DV, Shinde DB, Thore SN, Bhawsar SB. Synthesis of mannich bases of possible antiviral agents, Asian J. Chem., 1996; 8(2): 225-228.
12.Sreena K,Ratheesh R, Rachana M, Poornima M, Shyni C. Synthesis and anthelmintic activity of benzimidazole derivatives. HYGEIA. 2009; 1(1): 21-22.
13.Walia R, Hedaitulla Md, Nazz SF, Iqbal K, Lamba HS. Benzimidazole derivatives-An overview. Int. J. Res. Pharm. Chem. 2011; 1(3): 565-574.
14.B Cakir, E Yildirim, T Ercanli, K Erol, MF Sahin, Synthesis and anticonvulsant activity of some (2:4-substituted) benzaldehyde (2-oxobenzothiazolin-3-yl) acetohydrazones. iL Farmaco, 1999; 54(11-12): 842-845.
15.Kalyankar TM, Pekamwar SS, Wadher SJ, Tiprale PS, Shinde GH. Review on benzimidazole derivative. Int. J. Chem. Pharm. Sci., 2012; 3(4): 1-10.
16.Kapuriya K, Ganure A, Davda S, Kitawala M, Topiya H. Benzimidazole: a promising lead for AntiCancer drug design. UJP 2013; 02(03): 57-62.
17.Patil A, Ganguly S, Surana S. A systemic review of benzimidazole derivatives as an antiulcer agent. Rasayan J. Chem., 2008; 1(3): 447-460.
18.Reddy BA., Synthesis and characterization of some benzimidazole derivatives using as antihypertensive agents. JPRHS, 2010; 2(1): 103-113.
19.Hussain MMM, Bhat KI, Revanasiddappa BC, Bharathi DR. Synthesis and biological evaluation of some novel 2-mercapto pyrimidines. Int. J. Pharm. Pharm. Sci., 2013; 5 (2): 471-473.
20.Mohamed MS, Awad SM, Zohny YM, Mohamed ZM. New thiopyrimidine derivatives of expected antiinflammatory activity. Pharmacophore. 2012; 3(1): 62-75.
21.Nag S, Pathak R, Kumar M, Shukla PK, Batra S. Synthesis and antibacterial evaluation of ureides of Baylis-Hillman derivatives. Bioorg. Med. Chem.,2006;16(14): 3824-3828.
22.Hoffmann HH, Kunz A, Simon VA, Palese P, Shaw ML. Broad-spectrum antiviral that interferes with de novo pyrimidine biosynthesis. Proc Natl Acad Sci U S A.2011; 108 (14):5777-5782.
23.Clercq ED, Holý A. Acyclic nucleoside phosphonates: a key class of antiviral drugs. Nat. Rev. Drug Discov., **2005;** 4(11): 928-940.
24.Trivedi AR, Siddiqui AB, Shah VH. Design, synthesis, characterization and antitubercular activity of some 2- heterocycle-substituted phenothiazines. ARKIVOC 2008; (ii): 210-217.
25.Agarwal A, Srivastava K, Puri SK, Sinha S, Chauhan PMS. A small library of

trisubstituted pyrimidines as antimalarial and antitubercular agents. Bioorg. Med. Chem. Lett. 2005;15(23): 5218-5221.
26. Sondhi SM, Dinodia M, Rani R, Shukla R, Raghubir R. Synthesis, anti-inflammatory and analgesic activity evaluation of some pyrimidine derivatives. Indian J. Chem.,2009; 49b: 273-281.
27. Majeed J, Shaharyar M. Synthesis and in vivo diuretic activity of some novel pyrimidine derivatives. J. Enzyme Inhib. Med. Chem., 2011; 26(6): 819-826.
28. Reading SA, Earley S, Waldron BJ, Welsh DG, Brayden JE. TRPC3 mediates pyrimidine receptor-induced depolarization of cerebral arteries. Am. J. Physiol. Heart Circ. Physiol 2005; 288(5): H2055-H2061.
29. Jain KS, Chitre TS, Miniyar PB, Kathiravan MK, Bendre VS, Veer VS, Shahane SR, Shishoo J. Biological and medicinal significance of pyrimidines. Curr. Sci., 2006; 90(6): 793-803.
30. Mishra R, Tomar I. Pyrimidine: the molecule of diverse biological and medicinal importance. Int. J. Pharm. Sci. Res.,2011; 2(4):758-771.
31. Abu-Hashem AA, El-Shehry MF, Badria FA. Design and synthesis of novel thiophene-carbohydrazide, thienopyrazole and thienopyrimidine derivatives as antioxidant and antitumor agents. Acta Pharm.,2010; 60(3): 311-323.
32. Prakash O, Bhardwaj V, Kumar R, Tyagi P, Aneja K.R. Organoiodine (III) mediated synthesis of 3-aryl/hetryl-5,7-dimethyl-1,2,4-triazolo[4,3-a]pyrimidines as antibacterial agents. Eur. J. Med. Chem., 2004;39(12): 1073-1077.
33. BasavarajaHS,SreenivasaGM, JayachandranE. Synthesis and biological activity of novel pyrimidino imidazolines, Indian J. Heterocycl. Chem., 2005; 15: 69.