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Synthesis, Characterization and Biological Evaluation of New N-alkylated/N-acylated 2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole Derivatives

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ABSTRACT: In present study of potassium ethyl xanthate was treated with *O*-pheylenediamine to form 2-mercaptobenzimidazole, which was treated with1-bromo-4-(bromomethyl) benzene to obtained 2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole. Using this compound alkylation and acylation done at the benzimidazole –NH position with different alkyl and acyl halide reagent leading to the functionalized derivatives. Newly synthesized derivatives (6a to 6i) have been evaluated on the basis of spectral and analytical data like melting point, IR, ^{1}H-NMR and Mass spectroscopy. All the synthesized compounds were screened for their antimicrobial activity. This displayed some promising results towards testing organism in-vitro.

Keywords: Cyclisation; Alkylation; Acylation; Condensation; Anti-bacterial activity and Anti-fungal activity.

INTRODUCTION: Recent years heterocyclic compounds are acquiring great importance due to the pharmacological activities[1] therefore, the development of new efficient methods to synthesize heterocycles is of considerable interest.[2] Benzimidazole and its derivatives are the significant class of compounds in medicinal chemistry.[3]

They display a wide range of activities such as anti-inflammatory, diuretic, antimicrobial, antibacterial, antiviral, antitumor, antiprotozoal, antiulcer, protein kinase CK2, antioxidants, antiasthmatic, antidiabetic, 5-HT3 receptor antagonist, analgesic, hypotensive, anti-mycobacterial, anthelmintic, histamine H4 receptor antagonist, and anticonvulsant activity.[4-5] 2-Mercapto benzimidazole derivatives are one of the most important derivatives of benzimidazole known to possess varied biological activities, such as antihistamine[6], anti-diabetic,[7] hypocholesterolemic activity,[8] anxiolytic,[9] anti-cancer,[10] anti-convulsant,[11] analgesic,[12] anti–inflammatory,[13] actoprotector,[14] anti-ulcer,[15] antifungal,[16] antibacterial,[16] antiviral,[17] anti-fungal,[18] antioxidant[19] and antiprotozoal[20]. The aim of the present study is to design, synthesize and evaluate *in vitro* the antibacterial activity of new derivatives of N-alkylated/N-acylated 2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole, which were synthesized by S-alkylation with alkyl halides, N-acylation and N-alkylation to form different derivatives of 2-[(4-bromobenzyl)sulfanyl]-1*H*-benzimidazole.

MATERIALS AND METHODS: O- phenylene diamine, potassium ethyl xanthate, 1-bromo-4-(bromomethyl)benzene, acetic acid, potassium carbonate, potassium iodide, alkylating and acylating agent, all the chemical reagents and solvents are commercial grade which were procured locally and are used in the study. For reaction monitoring thin layer chromatography (TLC) was used. TLC viewed under UV lamp and Iodine chamber. Melting points were determined in an open capillary using melting point apparatus. Infrared spectra of compounds were recorded in KBr on Jasco, FT/IR-4100 type-A. The proton magnetic resonance (^{1}H -NMR) spectraof the compounds were recorded on JEOL 500 MHz NMR spectrometer.

RESULTS AND DISCUSSION: 2-[(4-bromobenzyl)sulfanyl]-1*H*-benzimidazole(4) was synthesized by known method using o-phenylenediamine, treated with potassium ethyl xanthate in presence of ethanol at reflux temp to form potassium 1*H*-benzimidazole-2-thiolate[1], which was treated with acetic acid to form 1*H*-benzimidazole-2-thiol[21][2] and then which was alkylation with 1-bromo-4-

(bromomethyl) benzene [3] in presence of potassium carbonate and acetone at reflux temperature to obtained 90% yield having m.p.296-298°C. Based on the spectral and analytical data the compound was assigned to be derivatives 2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole (4) (Scheme-1). The alkylation of compound 4 with various electrophilic reagents such as (5a,5f,5g)in presence of acetone and potassium carbonate as base yielded the N-alkylated derivatives obtained Compounds (6a,6f,6g) (Scheme-2) and the acylation of compound [4] with various electrophilic reagents such as (5b,5c,5d,5e) in presence of acetone and potassium carbonate as base yielded the N-acylated derivatives obtained Compounds (6b,6c,6d,6e) (Scheme-2) .

The alkylation of compounds [4] with various electrophilic reagents such as (5h,5i) in presence of DMF and potassium carbonate as base yielded the N-alkylated derivatives obtained Compounds (6h,6i) (Scheme-3).

General Procedure for the synthesis of 1*H*-benzimidazole-2-thiol (2): A mixture of 64.8g. (0.60mole) of *o*-phenylenedimine, 105.6g. (0.66mole) of potassium ethyl xanthate 600 ml. of 95% ethanol, and 90 ml. of water in a 2 lit. flask is heated under reflux for 3 hours. Norit (24 g.) is then added cautiously, and after the mixture has been heated at the reflux temperature for 10 minutes the Norit is removed by filtration. The filtrate is heated to 60–70°C, 600 ml. of warm tap water (60–70°C) is added, and then 50 ml. of acetic acid in 50 ml. of water is added with good stirring. The product separates as glistening white crystals and the mixture is placed in a refrigerator for 3 hours to complete the crystallization.

The product is collected on a Buchner funnel and dried overnight at 40°C. The yield is 78 g. (86.5%) of 1*H*-benzimidazole-2-thiol[21] melting at 303-304°C (cor.)

Synthesis of* 2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole *(4): To the solution of *H*-benzimidazole-2-thiol (3.30 mmoles) in THF (20ml) was added potassium carbonate (3.60 mmoles), tetra butyl ammonium bromide (0.30 mmoles) followed by the addition of 1-bromo-4-(bromomethyl) benzene (3.60 mmoles).

The reaction mixture was then reflux for 3 hrs(TLC monitoring), THF from the reaction mixture was evaporated under vacuum at 40-50°C and added 30ml water and 30 ml ethyl acetate and stirred for 10 min.

Ethyl acetate and aqueous layers were separated. Ethyl acetate layer was washed with 30 ml water, Distilled out ethyl acetate under reduced pressure to get degas mass and which was recrystallization in ethanol to obtained corresponding s-substituted derivative (**4)** 2-[(4-bromobenzyl)sulfanyl]-1*H*-benzimidazole with yield 22.73g (90%), Melting point 201-205°C (Scheme-1).

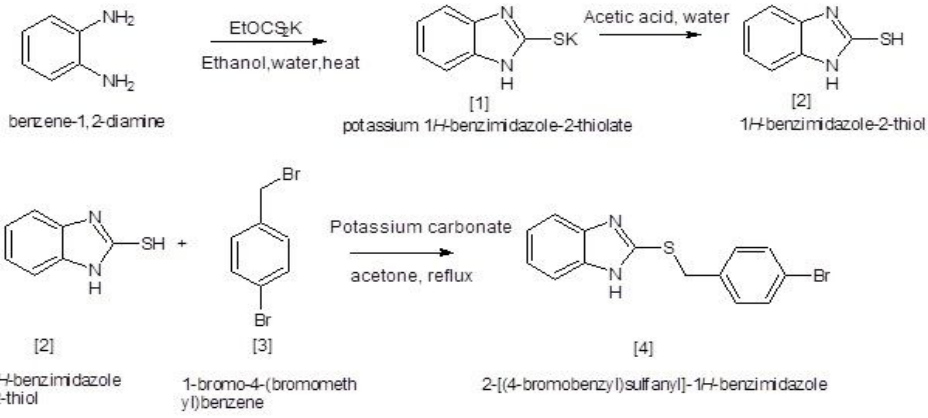
General procedure for the synthesis of N-alkylated derivatives of 2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole compounds (6a-6g): To a solution of 2-(4-bromophenyl)-1*H*-benzimidazole [**4]** (3.15 mmoles) in acetone(25ml) was added powder potassium carbonate (3.47 mmoles), tetra butyl ammonium bromide(0.34 mmoles) followed by addition of alkylating agent (5a-5g, 3.60 mmoles) at RT. The reaction mixture was heated to reflux for 4 hrs.

Reaction progress was monitored on TLC. After reaction completion, Distilled out solvent under reduce pressure at 40-50°C and added 25ml water and 50 ml ethyl acetate and stirred for 10 min. Ethyl acetate and aqueous layers were separated. Ethyl acetate layer was washed with 30 ml water, Distilled out ethyl acetate under reduced pressure to get degas mass and which was recrystallization in ethanol to obtained corresponding N-substituted derivative (6a-6g). (Scheme-2)

General procedure for the synthesis of N-alkylated derivatives of 2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazolecompounds(6h-6i): To a solution of 2-[(4-bromobenzyl)sulfanyl]-1*H*-benzimidazole (**4**) (3.15mmoles) in acetone (25ml) was added powder potassium carbonate (3.47mmoles), Potassium iodide (3.15 mmoles) in N,N –dimethyl formamide (30 ml) was added alkyation compound (**5h-5i,** 3.6mmoles) at RT. The reaction mixture was then warmed 80–90°C for 5-6 hrs. Reaction progress was monitored on TLC. After reaction completion, Reaction mass was quenched with 25 ml water and 50 ml ethyl acetate and stirred for 10 min.

Ethyl acetate and aqueous layers were separated. Ethyl acetate layer was washed with 25 ml water, Distilled out ethyl acetate under reduced pressure to get degas mass and which was recrystallization in ethanol to obtained corresponding N-substituted derivative (**6h-6i**). (Scheme-3)

Scheme - 1



benzene-1,2-diamine

[1]

potassium 1*H*-benzimidazole-2-thiolate

[2]

1*H*-benzimidazole-2-thiol

[2]

1*H*-benzimidazole -2-thiol

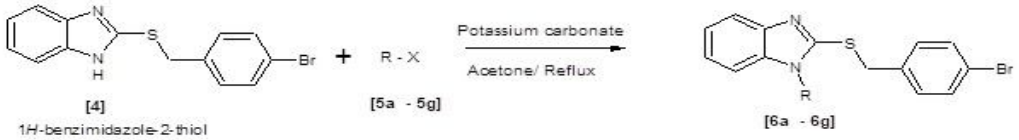
[3]

1-bromo-4-(bromomethyl)benzene

[4]

2-[(4-bromobenzyl)sulfanyl]-1*H*-benzimidazole

Scheme - 2



[4]

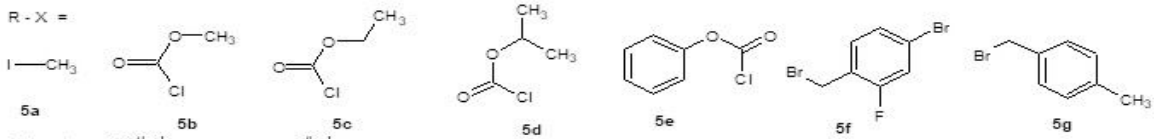
1*H*-benzimidazole-2-thiol

[5a - 5g]

[6a - 6g]

Where

R - X =



5a

iodomethane

5b

methyl carbonochloridate

5c

ethyl carbonochloridate

5d

propan-2-yl carbonochloridate

5e

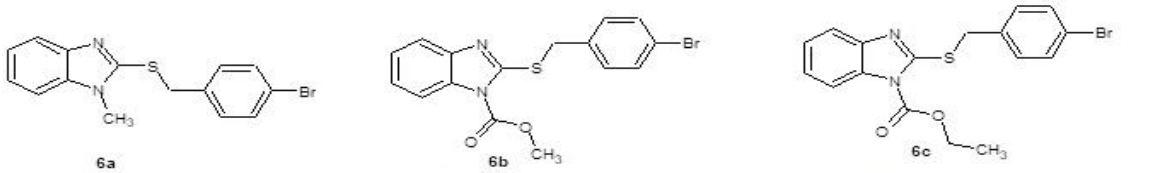
phenyl carbonochloridate

5f

4-bromo-1-(bromomethyl)-2-fluorobenzene

5g

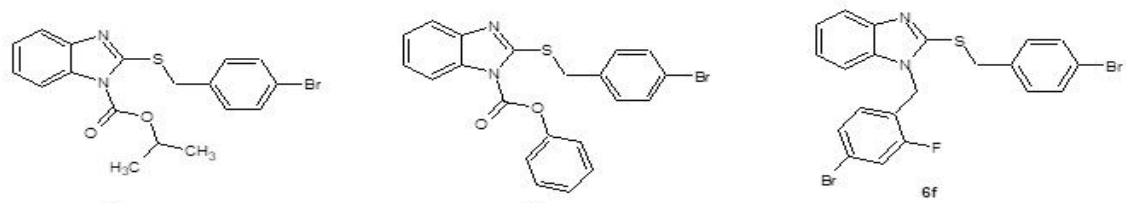
1-(bromomethyl)-4-methylbenzene



2-[(4-bromobenzyl)sulfanyl]-1-methyl-1*H*-benzimidazole

methyl 2-[(4-bromobenzyl)sulfanyl]-1*H*-benzimidazole-1-carboxylate

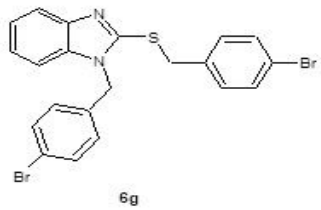
ethyl 2-[(4-bromobenzyl)sulfanyl]-1*H*-benzimidazole-1-carboxylate



propan-2-yl 2-[(4-bromobenzyl)sulfanyl]-1*H*-benzimidazole-1-carboxylate

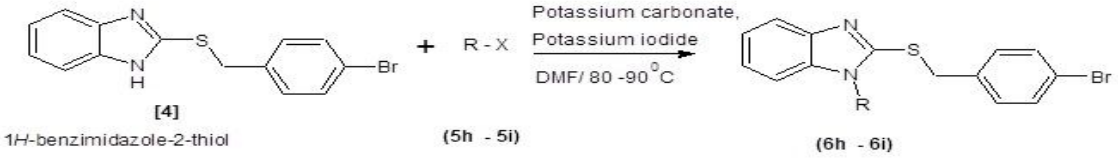
phenyl 2-[(4-bromobenzyl)sulfanyl]-1*H*-benzimidazole-1-carboxylate

2-[(4-bromobenzyl)sulfanyl]-1-(4-bromo-2-fluorobenzyl)-1*H*-benzimidazole

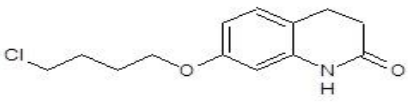


1-(4-bromobenzyl)-2-[(4-bromobenzyl)sulfanyl]-1*H*-benzimidazole

Scheme - 3

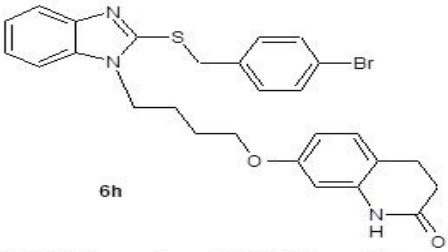


Where R - X =



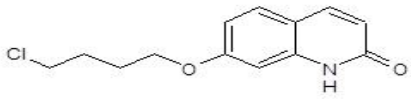
5h

7-(4-chlorobutoxy)-3,4-dihydro quinolin-2(1*H*)-one



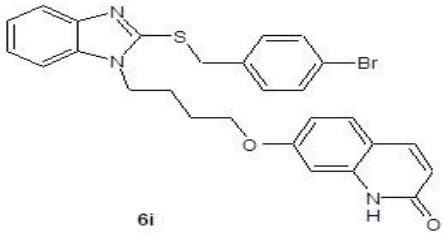
6h

7-(4-(2-(4-bromobenzylthio)-1H benzo[d] imidazol-1-yl) butoxy)-3, 4dihydroquinolin-2(1H) one



5i

7-(4-chlorobutoxy) quinolin-2(1*H*)-one



6i

7-(4-(2-(4-bromobenzylthio)-1H-benzo[d] imidazol-1-yl) butoxy) quinolin-2(1H)-one

Analytical Characterization:

2-[(4-bromobenzyl) sulfanyl]-1-methyl-1*H*-benzimidazole *(4)*

Yield=90%; M.P.=201-205°C; IR(KBr):672(C-S), 741(C-Br), 1069(C=N),1406(C=C), 3066 (Ar C-H), 3128(N-H)cm^{1}.

^{1}1H-NMR(DMSO-D_6):δ4.54(S,2H),7.10-7.14 (m,2H), 7.40-7.42(d,*J1=8.5Hz*,2H), 7.43-7.46 (q,*J1=3.0Hz*, 2H), 7.48-7.50(d,*J1=8.5Hz*,2H), 12.57(s, 1H); MS (EI, *m/z*): 319.06 (M^{+}+1).

2-[(4-bromobenzyl) sulfanyl]-1-methyl-1*H*-benzimidazole *(6a)*

Yield=75%; M.P.=123-129°C; IR (KBr):667(C-S), 753(C-Br), 1068(C=N), 1285(Ar C-N), 1421(C=C), 3042(Ar C-H)cm^{1}.

^{1}H-NMR (CDCl3):δ3.61(S,3H), 4.55(S,2H), 7.21-7.24 (m,3H), 7.26-7.30 (m,2H), 7.39-7.43 (d,t, *J1=8.8Hz, J2=2.1,,2H*).7.68-7.71 (m,1H), MS (EI, *m/z*): 333.09 (M^{+}+1).

Methyl 2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole-1-carboxylate *(6b)*

Yield=92%; M.P.=142-145°C; ; IR(KBr):669(C-S), 745(C-Br), 1068(C=N), 1454(C=C), 1740(C=O), 3042(Ar C-H)cm^{1}.

^{1}H-NMR ($CDCl_3$):δ4.10(s, 3H), 4.51(s,2H), 7.24-7.28(d,d,J1=7.9*Hz*,J2=1.3*Hz*,1H), 7.29-7.34 (t,d, J1=7.6*Hz*, J2=1.4*Hz*,1H), 7.34-7.38(d,t,J1=8.7*Hz*, J2=2.1*Hz*,2H), 7.42-7.45(d,t,J1=8.7*Hz*, J2=2.1*Hz*, 2H) 7.62-7.64(m, 1H), 7.83-7.85 (m,1H), MS (EI, *m/z*): 377.14 (M^{+}+1).

Ethyl 2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole-1-carboxylate *(6c)*

Yield=91%; M.P=74-76°C; IR(KBr): 669(C-S), 741(C-Br), 1070(C=N), 1447(C=C),1746(C=O), 2992(C-C), 3077(Ar C-H)cm^{1}.

^{1}H-NMR($CDCl_3$):δ1.49-1.53(t,*J1*=7.1*Hz*,3H), 4.51-4.52(s,2H), 4.54-4.58(q,*J1*=7.1*Hz*,2H), 7.24-7.26 (m, 1H,), 7.22-7.31 (m, 1H), 7.33-7.38 (d,t *J1=8.7Hz,J2=2.1Hz*,2H),7.42-7.45(m,2H), 7.62-7.64 (m,1H), 7.84-7.87(m,1H). MS (EI, *m/z*): 391.15 (M^{+}+1).

Propan-2-yl 2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole-1-carboxylate *(6d)*
Yield=89%; M.P.=132-135°C; IR(KBr):667(C-S), 764(C-Br), 1078(C=N), 1452(C=C), 1743(C=O), 2987(C-C), 3055(Ar C-H)cm[1].
[1]H-NMR(CDCl3): δ1.49-1.50(d,*J1=6.3Hz*,6H), 4.51 (s, 2H), 5.26-5.35 (s, 1H), 7.25-7.29(m,1H),7.31-7.33(t,d,J1=7.6Hz, J2=1.4Hz1H), 7.35-7.38 (d,t,J1=8.76Hz, J2=2.1Hz,2H),7.42-7.45(d,t, J1=8.7Hz, J2=2.1Hz 2H), 7.62-7.64 (m,1H), 7.84-7.86 (m,1H). MS (EI, *m/z*): 405.19 (M+1).

Phenyl 2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole-1-carboxylate *(6e)*
Yield=85%; M.P.=125-130°C; IR(KBr):687(C-S), 743(C-Br), 1114(C=N), 1454(C=C), 1752(C=O), 3059(Ar C-H)cm[1].
[1]H-NMR(CDCl3):δ4.54 (s,2H), 7.28-7.33 (m, 3H), 7.34-7.38 (m,4H), 7,42-7.49 (m,4H), 7.67-7.69 (m, 1H), 7.96-7.98 (d,d, 1H). MS (EI, *m/z*): 439.21 (M^++1).

2-[(4-bromobenzyl) sulfanyl]-1-(4-bromo-2-fluorobenzyl)-1*H*-benzimidazole *(6f)*
Yield=77%; M.P.=130-134°C; IR(KBr):690(C-S), 743(C-Br), 1235(C=N), 1371(C-F), 1445(C=C), 3082(Ar C-H)cm[1].
[1]H-NMR(CDCl3):δ4.56 (s,2H),5.23 (s,2H),6.51-6.55(t,J1=8.1*Hz*,1H),7.07-7.09 (d,d,J1=8.3*Hz*, J2=1.6*Hz*,1H), 7.15-7.21 (m, 2H), 7.23-7.25(d,d J1=6.3*Hz*,J2=1.9*Hz*,2H)7.26-7.28 (d,d, J1=4.5*Hz*, J2=1.9*Hz*,2H), 7.37-7.41 (m, 2H), 7.72-7.74 (d,J1=7.8*Hz*,1H). MS (EI, *m/z*): 507.14 (M+1).

1-(4-bromobenzyl)-2-[(4-bromobenzyl)sulfanyl]1*H*-benzimidazole *(6g)*
Yield=74%; M.P.=113-118°C; IR(KBr):678(C-S), 743(C-Br), 1243(C=N), 1444(C=C), 3051(Ar C-H)cm[1].
[1]H-NMR(CDCl3): δ4.55 (s,2H),5.17 (s,2H),6.89-6.91(d,J1=8.4*Hz*,2H),7.12-7.15 (d, J1=7.6*Hz*,1H), 7.17-7.19 (d,d J1=7.1*Hz*,J2= 0..9*Hz*, 1H), 7.20-7.22 (m, 1H), 7.24-7.25 (d,J1=4.1*Hz*,3H), 7.36-7.40 (m, 4H), 7.71-7.73(d,J1=8.0*Hz*,1H). MS (EI, *m/z*): 489.12 (M+1).

7-(4-(2-(4-bromobenzylthio)-1H benzo[d] imidazol-1-yl) butoxy)-3, 4dihydroquinolin-2(1H) one *(6h)*
Yield=82%; M.P.=157-160°C; IR(KBr):679(C-S), 745(C-Br), 1192(C-O), 1264(C=N), 1436(C=C), 1671(C=O), 2955(C-H),3053(Ar C-H), 3199(N-H)cm[1].
[1]H-NMR (CDCl3): δ1.70-1.74 (m,2H),1.90-1.94 (m,2H), 2.58-2.62 (m,2H),2.86-2.90 (m,2H),3.85-3.88 (t, J1=6.0*Hz*, 2H), 4.10-4.13 (t, J1=7.1*Hz*, 2H), 4.56 (s, 2H), 6.25-6.45 (d, J1=2.3*Hz*, 1H), 6.45-6.47 (d,dJ1=8.3*Hz*,J2=2.4*Hz*, 1H), 7.o1-7.03 (d, J1=8.4*Hz*, 1H), 7.19-7.21 (m, 2H), 7.22-7.24 (m, 3H), 7.38-7.41 (m,2H), 7.70-7.72 (m, 1H), 8.01 (s, 1H), MS (EI, *m/z*): 536.37 (M+1).

7-(4-(2-(4-bromobenzylthio)-1H-benzo[d]imidazol-1-yl) butoxy) quinolin-2(1H)-one *(6i)*
Yield=84%; M.P.=175-178°C; IR(KBr):681(C-S), 747(C-Br),1221(C-O),1266(C=N),1435(C=C), 1620(C=O), 1654(C=O), 2955(C-H), 3062(Ar-C-H),cm[1].
[1]H-NMR (CDCl3):δ1.74-1.81 (m, 2H), 1.91-1.98 (m, 2H), 3.99-4.02 (t, J1=6.0*Hz*, 2H), 4.11-4.15 (tJ1= 7.1*Hz*, 2H), 4.56 (m,2H),6.51-6.54 (d, J1=9.3*Hz*, 1H), 6.73-6.79 (m, 2H),7.20-7.24 (m, 2H),7.27-7.29(m,3H),7.38-7.41 (d,d,J1=8.5*Hz*, J2=5.5*Hz*, 3H), 7.69-7.72 (m, 2H),12.35 (s, 1H), MS (EI, *m/z*): 534.31 (M+1).

Antimicrobial activity:

New N-alkylated **2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole** derivatives has been synthesized and evaluate on different bacterial and fungal strains. The synthesized compounds **(6a-6i)** were evaluated for their antibacterial activity[22] against human pathogenic Gram negative bacteria such as *Escherichia coli* MTCC442, *Pseudomonasaeruginosa* MTCC441 and Gram positive bacteria.
Some derivatives of benzimidazole **6a-6i** were synthesized by nucleophilic substitution of **2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole** (4) and were evaluated for antimicrobial activities[23-25] toward *Candida albicans* MTCC227, *Aspergillus Niger* MTCC282 and *Aspergillusclavatus* MTCC1323. Broth dilution method was used to evaluate the antibacterial activity. It is carried out in tubes. Mueller Hinton Broth[26] was used as nutrient medium. Serial dilutions were prepared in primary and secondary screening. Each synthesized drug was diluted obtaining 2000 µg/mL concentration, as a stock solution. In primary screening 1000, 500 and 250 µg/mL concentrations of the synthesized drugs were taken. The drugs found active in primary screening were similarly diluted to obtain 200, 100, 50, 25, 12.5, and 6.250 µg/mL, and concentrations. The highest dilution showing at least 99% inhibition zone was taken as MIC.

We have synthesized *N*-substituted **2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole.** derivatives by using different condensation conditions and

were thoroughly evaluated biological activity of compound (6a-6i) such as antibacterial(Table-1) and antifungal(Table-2). Some of the compounds were found to have promising antibacterial activity against E. *coli* such as **6g and 6i**. Whereas **6a, 6b, 6c, 6d, 6e 6f**, **6g, 6h and 6i** the compounds were highly active against S. *aureus* when compared to the Ampicillin as a standard. These compounds were also screened against C. *albicans*, A. *Niger* and A. *Clavatus* for antifungal activity. Unfortunately, not a single compound shows the prominent antifungal activity when compared to the Greseofulvin and Nystatin as standard.

Table 1: Antibacterial activity (minimal inhibition concentration; MIC µg/ml) of 6a-6i.

Antibacterial activity (MIC, µg/ml)				
Compound	**E. coli (Gram negative)**	**P. Aeruginosa (Gram negative)**	**S.Aureus (Gram positive)**	**S.Pyogenus (Gram positive)**
4	100	100	125	100
6a	100	100	150	100
6b	125	100	150	125
6c	100	100	125	100
6d	125	100	150	125
6e	100	100	150	125
6f	62.5	100	125	250
6g	75	100	125	150
6h	100	100	150	150
6i	75	100	75	100
Gentamycin	0.05	1	0.25	0.5
Ampicillin	100	-	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

Table 2: Antifungal activity (minimal inhibition concentration; MIC µg/ml) of 6a-6i.

Compound	**C. *albicans***	**A. *Niger***	**A. *clavatus***
4	>1000	>1000	>1000
6a	>1000	500	1000
6b	>1000	500	1000
6c	>1000	>1000	500
6d	>1000	500	500
6e	500	500	500
6f	250	500	500
6g	500	500	500
6h	500	500	1000
6i	250	500	500
Nystatin	100	100	100
Greseofulvin	500	100	100

CONCLUSION: The present study concluded that the experimental procedures make this methodology a better modesty for the synthesis of the titled compounds for possible antimicrobial activity. All the tested compounds with structural modifications exhibited promising antimicrobial activity. From these findings, it can be suggested that the designing of new chemical analogues with N- alkylated/acylated **2-[(4-**

bromobenzyl) sulfanyl]-1*H*-benzimidazole lead the necessity for the development of further research. A new series of N- alkylated/acylated **2-[(4-bromobenzyl) sulfanyl]-1*H*-benzimidazole** were synthesized. These were characterized by IR, NMR, and mass spectrometry study. All the compounds were screened for their antibacterial and antifungal activity by serial dilution method. Compounds 6a-6i exhibited the excellent antibacterial activity as that of the standard drug Ampicilline against S. aureus. Compounds 6g and 6i have showed excellent antibacterial activity as that of the standard drug Ampicilline against E. coli. However, antifungal activity of all synthesized compounds was unsatisfactory.

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