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Research Article

SYNTHESIS OF SOME NOVEL N-SUBSTITUTED 2-(4-BROMO-PHENOXYMETHYL)-1*H*-BENZIMIDAZOLE DERIVATIVES AND THEIR ANTIMICROBIAL EVALUATION

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ABSTRACT
The synthesis of a series of novel substituted benzimidazole derivatives by the condensation of *o*-phenylenediamine (1) with 4-bromophenoxy acetic acid (2). The latter compounds were reacted with different alkyl, benzyl or acyl halides and alkyl or arylsulfonyl chlorides. The synthesized compounds were characterized by IR, ^{1}H-NMR, Mass spectroscopy and elemental analysis for their structures. All the synthesized compounds were tested for their potential anti-bacterial and anti-fungal activities. This exhibited some promising results towards testing organism *in vitro*.
Keywords: Anti-bacterial activity, Anti-fungal activity, Alkylation, Benzimidazole.

INTRODUCTION

The benzimidazole nucleus, which is a useful structure for research and development of new pharmaceutical molecules, Benzimidazoles are among the important heterocyclic compounds found in several natural and non-natural products such as vitamin B_{12}[1], marine alkaloid kealiiquinone[2], and benzimidazole nucleosides[3] etc. Some of the benzimidazole derivatives are marketed as anti-fungal[4], anti-helmintic[5] and anti-psychotic[6] drugs and other derivatives have been found to possess some interesting bioactivities such as anti-tubercular[7], anti-cancer[8], HIV-Inhibitors[9], Anti-Hypertensive Agent[10], Anti-Inflammatory activity[11], Anti-allergic activity[12], Anti-diabetic Activity[13], Anticonvulsant activity[14] and DNA Inhibitory Activity[15] etc. Considering the immense biological importance of benzimidazole derivatives, we now synthesized some novel class of benzimidazole derivatives and their biological activity screening studies.

MATERIALS AND METHODS

All the solvents used were of commercial grade only. *o*-phenylenediamine, 4-bromophenol, methylchloroacetate, alkylating agents, sodium hydride and solvents were obtained from commercial suppliers. Melting points recorded on a MRVIS Series, Lab India Instrument, TLC analysis was done using pre-coated silica gel plates and visualization was done using Iodine / UV lamp. IR spectra were recorded on Perkin Elmer model FTIR for KBr disc. 'HNMR spectra were recorded on BRUKER AVANCE II 400MHz NMR spectrometer with $CDCl_3$ as solvent unless otherwise mentioned. Elemental analysis was carried out on a Perkin–Elmer Series–II CHNS/O Analyzer 2400.

RESULTS

4-bromophenoxy acetic acid 1 was synthesized by *o*-alkylation of 4-bromophenol with methylchloroacetate in acetone at reflux temperature for 6 h and by the subsequent hydrolysis with aq. NaOH. The condensation of *o*-phenylenediamine 2 (OPDA) with 4-bromophenoxy acetic acid 1 under Philips' condition[16] in refluxing 4*N* HCl for 6 h and subsequent work-up resulted in the formation of a white solid having m.p. 260-262°C and in 89 % yield. Based on the spectral and analytical data the compound was assigned to be 2-(4-bromo-phenoxymethyl)-1*H*-benzimidazole (3)[17] (Scheme-1). The alkylation of 3 with various electrophilic reagents in presence of base yielded the N-alkylated, acylated or sulphonated derivatives[18] obtained Compounds 4a-4j. (Scheme-2)

General Procedure of synthesis

Synthesis of 4-bromophenoxy acetic acid (2)

To the solution of 4-bromophenol (1.0 eq.) in acetone (8 vol) was added potassium carbonate (1.5 eq.) and KI (0.1 eq.) at room temperature. It was then stirred at RT for 1.0 h and added methylchloro acetate (1.2 eq.) drop wise. Reaction mixture was heated to reflux temperature for 5-6 h and was monitored by TLC. After completion of the reaction it was then cooled to RT and solvent was concentrated. Added Water and extracted with ethyl acetate. Organic layer was washed with brine solution, dried over sodium sulfate and concentrated to give oily product. Further hydrolysis was done in NaOH and water at 80-85°C, after subsequent work up gives (2) with 90 % yield and good purity. (Scheme-1)

Synthesis of 2-(4-bromo-phenoxymethyl)-1*H*-benzimidaziole (3)

To a solution of 4-bromophenoxy acetic acid (2) (10.8 g, 50 mmol) and 4N HCl (50 ml), OPDA (1) (5.40 g, 50 mmol), was added. The reaction mixture was heated slowly to reflux temperature for 6 hours (TLC monitoring). The reaction mixture was then cooled to room temperature and neutralized with aq. $NaHCO_3$ (10 %), till the neutral pH. The reaction mixture was stirred for 30 minutes resulted free flowing suspension. The solid separated out was filtered, washed with water (3 x 30 ml) and dried under vacuum to afford an off-white solid. The crude product was recrystallized from hot aq. ethanol to obtain the pure white crystalline compound 3. Yield (13.5 g, 89 %) M.P. 260-262°C (Scheme-1)

Synthesis of compound 3 *via* Microwave Irradiation

To a solution of 4-bromophenoxy acetic acid (2) (10.8 g, 50 mmol) and 4N HCl (50 ml), OPDA (1) (5.40 g, 50 mmol), was added. The reaction mixture was irradiated in a

microwave oven at 100W for 3 minutes at 100°C. The reaction mixture was then cooled to room temperature and neutralized with aq. $NaHCO_3$ (10 %), till the neutral pH. The reaction mixture was stirred for 30 minutes resulted free flowing suspension. The solid separated out was filtered, washed with water (3 x 30 ml) and dried under vacuum to afford an off-white solid (13.0 g, 87 %). The crude product was recrystallized from hot aq. ethanol to obtain the pure white crystalline compound 3. M.P. 260-262°C

General procedure for the synthesis of compounds 4a-4f

To a solution of 2-(4-bromo-phenoxymethyl)-1*H*-benzimidazole (3, 2 mmol) in dimethylformamide (10 ml) was added sodium hydride (60 %, 2.4 mmol) lot wise at 0°C. After completion of addition the temperature of the reaction mixture was slowly raised to room temperature and stirred at this temperature for 1 h. The reaction mixture was again cooled to 0°C and the respective alkyl halide (2.4 mmol) was added at 0°C. The temperature of the reaction mixture was then allowed to warm to room temperature and stirred for 2 h. After completion of the reaction, water (50 ml) was slowly added to reaction mixture the solid separated was filtered, washed with water (2 x 30 ml) and dried under vacuum to yield the corresponding N-substituted derivatives 4a-4f. The crude compounds were recrystallized from hot aq. ethanol to obtain pure products. (Scheme-2)

General procedure for the synthesis of compounds 4g-4j

To a solution of 2-(4-bromo-phenoxymethyl)-1*H*-benzimidazole (3, 2 mmol) in pyridine (5 ml) was added slowly respective acyl or arylsulfonyl chloride (3 mmole) at 0°C. After the addition was complete, reaction mixture was allowed slowly rise to room temperature and stirred at this temperature for 2-3 h (TLC monitoring). Then 2N HCl solution was added to the reaction mixture until neutral to pH, when a solid separated out. The solid was filtered, washed with water (2 x 30 ml) and dried under vacuum to obtain the corresponding N-substituted derivatives 4g-4j. The crude products were recrystallized from hot aq. ethanol to obtain pure products. (Scheme-2)

Analytical and Spectral data

2-(4-bromo-phenoxymethyl)-1*H*-benzimidazole (3) Yield 89 %; mp. 260-262°C; IR (KBr): 3383, 2931, 1314, 1222, 1153, 1031 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ5.30 (s, 2H, CH_2), 7.02-7.04 (d, 1H, ArH), 7.16-7.20 (m, 2H, ArH), 7.39-7.42 (d, 2H, ArH), 7.53-7.55 (m, 2H, ArH), 7.78-7.82 (m, 1H, ArH), 15.58 (bs, 1H, NH); MS (m/z): 304.2 (M^++1) Elemental Anal.-calcd. For $C_{14}H_{11}BrN_2O$: C=55.47, H=3.66, N=9.24. Found: C=55.59, H=3.60, N=9.26.

2-(4-Bromo-phenoxymethyl)-1-methyl-1H-benzimidazole (4a) Yield 75 %; mp. 160-163°C; IR (KBr): 3383, 2931, 1377, 1153, 1031 cm^{-1}; MS (m/z): 318.2 (M^++1); Elemental Anal.-calcd. For $C_{15}H_{13}BrN_2O$ C=56.80, H=4.13, N=8.83. Found: C=56.89, H=4.09, N=8.81.

2-(4-Bromo-phenoxymethyl)-1-ethyl-1H-benzimidazole (4b) Yield 73 %; mp. 148-151°C; IR (KBr): 3332, 2935, 1378, 1153, 1024 cm^{-1}; MS (m/z): 332.2 (M^++1); Elemental Anal.-calcd. For $C_{16}H_{15}BrN_2O$: C=58.02, H=4.56, N=8.46. Found: C=81.55, H=6.50, N=7.68.

2-(4-Bromo-phenoxymethyl)-1-propyl-1H-benzimidazole (4c) Yield 77 %; mp. 139- 141°C; IR (KBr): 3363, 2941, 1317, 1158, 1055cm^{-1}; MS (m/z): 346.2 (M^++1); Elemental Anal.-calcd. For $C_{26}H_{26}N_2O$: C=81.64, H=6.85, N=7.32. Found: C=81.60, H=6.91, N=7.25.

2-(4-Bromo-phenoxymethyl)-1-butyl-1H-benzimidazole (4d) Yield 69 %; mp. 146-149°C; IR (KBr): 3362, 2941, 1368, 1215, 1031cm^{-1}; Elemental Anal.-calcd. For $C_{18}H_{19}BrN_2O$: C=60.18, H=5.33, N=7.80. Found: C=60.11, H=5.36, N=7.76.

2-(4-Bromo-phenoxymethyl)-1-isobutyl-1H-benzimidazole (4e) Yield 71 %; mp. 153-155°C; IR (KBr): 3332, 2935, 1378, 1153, 1024 cm^{-1}; Elemental Anal.-calcd. For $C_{18}H_{19}BrN_2O$: C=60.18, H=5.33, N=7.80. Found: C=60.20, H=5.40, N=7.85.

2-(4-Bromo-phenoxymethyl)-1-phenyl-1H-benzimidazole (4f) Yield 71 %; mp. 171-174°C; IR (KBr): 3672, 2939, 1543, 1379, 1154, 1055 cm^{-1}; MS (m/z): 380.2 (M^++1); Elemental Anal.-calcd. For $C_{20}H_{15}BrN_2O$: C=64.13, H=4.36, N=7.12. Found: C=64.03, H=4.40, N=7.16.

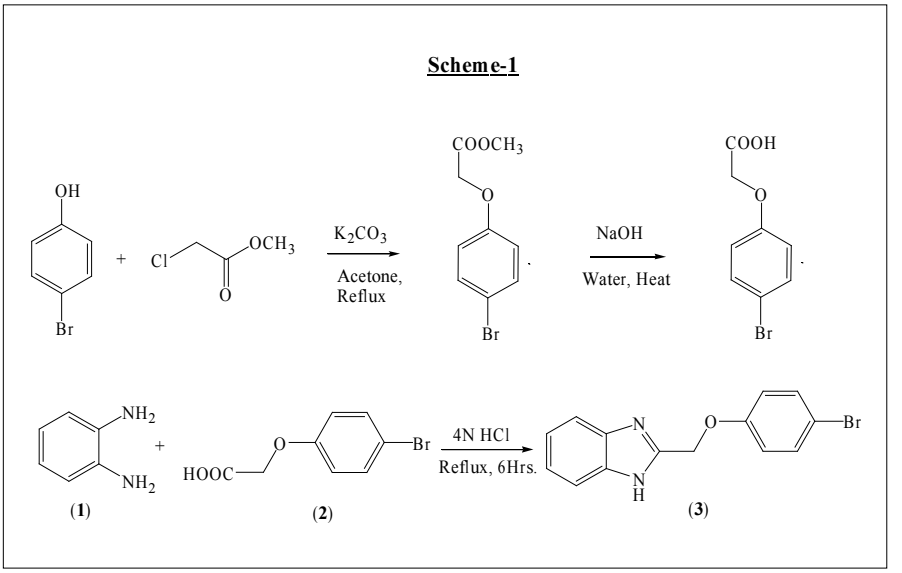
2-(4-Bromo-phenoxymethyl)-1-trifluoromethanesulfonyl-1*H*-benzimidazole (4g) Yield 65 %; mp. 112-115°C; IR (KBr): 3356, 2932, 1229, 1151, 1026 cm^{-1}; Elemental Anal.-calcd. For $C_{15}H_{10}BrN_2O_3F_3S$: C=41.40, H=2.32, N=6.44. Found: C=41.32, H=2.40, N=6.43.

2-(4-Bromo-phenoxymethyl)-1-(toluene-4-sulfonyl) -1*H*-benzimidazole (4h) Yield 63 %; mp. 119-122°C; IR (KBr): 3665, 2938, 1227, 1151, 1055 cm^{-1}; ^{1}H-NMR($CDCl_3$): δδ2.39 (s, 3H, CH_3), 5.56 (s, 2H, CH_2), 6.86-6.89 (m, 2H, ArH), 7.26-7.28 (d, *J*=8Hz, 2H, ArH), 7.35-7.45 (m, 4H, ArH), 7.74-7.76 (d, *J*=8Hz, 1H, ArH), 7.90-7.92 (d, *J*=8Hz, 1H, ArH), 8.01-8.03 (d, *J*=8Hz, 1H, ArH); Elemental Anal.-calcd. For $C_{21}H_{17}BrN_2O_3S$: C=55.15, H=3.75, N=6.13. Found: C=55.21, H=3.71, N=6.06.

Acetic acid 2-(4-bromophenoxymethyl)-benzimidazole-1-yl ester (4i) Yield 61 %; mp. 135-138°C; IR (KBr): 3312, 2930, 1714, 1305, 1154, 1024 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ4.10 (s, 3H, CH_3), 5.52 (s, 2H, CH_2), 6.94-6.96 (d, 2H, *J*=8Hz, ArH), 7.36-7.42 (m, 4H, ArH), 7.78-7.80 (m, 1H, ArH), 7.95-7.97 (m, 1H, ArH); Elemental Anal.-calcd. For $C_{16}H_{13}BrN_2O_3$: C=53.21, H=3.63, N=7.76. Found: C=53.25, H=3.59, N=7.78.

Propionic acid 2-(4-bromophenoxymethyl)-benzimidazole-1-yl ester (4j) Yield 64 %; mp. 140-142°C; IR (KBr): 3312, 2931, 1714, 1244, 1155, 1030 cm^{-1}; Elemental Anal.-calcd. For $C_{17}H_{15}BrN_2O_3$: C=54.42, H=4.03, N=7.47. Found: C=54.51, H=3.93, N=7.44.

General schemes of synthesis



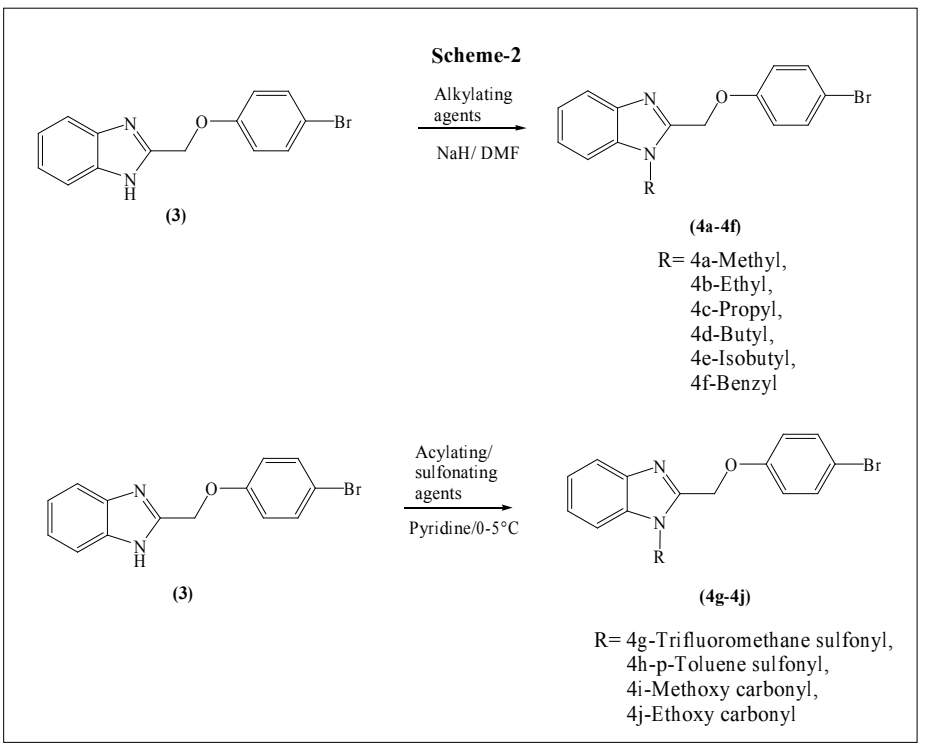


Table 1: Antibacterial activity (minimal inhibition concentration; MIC µg/ml) of 4a-4j

Compound	*E. coli* (Gram -ve)	*P. aeruginosa* (Gram +ve)	*S. aureus* (Gram +ve)	*S. ayogenus* (Gram +ve)
4a	100	62.5	200	200
4b	100	100	100	200
4c	100	100	125	250
4d	100	62.5	100	125
4e	100	62.5	100	200
4f	62.5	62.5	100	200
4g	62.5	100	125	100
4h	62.5	62.5	100	200
4i	62.5	62.5	125	125
4j	62.5	62.5	100	125
Gentamycin	0.05	1	0.25	0.05
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 4a-4j

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

Antimicrobial Activity

The microbial activity was undertaken to evaluate the effect of the synthesized compounds on different bacteria and fungal strains. The compounds 4a–5j were screened for their antibacterial activity[19] against human pathogenic gram negative bacteria such as *Escherichia coli* MTCC442, *Pseudomonas aeruginosa* MTCC441 and gram positive bacteria *Staphylococcus aureus* MTCC96 and *Streptococcus pyogenes* MTCC443. DMSO was used as diluents and Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin as standard. These compounds were also screened for their antifungal activity[20] against *Candida albicans* MTCC227, *Aspergillus niger* MTCC282 and *Aspergillus clavatus* MTCC1323. Broth dilution method was used to evaluate the antibacterial activity. It is carried out in tubes. Mueller Hinton Broth[21] was used as nutrient medium. Serial dilutions were prepared in primary and secondary screening. Each synthesized drug was diluted obtaining 2000 microgram /ml concentration, as a stock solution. In primary screening 1000 micro/ml, 500 micro/ml and 250 micro/ml concentrations of the synthesized drugs were taken. The drugs found active in primary screening were similarly diluted to obtain 200 micro/ml 100 micro/ml, 50 micro/ml, 25 micro/ml, 12.5 micro/ml, 6.250 micro/ml, and concentrations. The highest dilution showing at least 99 % inhibition zone was taken as MIC.

DISCUSSION

Synthesis

In view of synthesis of novel benzimidazoles; initially we have carried out the synthesis of 4-bromophenoxy acetic acid (2) by using 4-bromophenol and methylchloroacetate as a very simple starting materials. Then the condensation of 4-bromophenoxy acetic acid (2) with o-phenylenediamine (1) gives 2-(4-bromo-phenoxymethyl)-1H-benzimidaziole (3). N-alkylation, acylation and sulphonation of condensed product get series of some novel N-substituted 2-(4-bromo-phenoxymethyl)-1*H*-benzimidazole derivatives. We have synthesized compound 3 alternatively by using another method such as microwave irradiation. This gives scope for the alternate route to synthesize benzimidazoles in less reaction time. The structures of all the synthesized compounds were characterized by spectroscopic data.

Antimicrobial Activity

All the synthesized molecules were tested for antibacterial and antifungal activities (Table 1 and 2). The examination of the data reveals that compounds 4f - 4j possess high activity against Escherichia *coli* whereas compounds 4a-4j were highly active against *Staphylococcus aureus* but the compounds doesn't show any promising activity against *Streptococcus pyogenes* employed for screening, the results are presented in Table 1. The compounds 4d-4h shows good activity against *Candida albicans*. But rests of other compounds are not displayed significant anti-fungal activity when compared to the standard Nystatin and Greseofulvin; the results are presented in Table 2.

CONCLUSION

In conclusion, we have demonstrated the synthesis of series of some novel N-substituted 1-*H*-benzimidazole derivatives by using Philip's condition and further by simple N-alkylation and acylation conditions. We have also evaluated their biological activity such as antibacterial and antifungal. Some of the compounds i.e. 4f-4j having carbonyl or sulphonyl functionalities were found to have promising antibacterial activity against *E. coli* where as all 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. The compounds 4d-4h shows good activity against *C. albicans*. However, antifungal activity results of the other synthesized compounds are not very promising.

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