Research Article

SYNTHESIS, ANTI-BACTERIAL, AND ANTI-FUNGAL ACTIVITIES OF SOME NOVEL N-SUBSTITUTED 2-(4-STYRYLPHENYL)-1H-BENZIMIDAZOLES

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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) and subsequent reactions of the benzimidazole with different electrophiles have been reported. The latter compounds were reacted with styrene following Heck Coupling reaction. The synthesized compounds were characterized by IR, ¹H-NMR, Mass 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, Heck Coupling.

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 B₁₂¹, marine alkaloid kealiquinone², and benzimidazole nucleosides³ etc. Some of the benzimidazole derivatives are marketed as anti-fungal⁴, anti-helminthic⁵ and anti-psychotic⁶ drugs and other derivatives have been found to possess some interesting bioactivities such as anti-tubercular⁷, anti-cancer⁸, HIV-Inhibitors⁹, Anti-Hypertensive Agent¹⁰, Anti-Inflammatory activity¹¹, Anti-allergic activity¹², Anti-diabetic Activity¹³, Anticonvulsant activity¹⁴ and DNA Inhibitory Activity¹⁵ 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, alkylating agents, triethylamine and sodium hydride were obtained from commercial suppliers. Styrene, Palladium acetate, tri-*o*-tolylphosphine obtained from Aldrich. 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. NMR spectra were recorded on BRUKER AVANCE II 400 MHz NMR spectrometer with CDCl₃ as solvent unless otherwise mentioned. Elemental analysis was carried out on a Perkin-Elmer Series-II CHNS/O Analyzer 2400.

RESULTS AND DISCUSSION

The condensation of *o*-phenylenediamine **1** (OPDA) with 4-bromophenoxy acetic acid **2** under Philip's condition¹⁶ in refluxing 4N 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-phenoxy-methyl)-1H-benzimidazole (**3**)¹⁷ (Step-1). The alkylation of **3** with various electrophilic reagents yielded the N-alkylated/acylated derivatives (Step-2). Having obtained Compound 4a-4g, we have carried out reaction with styrene in presence triethylamine, tri-*o*-tolylphosphine, and palladium acetate as catalyst and DMF as a solvent under Heck coupling conditions¹⁸ to obtain 5a-5g (Step 3).

General scheme of synthesis

General Procedure

Synthesis of 2-(4-bromo-phenoxy-methyl)-1H-benzimidazole (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. NaHCO₃ (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 %) mp 260-262°C (Lit 260°C).

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. NaHCO₃ (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. mp 260-262°C.

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

To a solution of known 2-(4-bromo-phenoxy-methyl)-1H-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 and extracted with ethyl acetate (2 x 25 ml). The organic layer was washed with water (2 x 25 ml), brine and dried over anhydrous sodium sulfate and concentrated under vacuum to yield the corresponding N-substituted derivatives 4a-4g. The crude compounds were recrystallized from hot aq. ethanol to obtain pure products.

General procedure for the synthesis of compounds 5a-5g under Heck coupling

To a solution of compounds 4a-4g (2.5 mmole) in DMF (50 ml) was added styrene (3 mmole), triethylamine (3 mmole), tri-(*o*-tolyl) phosphine (0.125 mmole) and palladium acetate (0.125 mmole). The reaction mixture was then heated to 100-110°C for 3 h. The reaction mixture was then allowed to cool to room temperature and filtered through hyflo. Added water and extracted with ethyl acetate. Dried over sodium sulphate and concentrated under vacuum yielded crude products, which were subjected to column chromatography to isolate the pure products (5a-5g).

Spectral data

1-Methyl-2-(4-styryl-phenoxy-methyl)-1H-benzimidazole (5a)

Yield 65 %, mp. 160-163°C; IR (KBr): 2748, 2469, 1582, 1469, 1213, 1136 cm⁻¹; ¹H-NMR(CDCl₃): 3.79 (s, 3H, CH₃), 5.44 (s, 2H, CH₂), 6.95-7.03 (m, 2H, ArH), 7.07-7.09 (d, J= 8.7 Hz, 2H, ethylene), 7.21-7.23 (d, J= 7.4 Hz, 1H, ArH), 7.28-7.41 (m, 5H, ArH), 7.45-7.49 (m, 4H, ArH), 7.80-7.82 (dd, J= 6.68 Hz, 1H, ArH); MS(m/z): 341.2 (M⁺+1); Elemental Anal.-calcd. For C₂₃H₂₀N₂O: C=81.15, H=5.92, N=8.23. Found: C=81.10, H=5.85, N=8.31.

1-Ethyl-2-(4-styryl-phenoxy-methyl)-1H-benzimidazole (5b)

Yield 67 %; mp. 148-151°C; IR(KBr): 2940, 2361, 1650, 1521, 1420, 1399 cm⁻¹; ¹H-NMR(CDCl₃): 1.46-1.50 (t, J= 7.24 Hz, 3H, CH₃), 4.27-4.31 (q, J= 7.68 Hz, 2H, CH₂), 5.40 (s, 2H, CH₂), 6.96-7.02 (m, 2H, ArH), 7.07-7.09 (d, J= 8.72 Hz, 2H, ethylene), 7.21-7.23 (d, J= 7.39 Hz, 1H, ArH),

7.28-7.42 (m, 5H, ArH), 7.46-7.49 (m, 4H, ArH), 7.80-7.82 (dd, J= 6.7 Hz, 1H, ArH); MS(m/z): 355.2 (M^+ +1); Elemental Anal.-calcd. For $C_{24}H_{22}N_2O$: C=81.33, H=6.26, N=7.90. Found: C=81.23, H=6.20, N=7.95.

1-Propyl-2-(4-styryl-phenoxyethyl)-1H-benzimidazole (5c)

Yield 63 %; mp. 139-141 $^{\circ}$ C; IR (KBr): 2817, 2470, 1583, 1470, 1404, 1380 cm^{-1} ; 1H -NMR($CDCl_3$): 1.02-1.05 (t, J= 7.40 Hz, 3H, CH_3), 1.82-1.89 (m, 2H, CH_2), 4.27-4.31 (t, J= 7.40 Hz, 2H, CH_2), 5.45 (s, 2H, CH_2), 6.95-7.02 (m, 2H, ArH), 7.07-7.09 (d, J= 8.01 Hz, 2H, ethylene), 7.21-7.23 (d, J= 7.45 Hz, 1H, ArH), 7.28-7.41 (m, 5H, ArH), 7.45-7.50 (m, 4H, ArH), 7.80-7.82 (dd, J= 6.75 Hz, 1H, ArH); MS(m/z): 369.2 (M^+ +1); Elemental Anal.-calcd. For $C_{25}H_{24}N_2O$: C=81.49, H=6.57, N=7.60. Found: C=81.55, H=6.50, N=7.68.

1-Butyl-2-(4-styryl-phenoxyethyl)-1H-benzimidazole (5d)

Yield 65 %; mp. 146-149 $^{\circ}$ C; IR (KBr): 2940, 2697, 2366, 1583, 1470, 1405, 1313, 1272 cm^{-1} ; 1H -NMR($CDCl_3$): 0.94-0.98 (t, J= 7.40 Hz, 3H, CH_3), 1.38-1.46 (m, 2H, CH_2), 1.82-1.89 (m, 2H, CH_2), 4.27-4.31 (t, J= 7.64 Hz, 2H, CH_2), 5.41 (s, 2H, CH_2), 6.95-7.02 (m, 2H, ArH), 7.07-7.09 (d, J= 8.87 Hz, 2H, ethylene), 7.21-7.23 (d, J= 7.34 Hz, 1H, ArH), 7.28-7.41 (m, 5H, ArH), 7.45-7.49 (m, 4H, ArH), 7.80-7.82 (dd, J= 6.6 Hz, 1H, ArH); MS(m/z): 383.2 (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=7.22.

1-Isobutyl-2-(4-styryl-phenoxyethyl)-1H-benzimidazole (5e)

Yield 67 %; mp. 153-155 $^{\circ}$ C; IR (KBr): 2940, 2678, 2469, 1582, 1469, 1213, 1136 cm^{-1} ; 1H -NMR($CDCl_3$): 0.97-0.99 (d, J= 6.68 Hz, 6H, CH_3), 2.33-2.38 (m, 1H, CH), 4.11-4.13 (d, J= 7.64 Hz, 2H, CH_2), 5.43 (s, 2H, CH_2), 6.95-7.02 (m, 2H, ArH), 7.07-7.09 (d, J= 8.8 Hz, 2H, ethylene), 7.21-7.23 (d, J= 7.38 Hz, 1H, ArH), 7.29-7.42 (m, 5H, ArH), 7.45-7.50 (m, 4H, ArH), 7.80-7.82 (dd, J= 6.68 Hz, 1H, ArH); MS(m/z): 383.2 (M^+ +1); Elemental Anal.-calcd. For $C_{26}H_{26}N_2O$: C=81.64, H=6.85, N=7.32. Found: C=81.69, H=6.95, N=7.20.

2-(4-Styryl-phenoxyethyl)-benzimidazole-1-carboxylic acid methyl ester (5f)

Yield 62 %; mp. 135-138 $^{\circ}$ C; IR (KBr): 2977, 2404, 1731, 1598, 1494, m 1218, 1141 cm^{-1} ; 1H -NMR($CDCl_3$): 2.42 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 6.95-7.10 (m, 2H, ArH), 7.07-7.09 (d, J= 7.8 Hz, 2H, ethylene), 7.21-7.23 (d, J= 7.4 Hz, 1H, ArH), 7.28-7.41 (m, 5H, ArH), 7.45-7.49 (m, 4H, ArH), 7.80-7.82 (dd, J= 6.68 Hz, 1H, ArH); MS(m/z): 385.2 (M^+ +1); Elemental Anal.-calcd. For $C_{24}H_{20}N_2O_2$: C=79.98, H=5.24, N=7.29. Found: C=80.08, H=5.29, N=7.25.

2-(4-Styryl-phenoxyethyl)-benzimidazole-1-carboxylic acid ethyl ester (5g)

Yield 65 %; mp. 140-142 $^{\circ}$ C; IR (KBr): 2937, 2476, 1720, 1612, 1495, 1446, 1259, 1220, 1142 cm^{-1} ; 1H -NMR($CDCl_3$): 1.40-1.44 (t, J= 7.44 Hz, 3H, CH_3), 4.27-4.31 (q, J= 7.68 Hz, 2H, CH_2), 5.43 (s, 2H, CH_2), 6.94-7.02 (m, 2H, ArH), 7.07-7.09 (d, J= 8.69 Hz, 2H, ethylene), 7.21-7.23 (d, J= 7.4 Hz, 1H, ArH), 7.28-7.41 (m, 5H, ArH), 7.45-7.49 (m, 4H, ArH),

7.80-7.82 (dd, J= 6.7 Hz, 1H, ArH); MS(m/z): 399.2 (M^+ +1); Elemental Anal.-calcd. For $C_{25}H_{20}N_2O_3$: C=75.36, H=5.57, N=7.03. Found: C=75.40, H=5.51, N=7.13.

Antimicrobial activity

The microbial activity was undertaken to evaluate the effect of the synthesized compounds on different bacteria and fungal strains. The compounds 5a-5g were screened for their antibacterial activity¹⁹ 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 activity²⁰ 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 Broth²¹ 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.

Synthesis

We have synthesized some novel benzimidazoles; initially we have carried out the condensation of o-phenylenediamine (OPDA) (1) with 4-bromophenoxy acetic acid (2) in 4N HCl at reflux temperature for 6 h. After workup of the reaction mixture gives 2-(4-bromo-phenoxyethyl)-1H-benzimidazole (3). The obtained compound 3, we have carried out N-Alkylation to get N-substituted 2-(biphenyl-4-yloxyethyl)-1H-benzimidazole and finally, 2-(4-Phenylethynyl-phenoxyethyl)-1H-benzimidazole derivatives were synthesized using Heck coupling reaction with good yield. It is noteworthy to mention here that we have synthesized compound 3 alternatively by 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 5d and 5f possess high activity against *Escherichia coli* whereas compounds 5a-g were highly active against *Staphylococcus aureus* and 5a, 5f and 5g have also exerted promising activity against *Streptococcus pyogenes* employed for screening, the results are presented in Table 1. The compounds 5a and 5b show good activity against *Candida albicans*. But rests of other compounds are not displayed significant anti-fungal activity when compared to the standard Nystatin and Griseofulvin; the results are presented in Table 2.

Table 1: Antibacterial activity (minimal inhibition concentration; MIC µg/ml) of 5a-5g

Compound	<i>E. coli</i> (Gram negative)	<i>P. aeruginosa</i> (Gram negative)	<i>S. aureus</i> (Gram positive)	<i>S. ayogenus</i> (Gram positive)
5a	100	100	125	100
5b	100	62.5	100	200
5c	125	125	200	250
5d	62.5	200	250	250
5e	125	200	200	250
5f	62.5	50	125	100
5g	125	62.5	125	100
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 5a-5g

Compound	<i>C. albicans</i>	<i>A. niger</i>	<i>A. clavatus</i>
5a	250	>1000	>1000
5b	250	500	1000
5c	500	500	500
5d	500	>1000	500
5e	>1000	1000	1000
5f	500	1000	500
5g	500	>1000	500
Nystatin	100	100	100
Greseofulvin	500	100	100

CONCLUSION

In conclusion, we have demonstrated the synthesis of series of some novel n-substituted 2-(4-styrylphenyl)-1H-benzimidazole derivatives by using Heck coupling conditions. We have also evaluated their biological activity such as antibacterial and antifungal. Some of the compounds were found to have promising antibacterial activity against *E. coli*, and *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 5a and 5b show good activity against *Candida albicans*. However, antifungal activity of the other synthesized compounds was disappointing.

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