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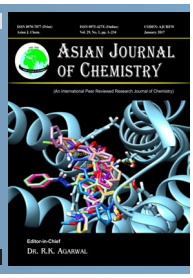

Synthesis and Antimicrobial Activity of Some Benzimidazole and 2-Methylbenzimidazole Derivatives

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In the present work, benzimidazole and 2-methylbenzimidazole derivatives were synthesized and evaluated for antimicrobial activity against *Escherichia coli* (Gram-negative bacteria), *Staphylococcus aureus* (Gram-positive bacteria) and *Candida albicans* (fungal stain). The structure of the synthesized compounds was confirmed by FTIR, ^{1}H NMR and mass spectroscopy. Antimicrobial activity of all the synthesized compounds was carried out by Broth dilution method to determine MIC value. Compounds **P2**, **P7** and **P10** showed better antibacterial activity against *Escherichia coli* as compared to benzimidazole, 2-methylbenzimidazole and ampicillin. Compounds **P8** and **P12** showed better antibacterial activity against *Staphylococcus aureus* as compared to benzimidazole, 2-methylmenzimidazole and ampicillin. Compound **P2** and **P9** showed better antifungal activity against *Candida albicans* as compared to benzimidazole, 2-methylbenzimidazole and griseofulvin.

Keywords: Benzimidazole, 2-Methylbenzimidazole, Antimicrobial activity.

INTRODUCTION

Microbial diseases are pressing problem worldwide and problems of multidrug resistant organisms have reached an alarming level. Novel drugs are urgently required in the therapy of microbial infectious diseases. Millions of people are infected and around 20,000 deaths are reported in the tropical region every year because of microbial infections. The incidence of microbial infection has increased at an alarming level all over the world as a result of antimicrobial resistance in past 25 years [1-4].

Benzimidazole is a heterocyclic aromatic organic compound, consists of the fused benzene and imidazole. It is important pharmacophore and a privileged structure in medicinal chemistry. It shows various pharmacological activities such as anticancer, antihistaminic, antihypertensive and antiulcer [5-7]. This has drawn more and more attention to investigate the other medicinal applications of benzimidazole. Recently, extensive biochemical and pharmacological studies revealed that benzimidazole possessed large potential to inhibit the growth of bacteria and fungi [8-10].

Benzimidazole blocks DNA replication, exerting powerful antimicrobial action, indicating that benzimidazole derivatives are promising candidates for developing new antimicrobial agents [11-14]. In literature sodium benzoate has been reported to possess antimicrobial property. So keeping the above observation in consideration, benzimidazole derivatives with substituted benzoic acid were prepared.

In the present work, we have synthesized benzimidazole and 2-methylbenzimidazole derivatives and evaluated anti-microbial activity against *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans* [14-16].

EXPERIMENTAL

o-Phenylenediamine, acetic acid, formic acid and methanol were purchased from Spectrochem Pvt. Ltd. Mumbai, India. substituted benzoic acid were purchased from Himedia Pvt. Ltd. Mumbai, India. Ammonia and sodium bicarbonate were purchased from Lobachemie Pvt. Ltd. Mumbai, India. The melting point of synthesized compounds was determined by capillary tube method. The progress of reaction and purity of synthesized compounds was checked by TLC using pre coated aluminium sheets with GF-254 silica gel purchased from Merk specialities Pvt. Ltd. Mumbai, India. using mobile phase chloroform: methanol (9:1). The spots were visualized in UV light chamber. The λ_{max} (nm) of the synthesized compounds was determined by Shimadzu 1700 UV-visible spectrophotometer. The FTIR spectra of the synthesized compounds was recorded on FTIR Alpha Bruker by KBr disc in the range of 4000-400 cm^{-1}. The proton NMR (^{1}H NMR) spectra were recorded using Bruker

Advance II 400 NMR spectrometer. The Mass spectra of synthesized compounds were recorded using CIF Mass facility IISER Bhopall.

A series of fifteen 1-sustituted benzimidazole (**P1-P8**) and 1-substituted 2-methylbenzimidazole (**P9-P15**) derivatives were synthesized according to the synthetic route presented in Fig. 1. On reaction of *o*-phenylenediamine and substituted acid under refluxed in the presence of ammonia solution the two intermediate benzimidazole (1*H*-benzo[d]imidazole) and 2-methylbenzimidazole (2-methyl-1*H*-benzo[d]imidazole) were synthesized. The final products (**P1-P15**) were obtained by the reaction between benzimidazole or 2-methylbenzimidazole and the corresponding substituted benzoyl derivatives. The formation of compound (**P1-P15**) was confirmed by m.p., R_f value, FTIR, ^{1}H NMR and mass spectra.

Synthesis of benzimidazole: A mixture of *o*-phenylenediamine 0.03 mol (3.24 g), formic acid 0.09 mol (5.05 mL) and 20 mL of water were refluxed for 45 min. The reaction mixture was cooled and made basic by the gradual addition of concentrated ammonia solution. The precipitated product was collected and recrystallized from 10 % ethanol [18-20].

Synthesis of benzimidazole derivative: 0.025 mol (3 g) of benzimidazole was dissolved in 30 mL of 10 % sodium hydrogen carbonate solution, 0.04 mol of substituted benzoyl chloride was added and the reaction mixture was shaken vigorously than acidified to congored with dilute HCl, the precipitate obtained was filtered, the product was recrystallized from ethanol [21,22].

Synthesis of 2-methylbenzimidazole: A mixture of *o*-phenylenediamine 0.03 mol (3.24 g), acetic acid 0.09 mol (5.67 mL) and 20 mL of water were refluxed for 45 min. The reaction mixture was cooled and made basic by the gradual addition of concentrated ammonia solution. The precipitated product was collected and recrystallized from 10 % ethanol [17-19].

Synthesis of 2-methylbenzimidazole derivatives: 0.025 mol (3.30 g) of 2-methylbenzimidazole was dissolved in 30 mL of 10 % sodium hydrogen carbonate solution, 0.04 mol of substituted benzoyl chloride was added and the reaction mixture was shaken vigorously than acidified to congored with dilute HCl, the precipitate obtained was filtered, the product was recrystallized from ethanol [20,21].

Spectral data of synthesized compounds

(1*H*-Benzo[d]imidazole-1-yl)(phenyl)methanone (P1): Off white colour, yield 62 %, m.p.: 236-238 °C, R_f (methanol: chloroform, 9:1) 0.67, IR (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1656, (-C=C, aromatic) 1597, (-C-H, stretch) 2853, (-C-H, bend) 1446, (-C-N) 1229, (-C=N) 1577, (-N= tertiary amine) 3422, ^{1}H NMR (DMSO): 7.19-8.170 (m, 10H, Ar-H), *m/z*: 222.9 (M^+).

(4-Aminophenyl)(1*H*-benzo[d]imidazole-1-yl)-methanone (P2): Pale yellow colour, yield 77 %, m.p.: 240-242 °C, R_f (methanol:chloroform, 9:1) 0.72, IR (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1703, (-C=C, aromatic) 1610, (-C-H, stretch) 2869, (-C-H, bend) 1449, (-C-N) 1239, (-C=N) 1508, (-N= tertiary amine, N-H) 3424, ^{1}H NMR (DMSO): 6.35-8.00 (m, 9H, Ar-H), 3.43 (s, 2H, N-H), *m/z*: 238.0 (M+1).

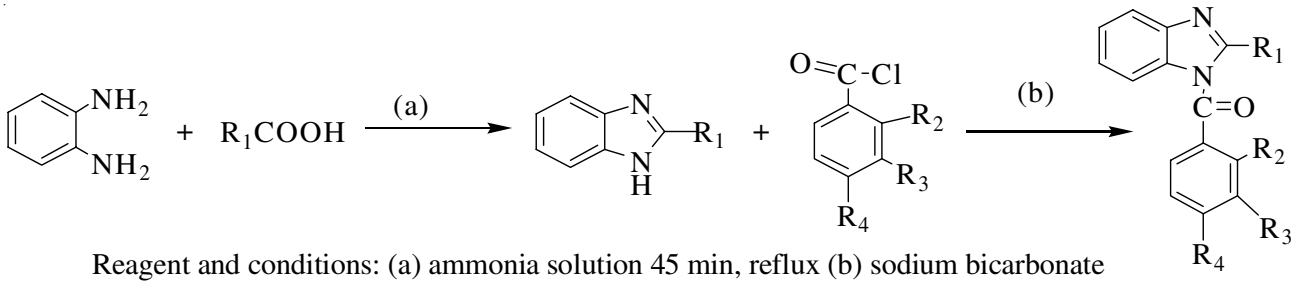
(1*H*-Benzo[d]imidazole-1-yl)(4-chlorophenyl)methanone (P3): Salmon pink colour, yield 85 %, m.p.: 270-272 °C, R_f (methanol:chloroform, 9:1) 0.73, IR (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1682, (-C=C, aromatic) 1494, (-C-H, stretch) 2841, (-C-H, bend) 1425, (-C-N) 1239, (-C=N) 1652, (-N= tertiary amine) 3416, (-C-Cl) 607, ^{1}H NMR (DMSO): 7.29-8.36 (m, 9H, Ar-H), *m/z*: 256.8 (M^+).

(1*H*-Benzo[d]imidazol-1-yl)(4-bromophenyl)methanone (P4): Pale yellow colour, yield 36 %, m.p.: 266-268 °C, R_f (methanol:chloroform, 9:1) 0.62, IR (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1679, (-C=C, aromatic) 1587, (-C-H, stretch) 3153, (-C-H, bend) 1399, (-C-N) 1234, (-C=N) 1587, (-N= tertiary amine) 3492, (-C-Br) 603, ^{1}H NMR (DMSO): 6.62-8.06 (m, 9H, Ar-H), *m/z*: 301.14 (M^+).

(3-Aminophenyl)(1*H*-benzo[d]imidazol-1-yl)methanone (P5): Dark brown colour, yield 26 %, m.p.: 265-267 °C, R_f (methanol:chloroform, 9:1) 0.70, IR (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1685, (-C=C, aromatic) 1591, (-C-H, stretch) 2983, (-C-H, bend) 1456, (-C-N) 1203, (-C=N) 1647, (-N= tertiary amine, N-H) 3423, ^{1}H NMR (DMSO): 7.28-8.02 (m, 9H, Ar-H), 3.51 (s, 2H, N-H), *m/z*: 238.6 (M+1).

(1*H*-Benzo[d]imidazol-1-yl)(3-chlorophenyl)methanone (P6): White colour, yield 54 %, m.p.: 251-253 °C, R_f (methanol:chloroform, 9:1) 0.68, IR (KBr, ν_{max}, cm^{-1}) (-C=O, amide) 1696, (-C=C, aromatic) 1597, (-C-H, stretch) 2850, (-C-H, bend) 1450, (-C-N) 1261, (-C=N) 1643, (-N= tertiary amine) 3391, (-C-Cl) 605, ^{1}H NMR (DMSO): 7.28-8.36 (m, 9H, Ar-H), *m/z*: 257.3 (M+1).

(1*H*-Benzo[d]imidazol-1-yl)(2-chlorophenyl)methanone (P7): White colour, yield 63 %, m.p.: 188-190 °C, R_f (methanol: chloroform, 9:1) 0.61, IR (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1685, (-C=C, aromatic) 1475, (-C-H, stretch) 2873, (-C-H, bend) 1437, (-C-N) 1266, (-C=N) 1591, (-N= tertiary amine) 3426, (-C-Cl) 605, ^{1}H NMR (DMSO): 7.30-8.36 (m, 9H, Ar-H), *m/z*: 257.6 (M+1).



Reagent and conditions: (a) ammonia solution 45 min, reflux (b) sodium bicarbonate
R_1 = H, CH_3, R_2 = H, Cl, R_3 = H, Cl, NH_2, R_4 = H, Cl, NH_2, Br

Fig. 1. Reaction scheme of synthesized compounds

(1*H*-Benzo[d]imidazol-1-yl)(2,4-dichlorophenyl)-methanone (P8): Pale yellow colour, yield 34 %, m.p.: 288-290 °C, R_f (methanol:chloroform, 9:1) 0.78, IR (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1651, (-C=C, aromatic) 1607, (-C-H, stretch) 2860, (-C-H, bend) 1378, (-C-N) 1243, (-C=N) 1587, (-N= tertiary amine) 3181, (-C-Cl) 623, ^{1}H NMR (DMSO): 7.29-8.16 (m, 8H, Ar-H), *m/z*: 291.1 (M^+).

(2-Methyl-1*H*-benzo[d]imidazol-1-yl)(phenyl)methanone (P9): Salmon pink colour, yield 61 %, m.p.: 242-244 °C, R_f (methanol:chloroform, 9:1) 0.66, IR (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1656, (-C=C, aromatic) 1597, (-C-H, stretch) 3056, (-C-H, bend) 1446, (-C-N) 1228, (-C=N) 1578, (-N= tertiary amine) 3444, ^{1}H NMR (DMSO): 7.28-8.22 (m, 9H, Ar-H), 2.50 (s, 3H, C-H), *m/z*: 236.9 (M^+).

(4-Aminophenyl)(2-methyl-1*H*-benzo[d]imidazol-1-yl)methanone (P10): Greenish brown colour, yield 62 %, m.p.: 246-248 °C, R_f (methanol:chloroform, 9:1) 0.64, IR (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1632, (-C=C, aromatic) 1605, (-C-H, stretch) 2880, (-C-H, bend) 1441, (-C-N) 1268, (-C=N) 1505, (-N= tertiary amine, N-H) 3422, ^{1}H NMR (DMSO): 6.36- 8.05 (m, 8H, Ar-H), 3.43 (s, 2H, N-H), 2.49 (s, 3H, C-H), *m/z*: 252.3 (M+1).

(4-Chlorophenyl)(2-methyl-1*H*-benzo[d]imidazol-1-yl)methanone (P11): Salmon pink colour, yield 98 %, m.p.: 285-287 °C, R_f (methanol:chloroform, 9:1) 0.69, IR (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1680, (-C=C, aromatic) 1593, (-C-H, stretch) 2677, (-C-H, bend) 1443, (-C-N) 1237, (-C=N) 1652, (-N= tertiary amine) 3442, (-C-Cl) 628, ^{1}H NMR (DMSO): 7.27-8.17 (m, 8H, Ar-H), 2.99 (s, 3H, C-H), *m/z*: 269.6 (M-1).

(3-Aminophenyl) (2-methyl-1*H*-benzo[d]imidazol-1-yl)methanone (P12): Dark brown colour, yield 27 %, m.p.: 271-273 °C, R_f (methanol:chloroform, 9:1) 0.63, IR (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1682, (-C=C, aromatic) 1649, (-C-H, stretch) 2982, (-C-H, bend) 1370, (-C-N) 1210, (-C=N) 1545, (-N= tertiary amine, N-H) 3443, ^{1}H NMR (DMSO): 6.35-7.97 (m, 8H, Ar-H), 3.43 (s, 2H, N-H), 2.49 (s, 3H, C-H), *m/z*: 251.3 (M^+).

(3-Chlorophenyl)(2-methyl-1*H*-benzo[d]imidazol-1-yl)methanone (P13): Salmon pink colour, yield 58 %, m.p.: 263-265 °C, R_f (methanol:chloroform, 9:1) 0.77, (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1694, (-C=C, aromatic) 1608, (-C-H, stretch) 3066, (-C-H, bend) 1450, (-C-N) 1259, (-C=N) 1597, (-N= tertiary amine) 3391, (-C-Cl) 603, ^{1}H NMR (DMSO): 6.36-7.89 (m, 8H, Ar-H), 2.49 (s, 3H, C-H), *m/z*: 269.3 (M-1).

(2-Chlorophenyl) (2-methyl-1*H*-benzo[d]imidazol-1-yl)methanone (P14): Salmon pink colour, yield 67 %, m.p.: 222-224 °C, R_f (methanol:chloroform, 9:1) 0.71, (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1691, (-C=C, aromatic) 1477, (-C-H, stretch) 2988, (-C-H, bend) 1435, (-C-N) 1266, (-C=N) 1691, (-N= tertiary amine) 3442, (-C-Cl) 646, ^{1}H NMR (DMSO): 7.29-7.99 (m, 8H, Ar-H), 2.51 (s, 3H, C-H), *m/z*: 269.8 (M-1).

(2,4-Dichlorophenyl)(2-methyl-1*H*-benzo[d]imidazol-1-yl)methanone (P15): Salmon pink colour, yield 74 %, m.p.: 294-296 °C, R_f (methanol:chloroform, 9:1) 0.65, (KBr, ν_{max}, cm^{-1}): (-C=O, amide) 1651, (-C=C, aromatic) 1606, (-C-H, stretch) 2926, (-C-H, bend) 1446, (-C-N) 1237, (-C=N) 1586, (-N= tertiary amine) 3195, (-C-Cl) 595, ^{1}H NMR (DMSO): 6.62-7.85 (m, 7H, Ar-H), 2.50 (s, 3H, C-H), *m/z*: 306.3 (M+1).

Antimicrobial activity [22,23]: The antimicrobial screening was carried out using Broth dilution method:

Serial dilutions were prepared in primary and secondary screening. The control tube containing no antimicrobial was immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and kept for incubation at 37 °C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the compounds concentrations. The lowest concentration for inhibiting growth of the organism was recorded as the MIC. The amount of growth from the control tube before incubation (which represents the original inoculums) was compared.

Primary screen: In primary screening solution containing 1000, 500 and 250 µg/mL concentrations of the synthesized compound were prepared. The active synthesized compounds found in this primary screening were further tested in a second set of dilution against all microorganisms.

Secondary screen: The compounds found active in primary screening were similarly diluted to obtain solution containing 200, 100, 62.5, 50, 25, 12.5, 6.250 µg/mL of synthesized compound.

Reading result: The highest dilution showing at least 99 % inhibition was taken as MIC.

RESULTS AND DISCUSSION

In the present study benzimidazole and 2-methylbenzimidazole derivatives were synthesized. The synthesis of these compounds involves cyclization reaction between *o*-phenylenediamine and corresponding carboxylic acid derivatives and was reacted with the substituted benzoyl chloride to form the corresponding benzoyl substituted benzimidazole. The structure of all synthesized compounds confirmed by FTIR, ^{1}H NMR and mass spectroscopy.

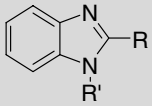
Antibacterial activity was carried out by Broth dilution method. All compounds were screened against *E. coli* (MTCC 442) and *S. aureus* (MTCC 96). The compounds were dissolved in DMSO and ampicillin was taken as the standard drug for the screening. The result showed that among the tested compounds, **P2**, **P7**, **P10**, **P12**, **P13** and **P14** better antibacterial activity against *E. coli* and compounds **P2**, **P4**, **P6**, **P8**, **P10**, **P11** and **P13** showed better antibacterial activity as compared to benzimidazole and 2-methyl benzimidazole. The results of the antibacterial screening are summarized in Table-1.

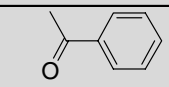
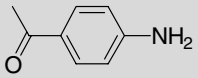
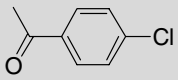
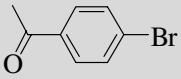
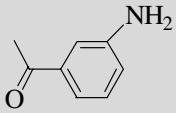
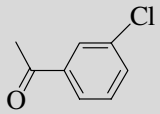
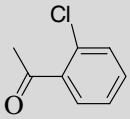
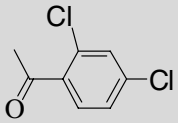
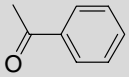
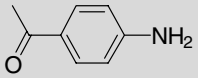
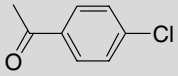
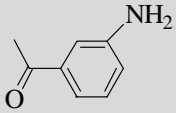
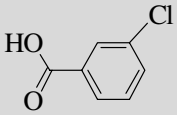
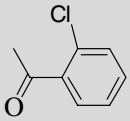
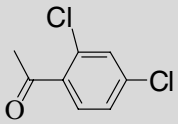
All compounds were screened for antifungal activity against *C. albicans* (MTCC 227). The compounds were dissolved in DMSO and antifungal activity was determined using the broth dilution method. Griseofulvin was taken as the standard drug. Compound **P1**, **P2**, **P3**, **P4**, **P6**, **P9** and **P11** showed better antifungal activity as compared to benzimidazole and 2-methyl benzimidazole. The results of the antifungal screening are summarized in Table-1.

Conclusion

In the present work N-1 of benzimidazole and 2-methylbenzimidazole derivatives were synthesized. Substitution by $-NH_2$ group (electron donating group) at *para* position of benzoyl moiety at N-1 of benzimidazole and 2-methylbenzimi-

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF SYNTHESIZED COMPOUNDS **P1-P15**



Compd. No.	R	R'	m.f.	Gram-negative bacteria	Gram-positive bacteria	Fungal stain
				E. coli MTCC442	*S. aureus* MTCC96	*C. albicans* MTCC227
P1		-H	$C_{14}H_{10}N_2O$	200	250	500
P2		-H	$C_{14}H_{11}N_3O$	62.5	200	250
P3		-H	$C_{14}H_9ClN_2O$	200	250	1000
P4		-H	$C_{14}H_9BrN_2O$	125	200	1000
P5		-H	$C_{14}H_{11}N_3O$	100	250	>1000
P6		-H	$C_{14}H_9ClN_3O$	200	200	500
P7		-H	$C_{14}H_9ClN_2O$	62.5	250	>1000
P8		-H	$C_{14}H_8Cl_2N_2O$	100	100	>1000
P9		$-CH_3$	$C_{15}H_{12}N_2O$	250	250	250
P10		$-CH_3$	$C_{15}H_{13}N_3O$	62.5	125	1000
P11		$-CH_3$	$C_{15}H_{11}ClN_2O$	200	125	500
P12		$-CH_3$	$C_{15}H_{13}ClN_3O$	125	100	1000
P13		$-CH_3$	$C_{15}H_{11}ClN_2O$	125	125	500
P14		$-CH_3$	$C_{15}H_{11}ClN_2O$	100	200	500
P15		$-CH_3$	$C_{15}H_{10}Cl_2N_2O$	200	200	>1000
Benzimidazole	-H	-H	$C_7H_6N_2$	100	250	>1000
2-Methy-benzimidazole	-H	$-CH_3$	$C_8H_8N_2$	200	125	500
Ampicillin				100	250	–
Griseofulvin				–	–	500

dazole increased the antibacterial activity against *Escherichia coli* while substitution by –Cl group (electron withdrawing group) at *meta* position of benzoyl moiety at N-1 of benzimidazole increased antibacterial activity against *Escherichia coli*. Disubsitution by –Cl group at *ortho* and *para* position in benzoyl moiety at N-1 position of benzimidazole increased antibacterial activity against *Staphylococcus aureus* and monosubstitution of –Cl group at meta position in benzoyl moiety at N-1 of 2-methylbenzimidazole increased antibacterial activity against *Staphylococcus aureus*. Substitution by -NH_2 group at *para* position in benzoyl moiety at N-1 position of benzimidazole increased antifungal activity against *Candida albicans*.

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