

SYNTHESIS AND BIOLOGICAL EVALUATION OF BENZIMIDAZOLE DERIVATIVES AS ANTIMICROBIAL AGENTS

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ABSTRACT

Objective: The present study aims to synthesize and biological evaluation of benzimidazole derivatives as antimicrobial agents.

Methods: 2-Methylbenzimidazole react with ethyl-chloroacetate gives N¹-Ethylacetate-2-methyl-benzimidazole (1), which on reaction with thiosemicarbazide gives N¹-acetylthiosemicarbazide-2-methyl-benzimidazole (2). The compound (2) on dehydrative annulation by mineral acid gives N¹-(2'-amino-5'-methylene)-1',3',4'-thiadiazole-2-methyl-benzimidazole(3), which on condensation with various aromatic and hetero aromatic aldehydes gives N¹-(2-substituted-Benzylidene-imino-5'-methylene)-1', 3', 4'-Thiadiazole]-2-methyl-benzimidazole(4a-4l).

Results: The reaction sequence involves microwave-induced preparation of N¹-Ethylacetate-2-methyl-benzimidazole (1) from reaction of 2-methylbenzimidazole with ethyl-chloroacetate. Further reaction with thiosemicarbazide gives N¹-acetylthiosemicarbazide-2-methyl-benzimidazole (2). The compound (2) on dehydrative annulation by sulfuric acid gives N¹-(2'-amino-5'-methylene)-1',3',4'-thiadiazole-2-methyl-benzimidazole(3), which on condensation with various aromatic and hetero aromatic aldehydes gives N¹-(2-substituted-Benzylidene-imino-5'-methylene)-1', 3', 4'-Thiadiazole]-2-methyl-benzimidazole(4a-4l). Which were characterized by IR and ¹H NMR spectral data.

Conclusion: All the synthesized compounds were screened for antimicrobial activity by cup plate method. Most of the derivatives showed good antimicrobial activity against Gram-Positive and Gram-negative bacteria.

Keywords: Benzimidazole, Thiadiazole, Microwave irradiation, Spectral studies, Antimicrobial activity

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INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consist of fusion of benzene and imidazole. Benzimidazole derivatives were reported to possess analgesic and anti-inflammatory activity [1], antimicrobial [2, 3], anticancer [4], anticonvulsant [5], antiviral [6], antioxidant [7], antihypertensive [8], anti-tubercular [9], anthelmintic [10], proton pump inhibitor activity [11]. In this present study benzimidazole derivatives of Schiff bases containing various aldehydes have been synthesized. These synthesized compounds were screened for antibacterial activity by cup plate method.

MATERIALS AND METHODS

Melting points of all synthesized compounds were determined in open capillary tubes and were uncorrected. The purity of the compounds was checked by TLC on pre-coated silica gel G plates and visualized in iodine vapour. The IR spectra were recorded on FT-IR 1800 (Perkin-Elmer)spectrophotometer by KBr pellets technique.¹H NMR spectra were recorded on Jasco 4100 spectrophotometer using DMSO-d₆ as solvent and TMS as internal standard.

Synthesis of N¹-Ethylacetate-2-methyl-benzimidazole (1)

A mixture of 2-methyl-benzimidazole(0.30 mole, 39.60 g) and ethyl-chloroacetate (0.30 mole,36.74 g) with K₂CO₃(6.16 g) was added and mixed thoroughly. The reaction mixture was air dried and subjected to microwave irradiation for 3 min. The completion of reaction was monitored by thin layer chromatography. The reaction mixture was cooled and separated, solid extracted with ethanol to give the desired product as a colourless crystalline solid.

Synthesis of N¹-Acetylthiosemicarbazide-2-methyl-benzimidazole (2)

The N¹-Ethylacetate-2-methyl-benzimidazole (0.15 mole, 32.70 g) and thiosemicarbazide (0.15 mole, 30.67 g) was ground in a mortar

using a pestle for uniform mixing. The mixture was kept inside a microwave irradiation for 10 min. The completion of the reaction was monitored by thin layer chromatography. The product was recrystallized using ethanol.

Synthesis of N¹-(2'-amino-5'-methylene)-1', 3',4'-thiadiazole-2-methyl-benzimidazole (3)

Equimolar solution of compound 2(0.10 mole, 26.30 g) dissolved in chloroform and concentrated H₂SO₄ (0.10 mole, 9.80 g) was added in to above solution at room temperature. This reaction mixture was subjected to microwave irradiation for 15 min. The sample was cooled in ice bath and irradiation was repeated several times. Completion of the reaction was monitored by TLC. The resulting product was neutralized with conc. Liq. ammonia. The final product was recrystallized from ethanol to give compound 3.

Synthesis of N¹-(2-Benzylidene-imino-5'-methylene)-1',3',4'-thiadiazole]-2-methyl-benzimidazole (4)

Equimolar solution of compound 3 (0.0085 mole, 2.08 g) and benzaldehyde (0.0085 mole, 0.902 g) in methanol (20 ml) with 4-5 drops of glacial acetic acid was subjected to microwave irradiation for 15 min. The sample was cooled in an ice bath and TLC was used to monitor the reaction progress. The reaction product was recrystallized with ethanol that gave the final compound.

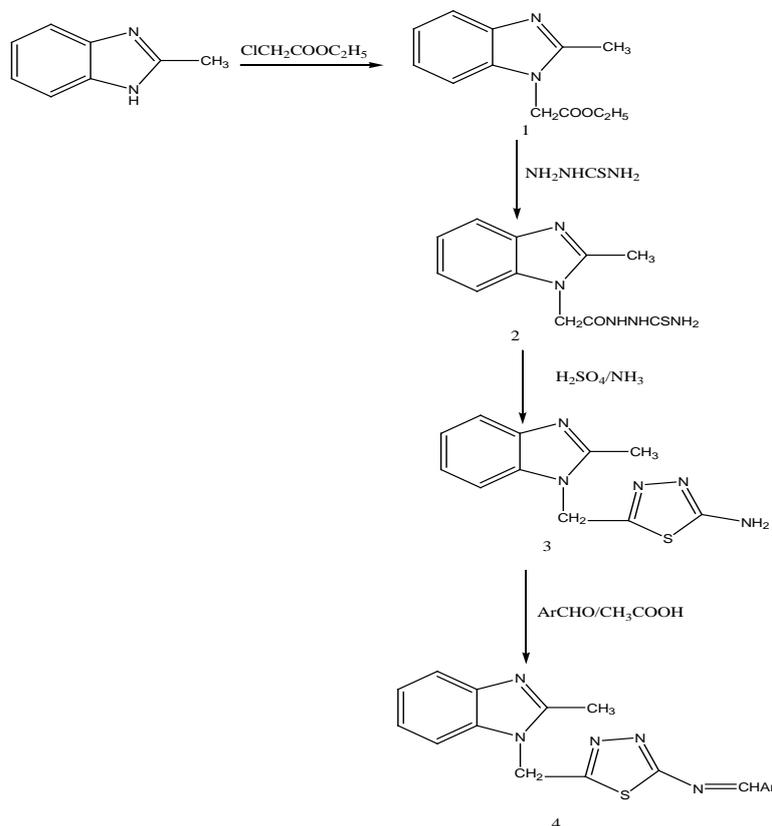
Synthesis of N¹-(2-substituted-Benzylidene-imino-5'-methylene)-1',3',4'-Thiadiazole]-2-methyl-benzimidazole (4a-4l)

The N¹-(2-amino-5'-methylene)-1', 3', 4'-thiadiazole 2-methyl-benzimidazole (0.0085 mole,2.08 g) and substituted aldehyde (0.0085 mole, 0.902 g) in methanol with 4-5 drops of glacial acetic acid was subjected to microwave irradiation for 15 min. The sample was cooled in an ice bath and TLC was used to monitor the reaction progress. The reaction product was recrystallized with ethanol that gave the final compound.

Biological activity**Antimicrobial activity**

All synthesized benzimidazole derivatives 4a-4l were screened for *in vitro* antibacterial activity against strain of gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*)

bacteria using cup plate method (agar diffusion method) [12]. Ampicillin was used as standard drug for antibacterial activity. The solutions of 25, 50, 100 µg/ml concentration of synthesized benzimidazole derivatives and standard drug were used to evaluate antimicrobial potential. The result of antibacterial activity is shown in table 3.

**RESULTS AND DISCUSSION**

2-Methyl benzimidazole react with ethyl-chloroacetate gives N¹-Ethylacetate-2-methyl-benzimidazole (1) which showed characteristic IR absorption band at 1427 (-CH₂ bending), 1720 (C=O str) and 1640 cm⁻¹ (C=N str). Compound (1) which on reaction with thiosemicarbazide gives N¹-Acetylthiosemicarbazide-2-methyl-benzimidazole (2). Further on dehydrative annulation by mineral acid gives N¹-(2'-amino-5'-

methylene)-1',3',4'-thiadiazole-2-methyl-benzimidazole (3) which showed characteristic IR absorption band at 1630 (C=N), 2830 cm⁻¹ (-CH₃). The compound (3) which on condensation with various aromatic and hetero aromatic aldehydes gives N¹-(2-substituted-Benzylidene-imino-5'-methylene)-1',3',4'-Thiadiazole]-2-methyl-benzimidazole (4a-4l). The physical and analytical data is presented in table 1. The structures of these newly synthesized compounds were characterized on the basis of IR and ¹H NMR spectroscopy. The result of spectral data is presented in table 2.

Table 1: Physical and analytical data of synthesized compounds

Compound code	Structure (Ar)	Molecular formula	Molecular weight	Melting point (°C)	Yield (%)
4a		C ₁₈ H ₁₅ N ₅ O ₄	365.45	201	89
4b		C ₁₆ H ₁₄ N ₆ O ₂ S	323.37	180	78
4c		C ₁₈ H ₁₄ N ₆ O ₂ S	378.40	171	80

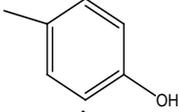
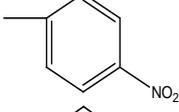
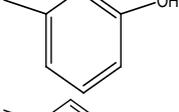
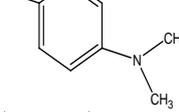
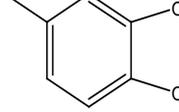
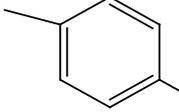
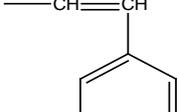
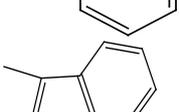
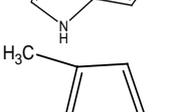
4d		C ₁₈ H ₁₅ N ₅ OS	349.40	191	79
4e		C ₁₈ H ₁₄ N ₆ O ₂ S	378.40	210	85
4f		C ₁₈ H ₁₅ N ₅ OS	349.40	185	71
4g		C ₂₀ H ₂₀ N ₆ S	376.47	211	76
4h		C ₂₀ H ₁₀ N ₅ O ₂ S	393.46	205	84
4i		C ₁₈ H ₁₄ FN ₅ S	351.40	197	90
4j		C ₂₀ H ₁₇ N ₅ S	359.44	178	88
4k		C ₂₀ H ₁₆ N ₅ S	372.46	223	73
4l		C ₁₇ H ₁₅ N ₅ S ₂	353.46	177	71

Table 2: Spectral data of synthesized compounds

Compound	Spectral data
1	1270, 1470 (-NCH ₂), 1427(-CH ₂ bending), 1384 (-CH ₃ bending), IR(cm ⁻¹) 1720 (>C=O of ester) 16.40 (benzimidazole ring)
¹ H NMR(δ)	1.90(t, 3H J=7.0 Hz,-COOCH ₂ CH ₃), 4.19 (q, 2H, J=7.0 Hz,-CH ₂ CH ₃), 2.64(s, 1H,-CH ₃), 7.35 (m, 4H, Ar-H), 3.63 (s, 2H,-NCH ₂)
2	1274,1471(-NCH ₂), 3275 (NH), 1128(>C=S), 2822(-CH ₃), 1601 IR(cm ⁻¹) (-C=N of benzimidazole ring)
¹ H NMR(δ)	8.26 (m, 4H,-NHNHCSNH ₂), 2.65(s, 1H,-CH ₃), 3.68(s, 2H,-NCH ₂), 7.36(m, 4H, Ar-H)
3	1279, 1463(-NCH ₂), 3396(-NH ₂), 1408, 1630(C=N,C-N of benzimidazole ring), 1603(Thiadiazole ring), 2830 (-CH ₃) IR(cm ⁻¹)
¹ H NMR(δ)	4.81(s, 1H,-NH ₂), 2.64(s, 1H,-CH ₃), 7.24(m, 4H, Ar-H)
4	1546(-N=CH), 2824(-CH ₃), 1276, 1467(-NCH ₂), 1632(Thiadiazole ring), 1610(benzimidazole ring) IR(cm ⁻¹)
¹ H NMR(δ)	7.24(m, 9H, Ar-H), 2.66(s, 1H,-CH ₃), 3.65(-NCH ₂), 4.91(s, 1H, -N=CH)
4k	1466(-NCH ₂), 2846(-CH ₃),1635 (benzimidazole ring),1631 IR(cm ⁻¹) (Thiadiazole ring), 1640(-NH)
¹ H NMR(δ)	2.57(s, 1H,-CH ₃), 3.34(-CH ₂), 4.91(s, 1H,-N=CH), 7.3(benzene), 8.02(imidazole ring)
4l	1465(-NCH ₂), 1630(benzimidazole ring), 1621(Thiadiazole ring), 2550 (C-S) IR(cm ⁻¹)
¹ H NMR(δ)	2.52(s, 1H, CH ₃), 3.30 (-CH ₂), 4.93(s, 1H,-N=CH) 7.4(benzene), 8.35 (Thiophene ring)

Table 3: Antimicrobial activity of synthesized compounds (zone of inhibition)

Compound	Zone of inhibition (in mm)					
	<i>S. aureus</i>			<i>E. coli</i>		
	25µg/ml	50µg/ml	100 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml
4a	14	15	16	15	16	17
4b	12	13	15	14	14	16
4c	16	18	20	12	13	14
4d	13	12	14	13	14	16
4e	15	18	19	11	12	13
4f	12	14	15	14	16	18
4g	16	15	19	10	12	13
4h	17	17	20	12	11	12
4i	11	12	13	13	15	17
4j	16	18	17	11	13	12
4k	13	12	14	14	14	16
4l	16	17	20	10	11	11
Ampicillin	17	19	21	16	17	19

CONCLUSION

A novel series of benzimidazole derivatives (4a-4l) were successfully synthesized and characterized by IR, NMR spectroscopy. The final compounds were screened for *in vitro* antibacterial activity against both Gram-positive and Gram-negative strains of bacteria by cup-plate method. Among all the various derivative, compounds 4a, 4b, 4d, 4f, 4g, 4k showed significant activity against *E. coli* and compounds 4c, 4e, 4g, 4h, 4j, 4l showed significant activity against *S. aureus* as compared to standard drug ampicillin.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interests

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