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SYNTHESIS AND BIOLOGICAL SCREENING OF SOME NEW BENZIMIDAZOLE DERIVATIVES AS STUDY OF ANTIMICROBIAL ACTIVITY

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ABSTRACT : To get Benzimidazole derivatives [IV(a) - (IV(h)]; N^1-Ethylacetate-2-methyl-benzimidazole (I) were prepared by the action of ethyl-chloroethanoate on 2-Methylbenzimidazole, which on reaction with thiosemicarbazide gives N^1-acetylthiosemicarbazide-2-methyl-benzimidazole (II). The compound (II) on dehydrative annulation by mineral acid gives N^1-(2′-amino-5′-methylene)-1′,3′,4′-thiadiazole-2-methyl-benzimidazole(III). The compound (III) on condensation with various aromatic and hetero aromatic aldehydes gives N^1-(2-substituted-Benzylidene-imino-5′-methylene)-1′,3′,4′-Thiadiazole]-2-methyl-benzimidazole[IV(a) - (IV(h)].

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

INTRODUCTION

Considerable attention has been focused on Benzimidazole and their derivatives due to their interesting biological activities. Benzimidazole is a heterocyclic aromatic organic compound consists 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.

EXPERIMENTAL

All the melting points were determined in the open capillary and are uncorrected. The reactions were monitored on TLC. The IR spectra were recorded on FT-IR 1800 (Perkin-Elmer) spectrophotometer by KBr pellets technique. ^{1}H NMR spectra were recorded on Jasco 4100 spectrophotometer using DMSO-d6 as solvent and TMS as internal standard.

Synthesis of N^1-Ethylacetate-2-methyl-benzimidazole (I)

A mixture of 2-methyl–benzimidazole(0.25 mole, 33.00 g) and ethyl-chloroethanoate(0.25 mole, 30.62 g) was added with K_2CO_3(6.12 g) and mixed thoroughly. The reaction mixture was air dried and subjected to microwave irradiation for 4 min. The completion of reaction was monitored by TLC. The reaction mixture was cooled and separated, solid extracted with ethanol to give the desired product as a colourless crystalline solid.

Synthesis of N^1-Acetylthiosemicarbazide-2-methyl- benzimidazole (II)

The N^1-Ethylacetate-2-methyl-benzimidazole (0.14 mole, 30.52 g) and thiosemicarbazide (0.14 mole, 28.63 g) was ground in a mortar using a pestle for uniform mixing. The mixture was kept inside a microwave irradiation for 9 min. The completion of the reaction was monitored by TLC. The product was recrystallized using ethanol.

Synthesis of N^1-(2′-amino-5′-methylene)-1′, 3′,4′-thiadiazole-2- methyl-benzimidazole (III)

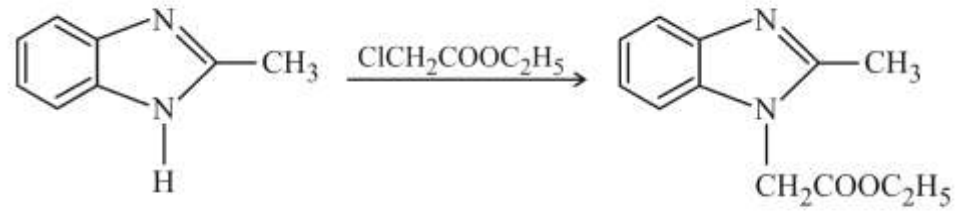
Equimolar solution of compound **2**(0.10 mole, 26.30 g) dissolved in chloroform and concentrated H_2SO_4 (0.10 mole, 9.80 g) was added in to above solution at room temperature. This reaction mixture was subjected to microwave irradiation for 14 min. The sample was cooled in ice bath and irradiation 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 **(III)**.

Synthesis of N^1-(2-Benzylidene-imino-5′-methylene)-1′, 3′, 4′- thiadiazole]-2-methyl-benzimidazole (IV)

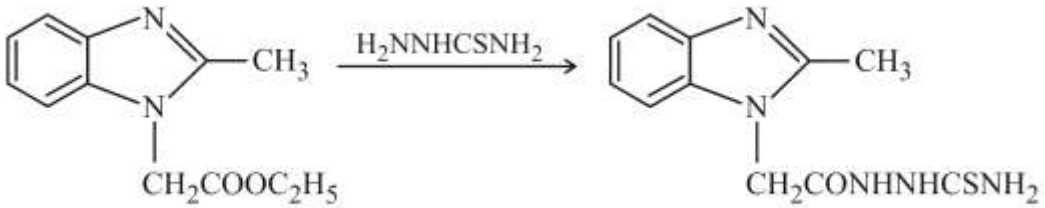
Equimolar solution of compound **(III)** (0.0085 mole, 2.08 g) and benzaldehyde (0.0085 mole, 0.902 g) in methanol (20 ml) with 5-6 drops of glacial acetic acid was subjected to microwave irradiation for 14 min. The sample was cooled in an ice bath and TLC was used to monitor the reaction progress. The reaction product was recrystallized with ethanol that gave the final compound.

Synthesis of N^1-(2-substituted-Benzylidene-imino-5'-methylene)- 1′, 3′, 4′-Thiadiazole]-2-methyl-benzimidazole [IV(a)-IV(h)]

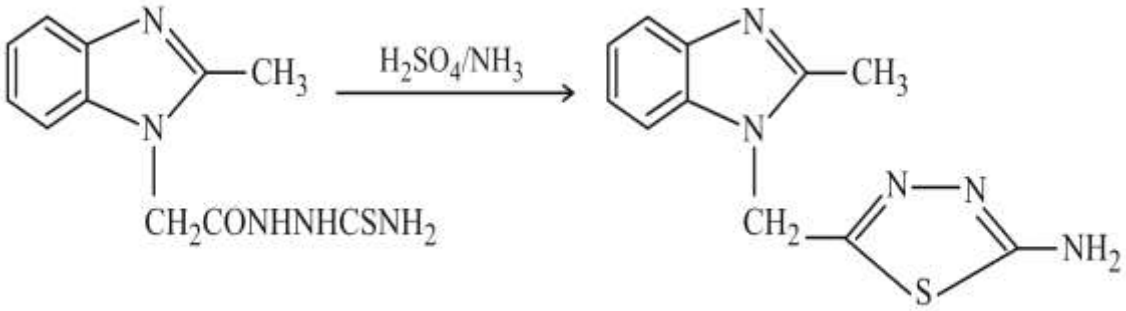
The N^1-(2-amino-5′-methylene)-1′, 3′, 4′-thiadiazole 2-methyl- benzimidazole (0.0085 mole,2.08 g) and substituted aldehyde (0.0085 mole, 0.902 g) in methanol with 5-6 drops of glacial acetic acid was subjected to microwave irradiation for 15 min. The sample was cooled in an ice bath and TLC was used to monitor the reaction progress. The reaction product was recrystallized with ethanol that gave the final compound.



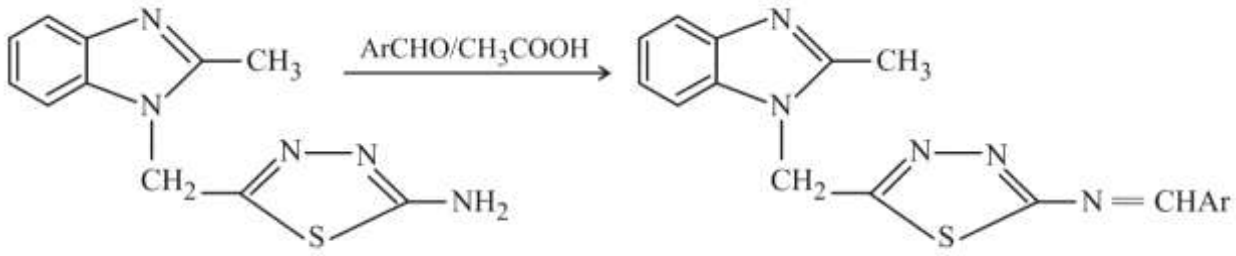
(I)



(I) (II)



(II) (III)



(III) (IV)

RESULTS AND DISCUSSION

2-Methyl benzimidazole on reaction with ethyl-chloroethanoate gives N^1- Ethylacetate-2-methyl-benzimidazole (I) which showed characteristic IR absorption band at 1428 (-CH_2 bending), 1721 (C=O str) and 1640 cm^{-1} (C=N str). Compound (I) on reaction with thiosemicarbazide gives N^1-Acetylthiosemicarbazide-2-methyl-benzimidazole(II). Further on dehydrative annulation by mineral acid gives N^1-(2′-amino-5′- methylene)-1′,3′,4′-thiadiazole-2-methyl-benzimidazole (III) which showed characteristic IR absorption band at 1631 (C=N), 2831 cm^{-1} (-CH_3). The compound (III) which on condensation with various aromatic and hetero aromatic aldehydes gives N^1-(2-substituted-Benzylidene-imino-5′-methylene)-1′,3′,4′-Thiadiazole]-2-methyl benzimidazole [IV(a)- IV(h)]). The physical and analytical data of synthesized compounds are presented in table 1. The structures of these newly synthesized compounds were characterized on the basis of IR and ^{1}H NMR spectroscopy. The result of spectral data of synthesized compounds are presented in table 2.

BIOLOGICAL ACTIVITY

The newly synthesized compounds were screened for *in vitro* antibacterial activity against strain of gram-positive (*Staphylococcus aureus)* and gram-negative (*Escherichia coli)* bacteria using cup plate method. 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.

Table 1: Physical and analytical data of synthesized compounds

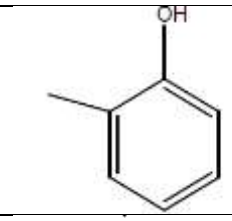
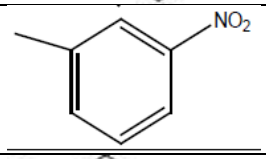
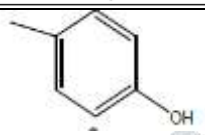
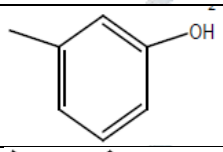
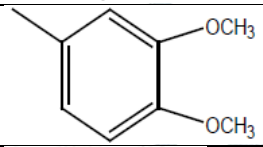
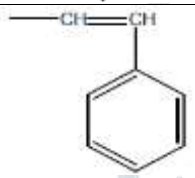
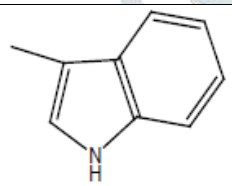
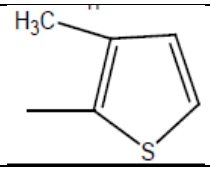
Compound code	Structure (Ar)	Molecular formula	Molecular weight	Melting point (°C)	Yield (%)
IV(a)		$C_{18}H_{15}N_5O_4$	365.45	202	87
IV(b)		$C_{18}H_{14}N_6O_2S$	378.40	170	84
IV(c)		$C_{18}H_{15}N_5OS$	349.40	193	81
IV(d)		$C_{18}H_{15}N_5OS$	349.40	183	74
IV(e)		$C_{20}H_{10}N_5O_2S$	393.46	205	83
IV(f)		$C_{20}H_{17}N_5S$	359.44	176	90
IV(g)		$C_{20}H_{16}N_5S$	372.46	222	74
IV(h)		$C_{17}H_{15}N_5S_2$	353.46	178	73

Table 2: Spectral data of synthesized compounds

Compound	Spectral data
I IR(cm^{-1}) ^1H NMR(δ)	1268, 1471 (-NCH_2), 1428(-CH_2 bending), 1383 (-CH_3 bending), 1721 (>C=O of ester) 16.40 (benzimidazole ring) 1.90(t, 3H J=7.0 Hz,-$COOCH_2CH_3$), 4.19 (q, 2H, J=7.0 Hz,-CH_2CH_3), 2.64(s, 1H,--CH_3), 7.35 (m, 4H, Ar-H), 3.63 (s, 2H,-NCH_2)
II IR(cm^{-1}) ^1H NMR(δ)	1275,1470(-NCH_2), 3273 (NH), 1127(>C=S), 2821(-CH_3) 1602 (-C=N of benzimidazole ring), 8.24 (m, 4H,-$NHNHCSNH_2$), 2.66(s, 1H,-CH_3), 3.67(s, 2H,-NCH_2), 7.36(m, 4H, Ar-H)
III IR(cm^{-1}) ^1H NMR(δ)	1278, 1465(-NCH_2), 3395(-NH_2), 1406, 1631(C=N,C-N of benzimidazole ring), 1604(Thiadiazole ring), 2831 (-CH_3) 4.81(s, 1H,-NH_2), 2.64(s, 1H,-CH_3), 7.24(m, 4H, Ar-H)
IV IR(cm^{-1}) ^1H NMR(δ)	1547(-N=CH), 2824(-CH3), 1276, 1467(-NCH_2)1632(Thiadiazole ring), 1610(benzimidazole ring) 7.24(m, 9H, Ar-H), 2.67(s, 1H,-CH), 3), 3.66(-NCH_2), 4.91(s, 1H, -N = CH)
IV(g) IR(cm^{-1}) ^1H NMR(δ)	1464(-NCH_2), 2843(-CH_3),1637 (benzimidazole ring),1631 (Thiadiazole ring), 1642(-NH) 2.57(s, 1H,-CH_3), 3.34(-CH_2), 4.91(s, 1H,-N=CH), 7.3(benzene), 8.01(imidazole ring)
IV(h) IR(cm^{-1}) ^1H NMR(δ)	1466(-NCH_2), 1630(benzimidazole ring), 1622(Thiadiazole ring), 2550 (C-S) 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)				
		S. aureus		E. coli		
	25µg/ml	50µg/ml	100 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml
IV(a)	13	14	15	14	17	16
IV(b)	17	19	21	13	14	14
IV(c)	14	13	13	13	14	17
IV(d)	11	13	16	14	15	19
IV(e)	18	18	21	13	11	13
IV(f)	15	17	18	12	12	12
IV(g)	14	13	15	13	16	15
IV(h)	18	18	21	11	12	11
Ampicillin	16	17	22	15	19	20

CONCLUSION

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

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