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Research Article

SYNTHESIS THROUGH MICROWAVE IRRADIATION, CHARACTERIZATION AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF 2-PHENYL-1, 3-BENZOXAZOLE DERIVATIVES

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ABSTRACT

A series of 2-phenyl-1,3-benzoxazoles were synthesized by the reaction of 2-aminophenol and acyl chlorides using microwave irradiation. Purity of compounds was determined by TLC. All the synthesized compounds were characterized by spectral analysis (FTIR, ^{1}H-NMR). The compounds were evaluated for in vitro antimicrobial activity against *Bacillus pumilus*, *Bacillus subtilis* (Gram positive); *Escherichia coli, Pseudomonas aeruginosa* (Gram negative) and *Candida albicans* and *Aspergillus niger* by agar-well diffusion method at 2.5, 5, 10mg/ml. Compounds 2-(2-methoxyphenyl)-1,3-benzoxazole, 2-(4-bromophenyl)-1,3-benzoxazole, 2-(3-cholorophenyl)-1,3-benzoxazole, 2-(2-nitrophenyl)-1,3-benzoxazole have been found to have good antibacterial activity. Compounds 2-pheny-1,3-benzoxazole, 2-(4-bromophenyl)-1,3-benzoxazole, were potent antifungal compounds amongst the series.

Keywords: Benzoxazoles, Microwave irradiation, Antimicrobial activity.

INTRODUCTION

The widespread use of antibiotics has resulted in the emergence of antibiotic-resistant organisms. Not only is antibiotic resistance on the rise, but emerging pathogens are seen in ever-growing populations. Newly identified pathogens are resistant to a broader panel of drugs and sometimes to entire classes of antibiotic agents.

Various nuclei have been explored for antimicrobial activity viz. benzothiazepine[1], triazole[2],indazole[3], quinazoline[4], pyrazole[5], imidazole[6], benzimidazole[7], benzoxazole[8]. During recent years there have been some interesting developments in the biological activities of benzoxazole derivatives. These compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities. Benzoxazole nucleus have been reported various types of biological activities such as Antidepressant, Antibacterial, Antifungal, Anti-inflammatory, Analgesic and Anticancer.[9]

Two commonly used approaches for the construction of the benzoxazole ring system are: the first approach involves the coupling of the 2-aminophenols with carboxylic acid derivatives under strongly acidic conditions at high reaction temperatures[10] while the second approach uses the reaction of 2-aminophenols with an aldehyde via the oxidative cyclization of imine intermediates[11]. Microwave induced organic reaction chemistry [12, 13] is becoming popular and considered as a step towards green chemistry. The present work aimed to synthesize a series of 2 –phenyl-1,3-benzoxazoles derivatives in order to determine their antimicrobial activities.

In this communication, results of synthesis, spectroscopic studies and antimicrobial activity of substituted 2-phenyl-1, 3-benzoxazole derivatives are presented.

MATERIALS AND METHODS

All the chemicals used for the study were obtained from Sigma Aldrich and LOBA-e. For synthesis, microwave synthesizer CEM-Labmet was used. The melting points of compounds were determined using Visual Melting Point Apparatus (Lab India MR-VIS). The progress of the reaction was monitored by Thin Layer Chromatographic technique by using glass plate coated with silica gel G. Solvent system used was ethyl acetate: n-hexane (9:1). The IR spectra of the compounds were recorded using KBr pellets on Fourier Transform Infrared Spectrophotometer (FTIR-Shimadzu) ^{1}H-NMR spectrum were recorded using Bruker spectrometer at DPX-300 MHz using TMS as internal standard (Chemical shifts in ppm). DMSO-d_6 was used as solvent.

Synthesis of 2-phenyl-1, 3-benzoxazole and substituted 2-phenyl-1, 3-benzoxazoles:

A dry vial charged with 1.8 mmol (0.196g) of o-aminophenol, 2.0 mmol of acyl chloride in 2.5ml of dioxan was placed in microwave synthesizer (CEM-Labmet) and irradiated at 150 W for 15 min while the temperature was set to 160^o C. The extent of the reaction was monitored by silica gel G coated TLC plates. After the reaction was completed, the reaction mixture was cooled and transferred to a stirred solution of 1N NaOH (50ml). The precipitate obtained was filtered, washed with water, dried and recrystallized from methanol. The yield and melting points are listed in Table-1.

2-phenyl-1, 3-benzoxazole (1a): 0.26g (73.42%), light yellow, m.p. 102-104^{o}C.

IR (KBr): 3134(Ar C-H str.), 1553(C=N str.), 1241(C-O str.)cm^{-1}

^{1}H-NMR (DMSO) δ (ppm): 7.362-8.246 (Ar-H, 9H).

2-(2-methoxyphenyl)-1, 3-benzoxazole (1b):0.26g (65.12%), beige, m.p. 54-56^{o}C.

IR (KBr): 3174(Ar C-H str.), 1593 (C=N str.), 1244(C-O str.)cm^{-1}

^{1}H-NMR (DMSO) δ (ppm):7.401-8.148 (Ar-H, 8H), 3.327(3H).

2-(3-methoxyphenyl)-1, 3-benzoxazole (1c): 0.39g (98%), Dark yellow, m.p. 70-73^{o}C.

IR (KBr): 3172(Ar C-H str.), 1607 (C=N str.), 1226(C-O str.)cm^{-1}.

^{1}H-NMR (DMSO) δ (ppm):7.378-8.219 (Ar-H, 8H), 3.377(3H).

2-(2-bromophenyl)-1, 3-benzoxazole (1d): 0.31g (63.2%), yellow, m.p. 53-56^{o}C

IR (KBr): 3150(Ar C-H str.), 1546 (C=N str.), 1256(C-O str.), 594(C-Br str.)cm^{-1}

^{1}H-NMR (DMSO) δ (ppm):7.477-8.455 (Ar-H, 8H).

2-(3-bromophenyl)-1, 3-benzoxazole (1e): 0.27g (54.6%), beige, m.p.128-130^{o}C

IR (KBr): 1591 (C=N str.), 1289(C-O str.), 598(C-Br str.)cm^{-1}

^{1}H-NMR (DMSO) δ(ppm):7.066-7.186 (Ar-H, 8H).

2-(4-bromophenyl)-1, 3-benzoxazole (1f)*:* 0.41g (83.2%), white, m.p. 155-156°C
IR (KBr): 1588 (C=N str.), 1287(C-O str.), 604(C-Br str.)cm^{-1}
^{1}H-NMR (DMSO) δ (ppm):7.449-8.110 (Ar-H, 8H).
2-(3-chlorophenyl)-1, 3-benzoxazole (1g):0.28g (68%), yellow, m.p.131-133°C
IR (KBr): 3123(Ar C-H str.), 1607 (C=N str.), 1207(C-O str.), 745(C-Cl str.)cm^{-1}
^{1}H-NMR (DMSO) δ (ppm):7.421-8.825 (Ar-H, 8H).
2-(4-chlorophenyl)-1, 3-benzoxazole (1h):0.35g (83.7%), light yellow, m.p.148-149°C.
IR (KBr): 3150(Ar C-H str.), 1549(C=N str.), 1230(C-O str.), 742(C-Cl str.)cm^{-1}
^{1}H-NMR (DMSO) δ (ppm):7.417-8.312 (m, Ar-H, 8H).
2-(2-nitrophenyl)-1, 3-benzoxazole (1i):0.24g (56.6%)**,** pale yellow**,** m.p.101-103°C
IR (KBr): 3160(Ar C-H str.), 1550(C=N str.), 1241(C-O str.), 1550(C-NO_2) cm^{-1}
^{1}H-NMR (DMSO) δ (ppm):7.415-8.159 (Ar-H, 8H).
2-(3-nitrophenyl)-1, 3-benzoxazole (1j):0.25g (57.8%), pale yellow, m.p.211-212°C
IR (KBr): 3090(Ar C-H str.), 1589(C=N str.), 1248(C-O str.), 1506(C-NO_2) cm^{-1}
^{1}H-NMR (DMSO) δ (ppm):7.199-7.850 (Ar-H, 8H).
2-(4-nitrophenyl)-1, 3-benzoxazole (1k):0.37g (85.6%)**,** yellow, m.p. 266-268°C
IR (KBr): 3215(Ar C-H str.), 1588(C=N str.), 1226(C-O str.), 1539(C-NO_2) cm^{-1}
^{1}H-NMR (DMSO) δ (ppm):7.450-8.237 (Ar-H, 8H).
2-(2,3,4,5,6-pentafluorophenyl)-1,3-benzoxazole (1l): 0.33g (68.9%), yellow, m.p.113-115°C
IR (KBr): 1576(C=N str.), 1302(C-O str.), 997(C-F)cm^{-1}
^{1}H-NMR (DMSO) δ (ppm):7.488-7.970 (Ar-H, 4H).

Antimicrobial activity[14]

The synthesized compounds were evaluated for the invitro antibacterial activity against Gram-positive bacteria: *Bacillus pumilus*, *Bacillus subtilis.* Gram-negative bacteria: *Escherichia coli, Pseudomonas aeruginosa.* The compound was also tested for the in-vitro antifungal activity against *Candida albicans* and *Aspergillus niger* by agar-well diffusion method at 2.5mg/ml, 5mg/ml and 10mg/ml concentration of test compounds. Ciprofloxacin was used as the standard
antibacterial agent whereas Fluconazole was used as standard antifungal agent. The diameter of the zone of inhibition was measured and recorded in Table-3 and 4.

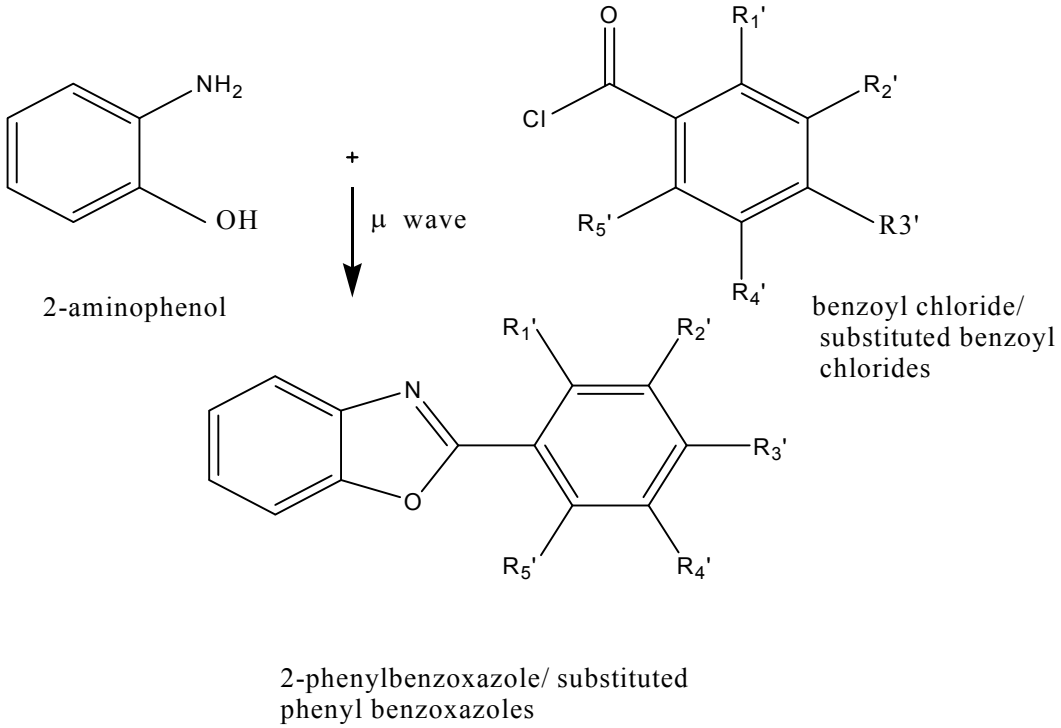
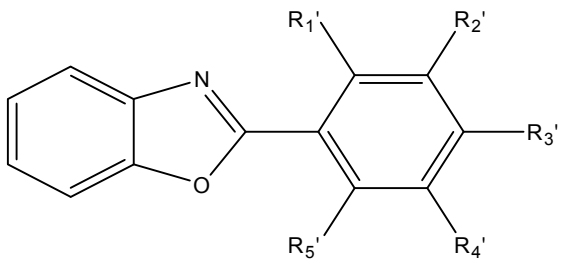


Fig.1 Scheme of synthesis of compounds (1a-1l)

Table-1 Yield and melting point data of the synthesized compounds



S.No.	Compound	Name of compound	R1'	R2'	R3'	R4'	R5'	Molecular formula	Yield (%)	m.p.(°C)
1	1a	2-pheny-1,3-benzoxazole	H	H	H	H	H	$C_{13}H_9NO$	83.42	102-104
2	1b	2-(2-methoxyphenyl)-1,3-benzoxazole	OCH_3	H	H	H	H	$C_{14}H_{11}NO_2$	65.12	54-56
3	1c	2-(3-methoxyphenyl)-1,3-benzoxazole	H	OCH_3	H	H	H	$C_{14}H_{11}NO_2$	98.00	70-73
4	1d	2-(2-bromophenyl)-1,3-benzoxazole	Br	H	H	H	H	$C_{13}H_8BrNO$	63.21	53-56
5	1e	2-(3-bromophenyl)-1,3-benzoxazole	H	Br	H	H	H	$C_{13}H_8BrNO$	54.60	128-130
6	1f	2-(4-bromophenyl)-1,3-benzoxazole	H	H	Br	H	H	$C_{13}H_8BrNO$	83.20	155-156
7	1g	2-(3-cholorophenyl)-1,3-benzoxazole	H	Cl	H	H	H	$C_{13}H_8ClNO$	68.00	131-133
8	1h	2-(4-chlorophenyl)-1,3-benzoxazole	H	H	Cl	H	H	$C_{13}H_8ClNO$	83.70	148-149
9	1i	2-(2-nitrophenyl)-1,3-benzoxazole	NO_2	H	H	H	H	$C_{13}H_8N_2O_3$	56.60	101-103
10	1j	2-(3-nitrophenyl)-1,3-benzoxazole	H	NO_2	H	H	H	$C_{13}H_8N_2O_3$	57.80	211-212
11	1k	2-(4-nitrophenyl)-1,3-benzoxazole	H	H	NO_2	H	H	$C_{13}H_8N_2O_3$	85.60	266-268
12	1l	2-(2,3,4.5.6pentafluorophenyl)-1,3-benzoxazole	F	F	F	F	F	$C_{13}H_5F_5NO$	68.90	113-115

Table-2 Antibactrial activity [Diameter of Zone of inhibition (mm)]

COMPOUND	*E.coli*			*P.aeruginosa*			*B.subtilis*			*B.pumilus*		
	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3
1a	0	0	10	0	10	8	0	14	0	12	12	0
1b	0	18	12	0	16	12	10	14	10	0	14	10
1c	0	12	10	0	14	12	12	14	12	0	10	12
1d	10	10	0	11	16	0	0	10	12	0	10	0
1e	0	14	0	10	16	12	0	16	16	0	14	0
1f	11	14	8	14	16	10	10	18	12	0	18	12
1g	0	12	8	0	16	0	0	16	14	0	10	16
1h	10	12	12	11	10	10	0	10	12	0	14	12
1i	14	18	14	12	18	14	0	20	12	0	12	12
1j	0	12	0	12	12	12	0	10	9	0	14	16
1k	8	10	10	0	9	8	12	11	0	12	10	0
1l	12	12	10	10	10	0	0	8	0	0	8	0
Std.	23			20			22			21		
DMSO	0	0	0	0	0	0	0	0	0	0	0	0

Table-3 Antifungal activity [Diameter of Zone of inhibition (mm)]

COMPOUND	*C.albicans*			*A.niger*		
	C1	C2	C3	C1	C2	C3
1a	0	10	8	0	0	0
1b	12	18	13	12	14	10
1c	0	16	0	0	12	12
1d	8	10	18	6	10	0
1e	6	12	1	14	14	12
1f	8	16	12	8	16	10
1g	12	12	0	0	14	12
1h	0	12	14	10	10	12
1i	0	8	0	0	10	8
1j	8	12	11	0	11	10
1k	10	12	0	0	0	0
1l	0	6	0	10	8	0
Std.	23			22		
DMSO	0	0	0	0	0	0

C1:2.5mg/ml. NZ: No Zone.
C2:5mg/ml. Std.: Ciprofloxacin for bacteria
C3:10mg/ml. Fluconazole for fungi.

Fig-1 Antibacterial activity

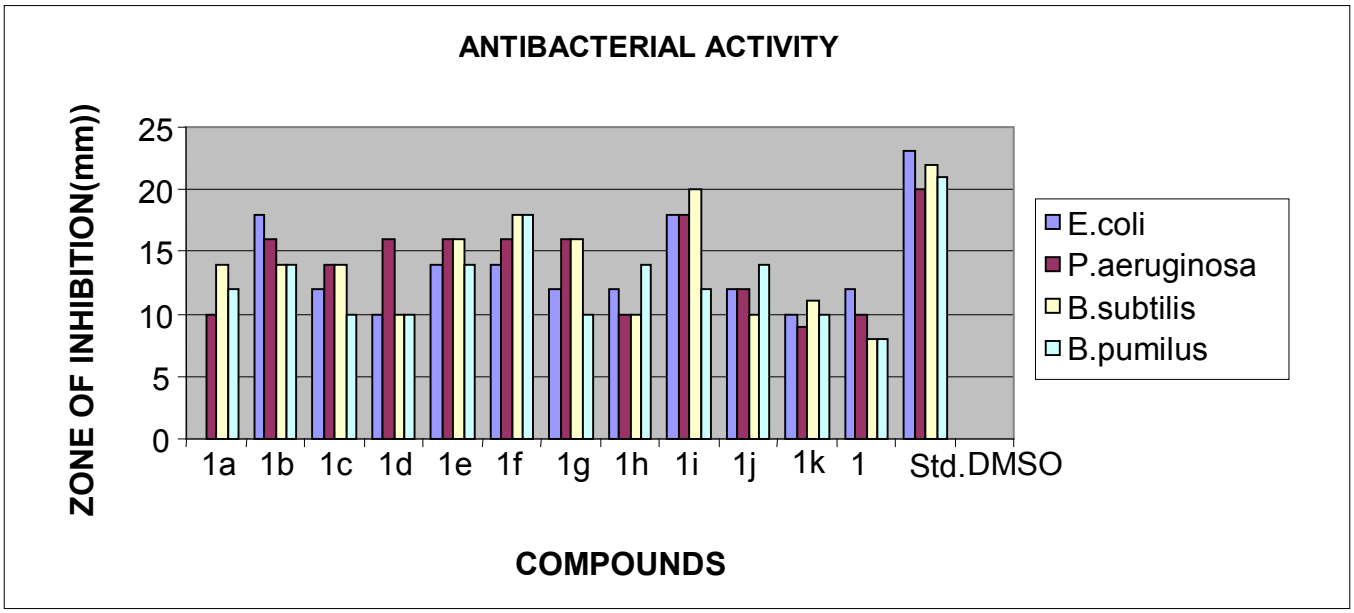
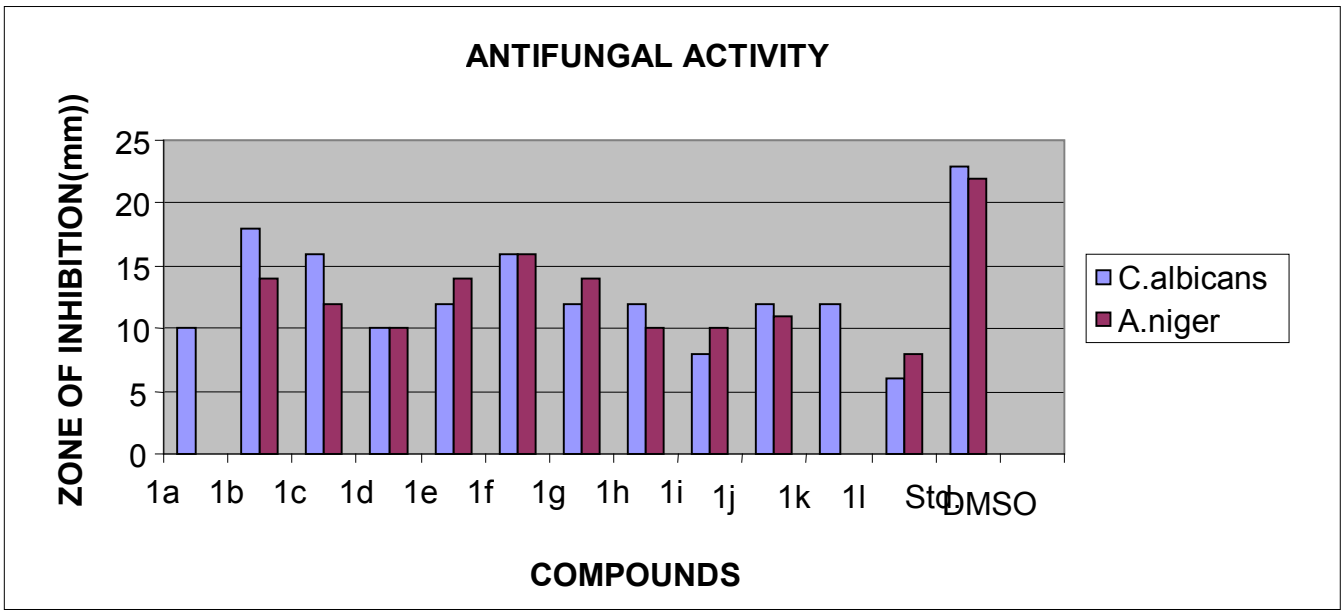


Fig-2 Antifungal activity



RESULTS

A series of 2-phenyl-1, 3-benzoxazoles were synthesized by the reaction of 2-aminophenol and acyl chlorides using microwave irradiation. The yields of the synthesized compounds are given in Table 1. Compounds were synthesized in moderate to good yield. Purity of compounds was determined by TLC on silica gel G plates. The spots were detected by exposure to iodine vapours. Synthesized compounds were characterized by spectral analysis (FTIR, ^{1}H-NMR). The spectra were found to be in agreement with the assigned molecular structures.

DISCUSSION

The synthesized compounds (1a-1l) were evaluated for in vitro antimicrobial activity by agar-well diffusion method. C2(5mg/ml) gave higher activity than C1(2.5mg/ml) and C3(10mg/ml).Compounds 1b{2-(2-methoxyphenyl)-1,3-benzoxazole}, 1f {2-(4-bromophenyl)-1,3-benzoxazole}, 1g {2-(3-cholorophenyl)-1,3-benzoxazole}, 1i {2-(2-nitrophenyl)-1,3-benzoxazole} were found to have good antibacterial activity

Compounds 1b {2-(2-methoxypheny)-1, 3-benzoxazole}, 1f {2-(4-bromophenyl)-1, 3-benzoxazole} were potent antifungal compounds amongst the series. (Fig-1 and 2)

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