



## Efficient Antimicrobial Activities of Microwave-assisted Synthesis of Benzisoxazole Derivatives

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### ABSTRACT

The present study deals with the synthesis of benzisoxazole derivatives beginning from 5,5-dimethyl cyclohexane-1,3-dione by making use of a microwave reactor. The microwave reactions are effortless, well-organized, clean, swift and financially viable for the synthesis of a huge amount of organic molecules, have offered the drive for many chemists to change from conventional heating methods to microwave-assisted chemistry. In latest years, microwave synthesized organic reaction has appeared as a new device in organic synthesis. The synthesized compounds were for the studie by using IR, NMR, mass spectra and antimicrobial studies also carried out.

**Keywords:** Benzisoxazole, IR, NMR, Antimicrobial.

### INTRODUCTION

Microwave assisted synthesis is an eco-friendly and well-organized synthesis of organic compounds in contrast to the conventional process. In this system, reaction takes place more swiftly, securely and with advanced chemical yields and thus, this method becomes greater to the conventional mode.

Benzisoxazole exhibits a remarkable prospective as antimicrobial, anticancer, anti-inflammatory actions. In medicinal chemistry

as it relates to the broad and general outline of the different benzisoxazole analogs, their application as beginning building blocks of diverse architectures on scales adequate to drive human drug experiments.<sup>1-5</sup> Heterocyclic molecules such as benzisoxazole derivatives, particularly 3-(piperidin-4-yl)-1,2-benzisoxazole have been extensively used as antipsychotic drugs.<sup>6</sup> Atypical antipsychotic drugs which are derived from benzisoxazole.<sup>7</sup> Benzisoxazole derivatives are oxygen, nitrogen holding heterocycles with broad variety of synthetic and pharmaceutical applications, and are renowned for biological activities. The high therapeutic



properties of these heterocycles have persuaded the medicinal chemist to synthesize a huge quantity of chemotherapeutic agents.<sup>8</sup>

Isoxazole is a vital heterocyclic core, which is broadly used as many pharmacological properties.<sup>9-12</sup> We herein detail the synthesis of benzisoxazole derivatives from dimedone with the use of microwave irradiation.

## EXPERIMENTAL

### MATERIALS AND METHOD

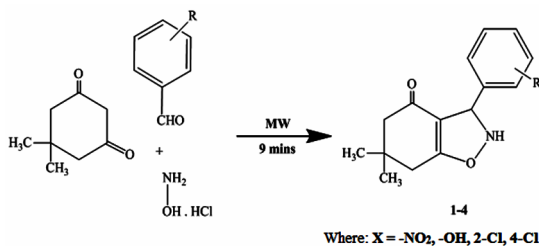
Dimedone, benzaldehyde and hydroxylamine hydrochloride were provided by Sigma-Aldrich (St. Louis, USA). IR spectra were documented in SHIMADZU FT-IR 8400S spectrometer by employing KBr pellets. <sup>1</sup>H NMR (500 MHz) and <sup>13</sup>C NMR (400 MHz) spectra recorded on Bruker spectrometer using CDCl<sub>3</sub> solvent. Microwave (Godrej GMS 17M 07 WHGX). Melting point was recorded in Royal Scientific RSW 138 B.

### Synthesis of benzisoxazole derivatives

5,5-dimethylcyclohexane-1,3-dione (0.001 mm) react with hydroxylamine hydrochloride (0.001 mm) and benzaldehyde (0.1 mL) under microwave irradiation at a suitable time (Table 1). The development of the reaction was monitored on TLC (Scheme 1). Following the completion of reaction, the reaction combination was quenched in distilled water and the precipitate was formed. It were filtered and dried.

**Table 1: Melting point, yield and time taken for microwave irradiation of the benzisoxazole derivatives 1-4**

Compounds	m.p (°C)	Yield (%)	Time (min)
1	158	86	7
2	162	75	9
3	152	78	8
4	144	80	7



**Scheme 1. Synthetic route of benzisoxazole derivatives**

### Antibacterial studies

Antibacterial studies, *Gram-positive* and *Gram-negative* strains have been used for the study *B. subtilis*, *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenes*. Antifungal studies, used following fungal strains, *A. flavus*, *A. niger*, *P. chryogenum*, *T. veride*, *F. oxysporum*.

## RESULTS AND DISCUSSION

### IR and NMR spectrum of benzisoxazole derivatives (1-4)

Synthesis of benzisoxazole derivatives (1-4) by utilizing microwave irradiation for suitable time (9 min) afforded remarkable yields with absolute transformation of reactants. The foundation of newly synthesized (1-4) was launched by IR and NMR spectroscopy.

### 3-(2-chlorophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzo[d]isoxazol-4(5H)-one (1)

FT-IR spectrum the carbonyl (C=O) and N-H stretching frequency were scrutinized in the area of 1688 and 3666-3750 cm<sup>-1</sup>. The C-N and aromatic C=C stretching frequency were examined at 2360 and 1548 cm<sup>-1</sup>.

Molecular formula is C<sub>15</sub>H<sub>16</sub>ClNO<sub>2</sub>: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.16 (s, 6H), 2.33 (s, 1H), 2.34 (s, 2H), 2.44 (s, 2H), 5.50 (s, 1H), 7.02 (d, J = 3.0 Hz, 3H), 7.24 (t, 2H), 7.45 (d, J = 8.0 Hz, 1H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 27.67, 31.76, 41.62, 51.16, 59.14, 104.47, 126.99, 128.05, 128.59, 129.35, 142.79, 187.47, 198.93. Theoretical value of MS: m/z. 277.75 [M<sup>+</sup>].

### 3-(4-chlorophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzo[d]isoxazol-4(5H)-one (2)

FT-IR spectrum the carbonyl (C=O) and N-H stretching frequency were surveyed in the region of 1688 and 3666-3750 cm<sup>-1</sup>. The C-N and aromatic C=C stretching frequency were examined at 2360 and 1548 cm<sup>-1</sup>.

Molecular formula is C<sub>15</sub>H<sub>16</sub>ClNO<sub>2</sub>: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 1.16 (s, 6H), 2.33 (s, 1H), 2.40 (s, 2H), 2.44 (s, 2H), 5.10 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 12.0 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 27.67, 31.76, 41.65, 51.14, 62.47, 104.45, 126.99, 128.59, 133.96, 141.56, 187.40, 198.91. Theoretical value of MS: m/z. 277.75 [M<sup>+</sup>].

**3-(4-hydroxyphenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzo[d] isoxazol-4(5H)-one (3)**

FT-IR spectrum the hydroxyl (–OH), carbonyl (C=O) and N-H stretching frequency were examined in the area of 3852, 1688 and 3666-3750  $\text{cm}^{-1}$ . The C-N and aromatic C=C stretching frequency were detected at 2360 and 1548  $\text{cm}^{-1}$ .

Molecular formula is  $\text{C}_{15}\text{H}_{17}\text{NO}_3$ :  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.14 (s, 3H), 1.29 (s, 3H), 2.25 (s, 1H), 2.37 (s, 2H), 2.49 (s, 2H), 5.56 (s, 1H), 7.02 (d,  $J = 8.0$  Hz, 1H), 7.24 (d,  $J = 12.0$  Hz, 1H), 7.37 (d,  $J = 7.5$  Hz, 1H), 7.45 (d,  $J = 7.9$  Hz, 1H), 11.88 (s, 1H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  27.66, 31.76, 41.65, 51.14, 61.47, 104.65, 115.17, 126.99, 135.96, 139.55, 156.59, 187.40, 198.91. Theoretical value of MS:  $m/z$ . 259.30 [ $\text{M}^+$ ].

**6,6-dimethyl-3-(3-nitrophenyl)-2,3,6,7-tetrahydrobenzo[d] isoxazol-4(5H)-one (4)**

FT-IR spectrum the carbonyl (C=O) and N-H stretching frequency were detected in the area of 1688 and 3666-3750  $\text{cm}^{-1}$ . The C-N and aromatic C=C stretching frequency were detected at 2360 and 1548  $\text{cm}^{-1}$ .

Molecular formula is  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$ :  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.15 (s, 3H), 1.27 (s, 3H), 2.25 (s, 1H), 2.37 (s, 2H), 2.49 (s, 2H), 5.56 (s, 1H), 7.56 (t, 1H), 7.89 (d,  $J = 8.0$  Hz, 1H), 7.72 (d,  $J = 7.9$  Hz, 1H), 8.43 (s, 1H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  27.66, 31.76, 41.65, 51.14, 61.47, 119.32, 121.68, 129.84, 135.96, 147.12, 187.59, 198.91. Theoretical value of MS:  $m/z$ . 288.30 [ $\text{M}^+$ ].

**Antimicrobial activities**

The preliminary antimicrobial activities of the moieties 1-4 are scrutinized using disc diffusion method. The bacterial strains viz., *B. subtilis*, *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenes* are used in this study. Dimethylsulphoxide is used as a control. Streptomycin and Amphotericin B are used as an indication for bacterial and fungal studies correspondingly.

The antibacterial screening studies indicated that the compound having 1, 2, 4 showed outstanding antibacterial against *B. subtilis*, *E. coli*, *S. pyogenes*, but no active against *P. aeruginosa* and *S. aureus*. The compound 1 is more active against *P. aeruginosa* and *S. pyogenes* (Fig. 1). The

results are given in Table 2. The antifungal activity screening studies confirmed that the 1, 2, 4 chloro substituted compound showed outstanding activity against *A. flavus*, *P. chryogenum*, *F. oxysporum* and less active against *A. niger*, *T. veride* (Fig. 2). The result is given in Table 3.

**Table 2: Antibacterial activity of compounds 1 to 4**

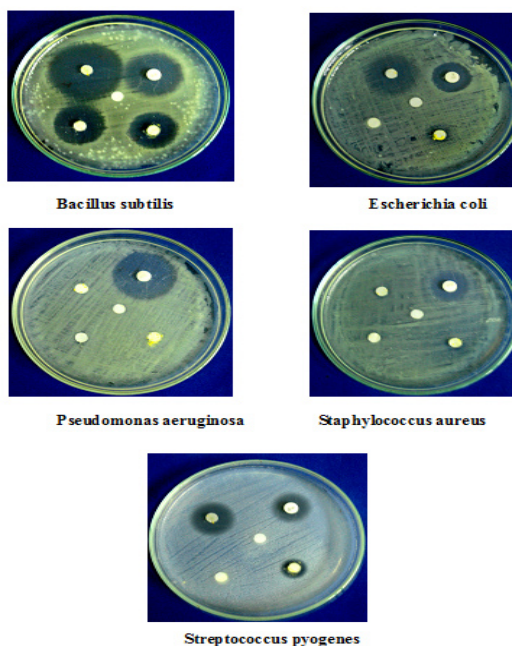
S. No.	Bacteria	Zone of inhibition mm in diameter			
		1	2	3	4
1	<i>B. subtilis</i>	25	20	20	31
2	<i>E. coli</i>	18	8	-	22
3	<i>P. aeruginosa</i>	26	-	-	-
4	<i>S. aureus</i>	18	8	-	-
5	<i>S. pyogenes</i>	17	12	-	19

\*Streptomycin

**Table 3: Antifungal activity of compounds 1 to 4**

S. No.	Fungi	Zone of inhibition mm in diameter			
		1	2	3	4
1	<i>Aspergillus flavus</i>	14	24	-	26
2	<i>Aspergillus niger</i>	19	18	-	11
3	<i>Penicillium chryogenum</i>	12	23	-	28
4	<i>Trichoderma veride</i>	20	17	-	8
5	<i>Fusarium oxysporum</i>	12	22	-	27

\*Amphotericin-B

**Fig. 1. Zone of inhibition of moieties 1-4 against *B. subtilis*, *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes***

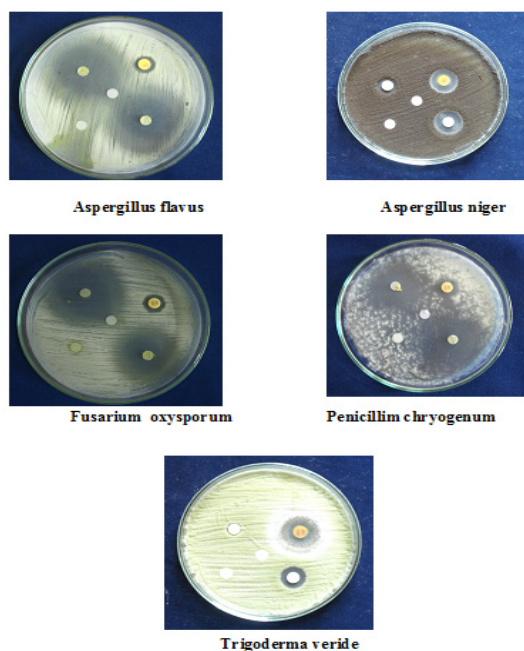


Fig. 2. Zone of inhibition of moieties 1-4 against *A. flavus*, *A. niger*, *F. oxysporum*, *P. chryogenum*, *T. veride*

## CONCLUSION

The depicted synthetic protocol permits for the preparation of a series of benzisoxazole derivatives as new arrangement which can be latently useful in various pharmacological applications. Chief benefits of these original techniques are equipped with effortlessness, high yield in a very tiny reaction time, eco-friendly conditions, very cheap, effortlessly available reagent and simple technique employed.

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## Conflict of interest

No conflict of interest

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