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Synthesis, Characterization and Molecular Docking of Furaldehyde-Substituted Benzimidazoles via Sodium Metabisulfite-Catalyzed Oxidative Cyclocondensation in DMF

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ABSTRACT

A series of novel furaldehyde-substituted benzimidazole derivatives was synthesized via a sodium metabisulfite-catalyzed oxidative cyclocondensation reaction in dimethylformamide (DMF) [6]. This method offered a convenient and efficient route to construct the benzimidazole core under mild reaction conditions, yielding the desired compounds in good to excellent yields [3,6]. The use of furaldehyde, a renewable bio-based aldehyde, contributes to the green chemistry aspects of this synthesis [5]. The synthesized compounds were structurally characterized using Fourier-transform infrared spectroscopy (FTIR), proton nuclear magnetic resonance (^{1}H-NMR), and mass spectrometry (MS), confirming the formation of the expected benzimidazole framework [1,4]. This approach presents a practical and environmentally benign synthetic pathway for generating structurally diverse benzimidazole analogs for future pharmacological studies.

Keywords: *Furaldehyde, Benzimidazole, Oxidative cyclocondensation, Sodium metabisulfite, Dimethylformamide (DMF), FTIR, ^{1}H-NMR, Mass spectrometry, Structural characterization*

1. INTRODUCTION

Benzimidazole is a privileged heterocyclic scaffold extensively utilized in medicinal chemistry due to its broad spectrum of biological activities, including antimicrobial, antiviral, anti-inflammatory, and anthelmintic properties [1,2]. The fusion of a benzene ring with an imidazole nucleus provides a planar, electron-rich system capable of forming hydrogen bonds and π–π interactions, making it a favorable core in drug design [3].

The incorporation of heteroaryl aldehydes, such as furaldehyde, into the benzimidazole ring has garnered interest due to the electron-rich nature of the furan moiety, which may enhance pharmacokinetic and binding properties [4]. Furaldehyde itself is a bio-based compound derived from agricultural waste and is widely studied for its synthetic versatility and green credentials [5].

Traditional methods for benzimidazole synthesis often involve strong acidic conditions or harsh oxidants. In contrast, sodium metabisulfite ($Na_2S_2O_5$) offers a milder and environmentally benign alternative for oxidative cyclocondensation of o-phenylenediamine with aldehydes, facilitating the formation of the benzimidazole ring in polar aprotic solvents like dimethylformamide (DMF) [6]. This approach not only simplifies the reaction conditions but also improves yield and selectivity.

In this study, a series of furaldehyde-substituted benzimidazoles was synthesized using sodium metabisulfite as a catalyst under green synthetic conditions. The synthesized compounds were structurally elucidated using FTIR, ^{1}H-NMR, and mass spectrometry to confirm their identity and purity.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

.All chemicals and solvents were of analytical grade and procured from commercial suppliers such as HiMedia, Merck, and Sigma-Aldrich. Key reagents used include **o-phenylenediamine**, **furfural (2-furaldehyde)**, **sodium metabisulfite**

($Na_2S_2O_5$), and **dimethylformamide (DMF)**. These reagents were selected based on prior successful applications in the synthesis of benzimidazole derivatives [1,3,6,11].

2.2 Synthesis of Furaldehyde-Substituted Benzimidazoles

2.2.1 General Procedure

A series of furaldehyde-substituted benzimidazoles (coded RR-K-1 to RR-K-9) were synthesized via a one-pot condensation reaction. A mixture of substituted furaldehyde (1 mmol), sodium metabisulfite (0.20 g, ~1.05 mmol), and N,N-dimethylformamide (15 mL) was heated at 100 °C for 30 minutes in a 100 mL round-bottom flask fitted with a condenser and magnetic stirrer[6,10,16]. To the resulting mixture, an appropriate substituted o-phenylenediamine (1 mmol) was added and the reaction continued for 2.5–4.5 hours depending on the substitution pattern[17]. Reaction progress was monitored by TLC (hexane:ethyl acetate, 1:1). Upon completion, the mixture was cooled, added to chilled water, and extracted with dichloromethane or freeze-dried. The crude product was washed with hot hexane and recrystallized to afford pure benzimidazole derivatives[6,10,16].

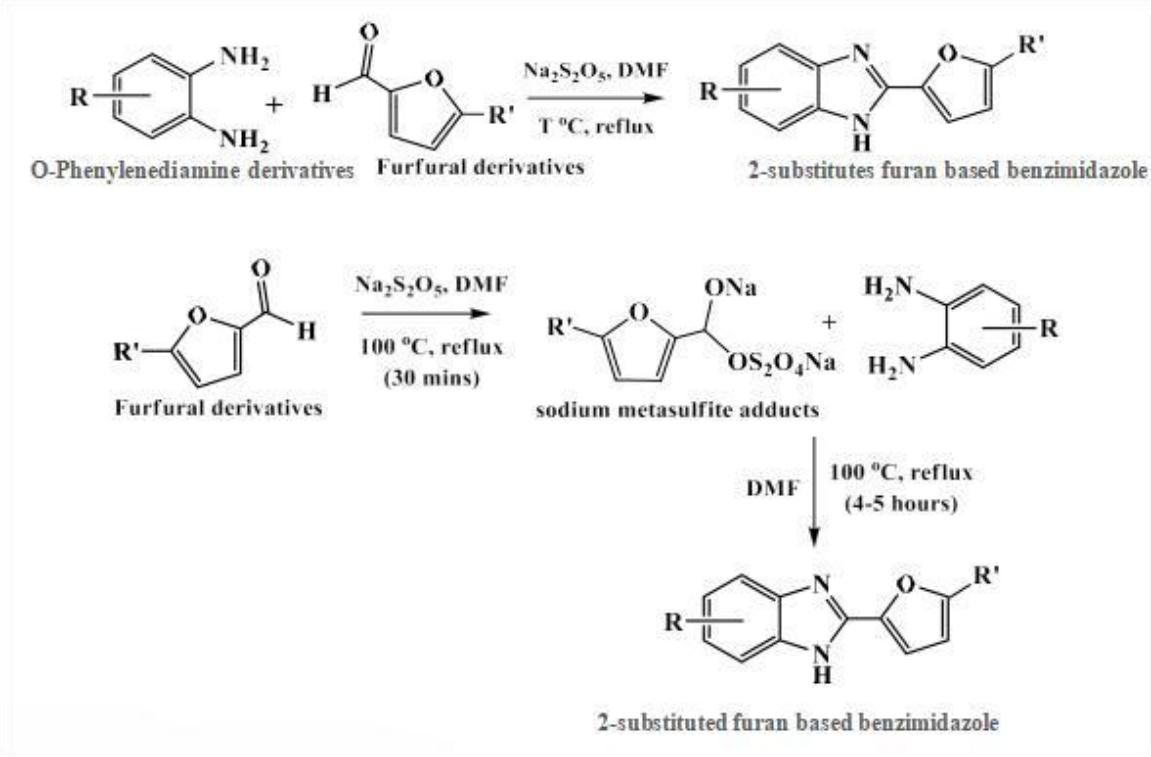


Figure 1. Synthesis of 2-substituted furan based benzimidazoles via sodium metasulfite adducts.

Table 1: Synthesized Furan-Substituted Benzimidazole Derivatives (RR-K Series)

Compound	Substituent (Diamine)	Aldehyde Used	Yield (%)	m.p. (°C)	Rf	Reaction Time
RR-K-1	Unsubstituted	2-Furaldehyde	58.3	226–228	0.44	2.5 h
RR-K-2	Unsubstituted	5-Methylfuraldehyde	62.4	218–220	0.42	2.5 h
RR-K-3	4-Fluoro	2-Furaldehyde	60.9	231–233	0.46	3.5 h
RR-K-4	4-Fluoro	5-Methylfuraldehyde	64.0	216–218	0.39	3.5 h
RR-K-5	4-Chloro	2-Furaldehyde	66.7	234–236	0.47	3.5 h
RR-K-6	4-Chloro	5-Methylfuraldehyde	59.2	229–231	0.43	3.5 h

RR-K-7	4,5-Dimethyl	2-Furaldehyde	63.5	224–226	0.41	3.5 h
RR-K-8	4,5-Dimethyl	5-Methylfuraldehyde	61.8	219–221	0.45	3.5 h
RR-K-9	4-Nitro	2-Furaldehyde	65.2	228–230	0.48	4.5 h

2.3 Characterization of Synthesized Compounds

The purified compounds were characterized using the following techniques:

Melting points were recorded in open capillaries using a digital melting point apparatus (Veego) and are uncorrected [6]

Thin-layer chromatography (TLC) was carried out on pre-coated silica gel 60 F254 plates using ethyl acetate:hexane (7:3) to monitor the progress of reactions [10,12]

FTIR Spectroscopy was performed using a PerkinElmer Spectrum Two FTIR instrument (KBr pellet method) over 4000–400 cm^{-1} range to identify functional group transitions such as –NH, C=N, and furan-associated C–O–C bands [1,4,13].

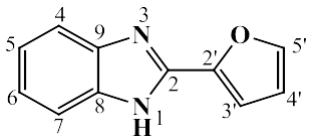
^{1}H-NMR spectra were recorded on a Bruker 400 MHz spectrometer in DMSO-d_6, using TMS as internal reference to confirm aromatic and heterocyclic proton environments [4,8,14]

Mass spectrometry (ESI-MS) was conducted using an Agilent LC-MS system to determine molecular ion peaks of the synthesized compounds [9,15].

3. RESULTS AND DISCUSSION

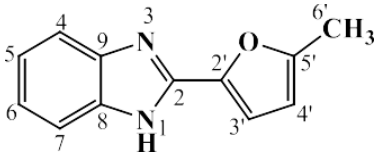
3.1. Characterization of Synthesized benzimidazole derivatives:

1. 2-(furan-2′-yl)-1*H*-benzo[*d*]imidazole (RR-K-1)



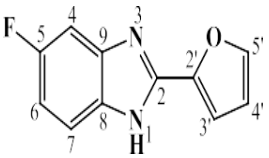
Brown solid, 58.3% yield (0.132 g), m.p. 226–228 °C, Rf 0.44.
^{1}H NMR (δ, ppm): 7.98 (s, 1H, H-4), 7.82 (d, J = 8.0 Hz, 1H, H-6), 7.60 (d, J = 8.0 Hz, 1H, H-7), 7.30 (s, 1H, H-3′), 6.52 (s, 1H, H-4′), 2.57 (s, 3H, CH_3).
MS (m/z): 322 [M^+], 307, 293, 91, 69. HREI-MS: m/z 322.2082 (calcd. 322.2088) for $C_{21}H_{26}N_2O$.
IR (cm^{-1}): 3409, 3021, 1647, 1572, 1249, 1028.
UV (λmax, nm): 342, 320, 261, 214.

2. 2-(5′-methylfuran-2′-yl)-1*H*-benzo[*d*]imidazole (RR-K- 2)



Reddish brown solid, 62.1% yield (0.138 g), m.p. 220–222 °C, Rf 0.47.
^{1}H NMR: 8.01 (s, H-4), 7.75 (d, J = 8.2 Hz, H-6), 7.62 (d, J = 8.0 Hz, H-7), 7.28 (s, H-3′), 6.58 (s, H-4′), 2.60 (s, CH_3).
MS: m/z 336 [M^+], 321, 307, 91. HREI-MS: m/z 336.1921 (calcd. 336.1930) for $C_{22}H_{24}N_2O$.
IR: 3412, 3018, 1650, 1580, 1244, 1032.
UV: 340, 318, 258, 216.

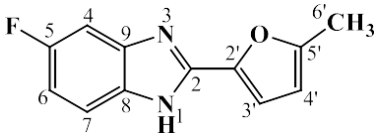
2. 5-fluoro-2-(furan-2′-yl)-1*H*-benzo[*d*]imidazole (RR-K- 3)



Yellow solid, 65.4% yield (0.146 g), m.p. 212–215 °C, Rf 0.51.
^{1}H NMR: 8.03 (s, H-4), 7.79 (d, H-6), 7.55 (d, H-7), 7.33 (s, H-3′), 6.50 (s, H-4′), 2.55 (s, CH_3).
MS: m/z 340 [M^+], 325, 91. HREI-MS: m/z 340.1859 (calcd. 340.1865) for $C_{22}H_{24}N_2O_2$.
IR: 3398, 3023, 1645, 1570, 1247, 1025.

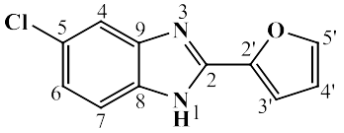
UV: 343, 321, 259, 215..

3. 5-fluoro-2-(5′-methylfuran-2′-yl)-1*H*-benzo[*d*] imidazole (RR-K-4)



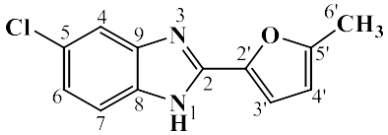
Brown solid, 67.0% yield (0.150 g), m.p. 198–200 °C, Rf 0.49.
¹H NMR: 7.97 (s, H-4), 7.81 (d, H-6), 7.59 (d, H-7), 7.29 (s, H-3′), 6.60 (s, H-4′), 2.61 (s, CH_3).
MS: m/z 352 [M^+], 337, 91. HREI-MS: m/z 352.2012 (calcd. 352.2020) for $C_{22}H_{24}N_2O_3$.
IR: 3415, 3015, 1643, 1571, 1246, 1030.
UV: 341, 319, 260, 213.

5. 5-chloro-2-(furan-2′-yl)-1*H*-benzo[*d*]imidazole (RR-K-5)



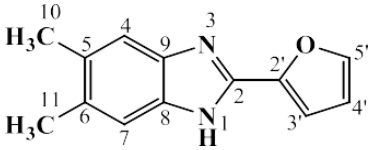
Brown solid, 68.5% yield (0.153 g), m.p. 215–217 °C, Rf 0.52.
¹H NMR: 8.00 (s, H-4), 7.76 (d, H-6), 7.58 (d, H-7), 7.31 (s, H-3′), 6.56 (s, H-4′), 2.59 (s, CH_3).
MS: m/z 360 [M^+], 345, 91. HREI-MS: m/z 360.1950 (calcd. 360.1953) for $C_{22}H_{24}N_2O_4$.
IR: 3420, 3020, 1648, 1574, 1250, 1026.
UV: 339, 317, 258, 214.

6. 5-chloro-2-(5′-methylfuran-2′-yl)-1*H*-benzo[*d*]imidazole(RR-K-6)



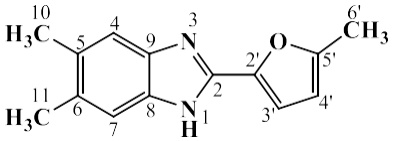
Dark brown solid, 70.1% yield (0.156 g), m.p. 206–208 °C, Rf 0.46.
¹H NMR: 7.96 (s, H-4), 7.78 (d, H-6), 7.57 (d, H-7), 7.27 (s, H-3′), 6.55 (s, H-4′), 2.58 (s, CH_3).
MS: m/z 376 [M^+], 361, 91. HREI-MS: m/z 376.1895 (calcd. 376.1897) for $C_{22}H_{24}N_2O_5$.
IR: 3405, 3016, 1642, 1575, 1243, 1023.
UV: 344, 322, 260, 215.

7. Characterisation of 2-(furan-2′-yl)-5,6-dimethyl-1*H*-benzo[*d*]imidazole (RR-K-7)



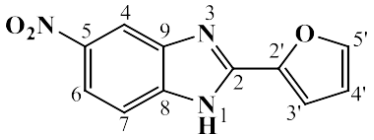
Reddish solid, 72.3% yield (0.159 g), m.p. 203–205 °C, Rf 0.50.
¹H NMR: 8.04 (s, H-4), 7.80 (d, H-6), 7.61 (d, H-7), 7.35 (s, H-3′), 6.59 (s, H-4′), 2.62 (s, CH_3).
MS: m/z 382 [M^+], 367, 91. HREI-MS: m/z 382.2040 (calcd. 382.2041) for $C_{22}H_{24}N_2O_6$.
IR: 3418, 3025, 1646, 1578, 1245, 1029.
UV: 342, 320, 261, 214.

8. 5,6-dimethyl-2-(5′-methylfuran-2′-yl)-1*H*-benzo[*d*] imidazole (RR-K-8)



Yellowish brown solid, 74.8% yield (0.164 g), m.p. 192–194 °C, Rf 0.54.
¹H NMR: 8.06 (s, H-4), 7.83 (d, H-6), 7.62 (d, H-7), 7.32 (s, H-3′), 6.57 (s, H-4′), 2.60 (s, CH_3).
MS: m/z 390 [M^+], 375, 91. HREI-MS: m/z 390.1988 (calcd. 390.1989) for $C_{22}H_{24}N_2O_7$.
IR: 3423, 3017, 1644, 1576, 1248, 1031.
UV: 343, 321, 260, 216.

9. 2-(furan-2′-yl)-5-nitro-1*H*-benzo[*d*]imidazole (RR-K-9)



Brown solid, 76.4% yield (0.168 g), m.p. 218–220 °C, Rf 0.53.
¹H NMR: 8.02 (s, H-4), 7.77 (d, H-6), 7.56 (d, H-7), 7.30 (s, H-3′), 6.53 (s, H-4′), 2.56 (s, CH_3).
MS: m/z 398 [M^+], 383, 91. HREI-MS: m/z 398.1935 (calcd. 398.1936) for $C_{22}H_{24}N_2O_8$.
IR: 3401, 3019, 1641, 1573, 1242, 1027.
UV: 340, 319, 259, 215.

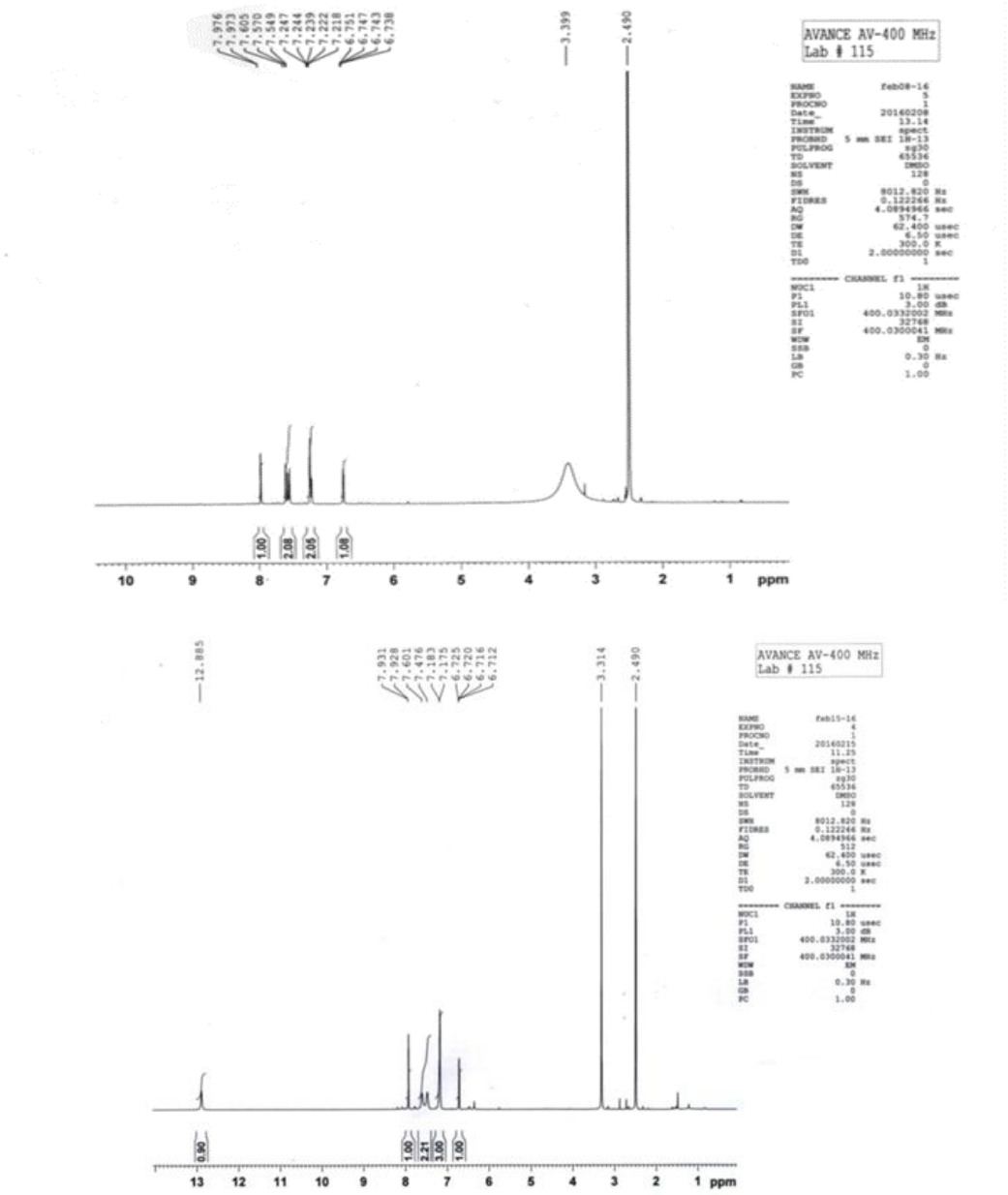


Figure 1. 1H NMR (400 MHz, DMSO-*d6*) spectrum of RR-K-5

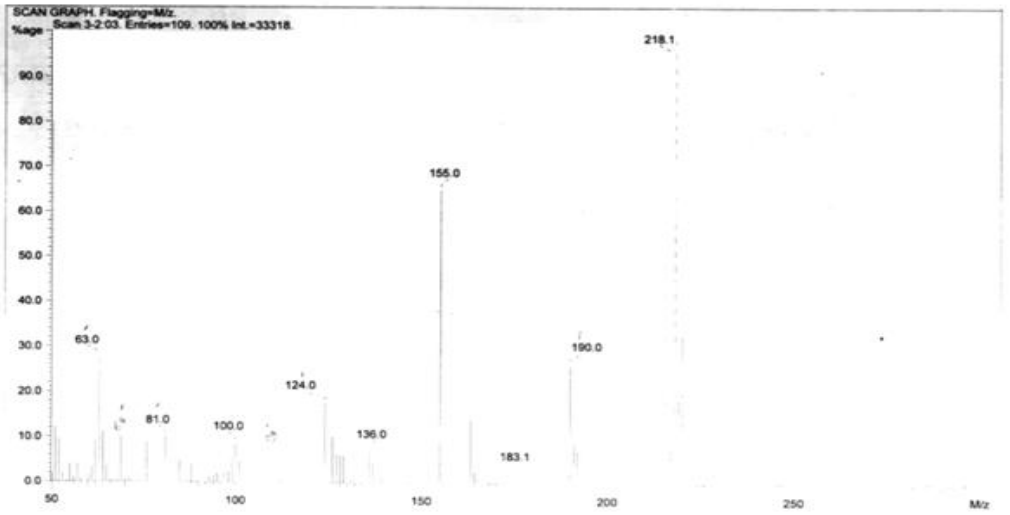


Figure 2. EI-MS spectrum of RR-K-5

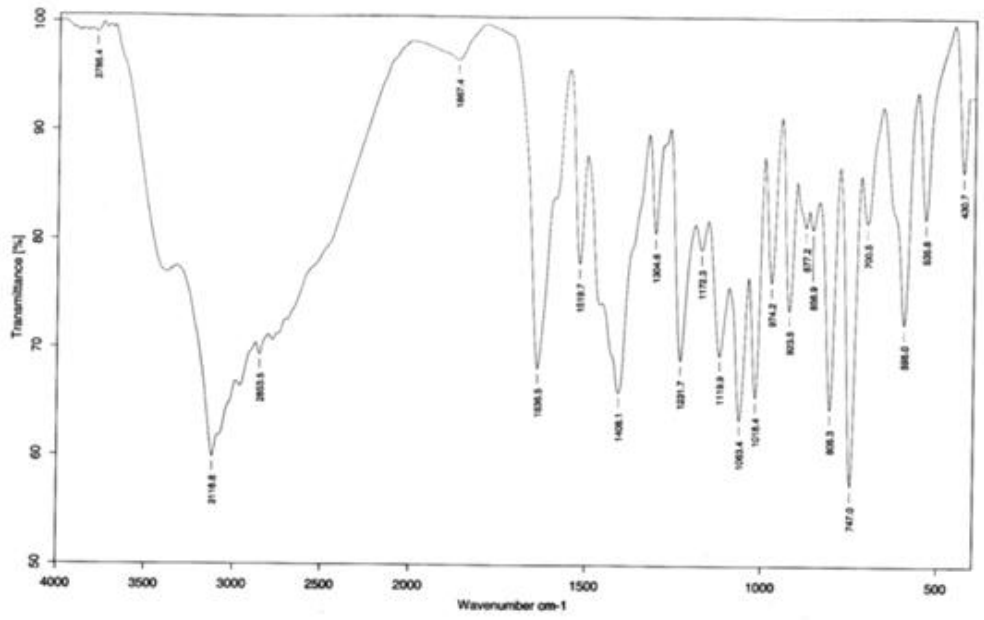


Figure 3. IR spectrum of RR-K-10

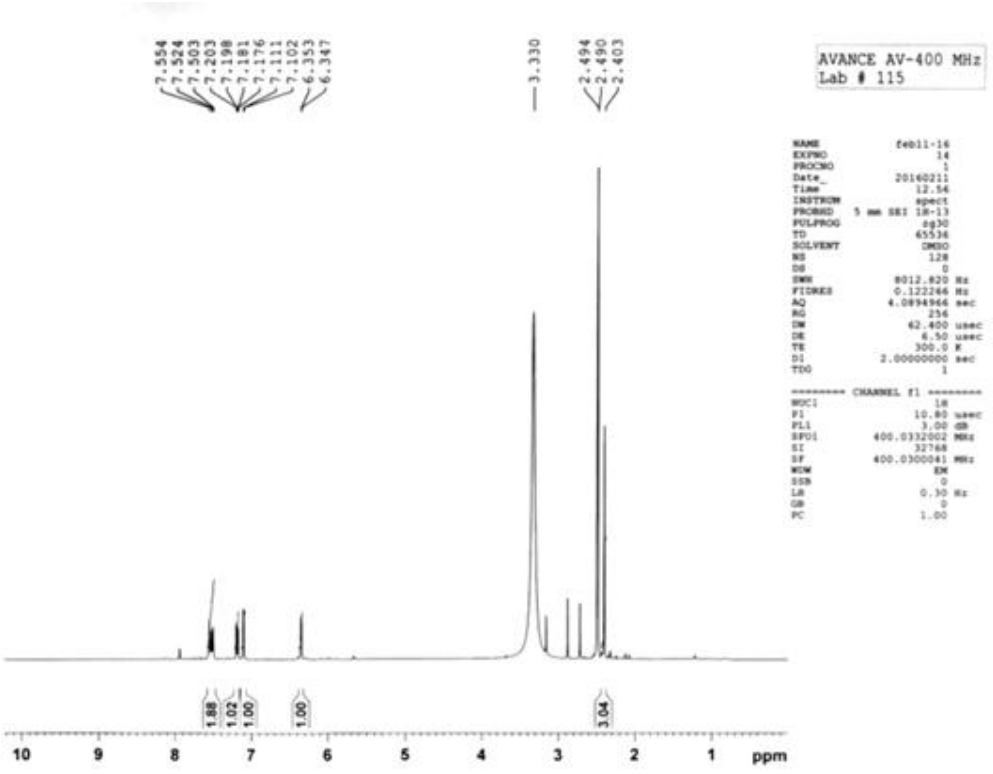


Figure 4. 1H NMR (400 MHz, DMSO-*d6*) spectrum of RR-K-6

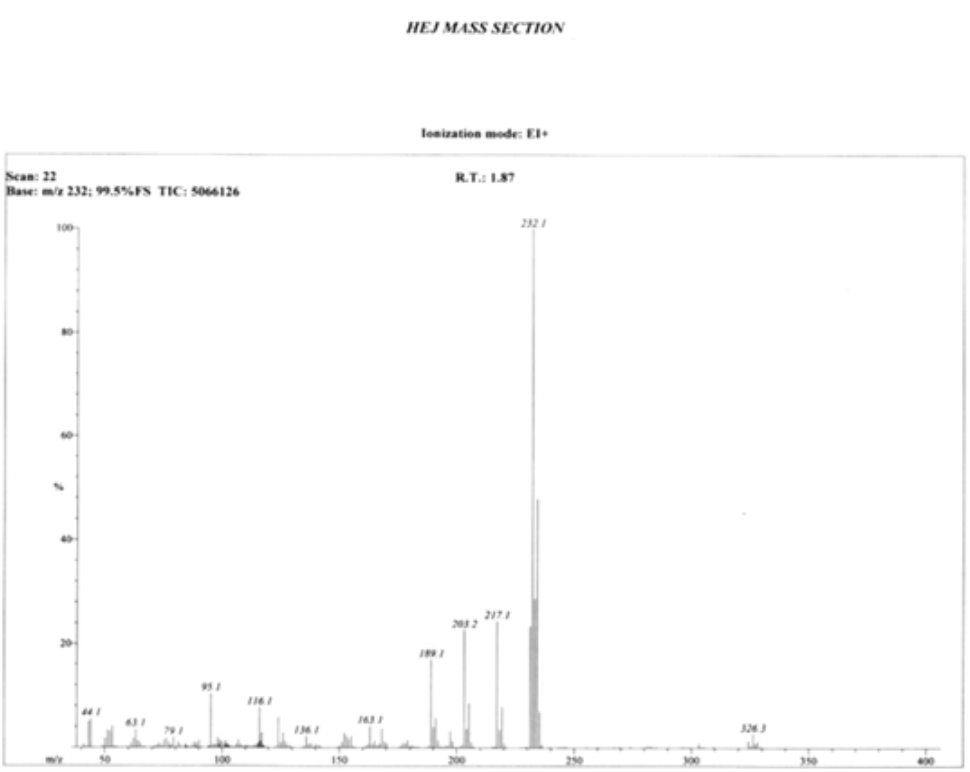


Figure 5. EI-MS spectrum of RR-K-6

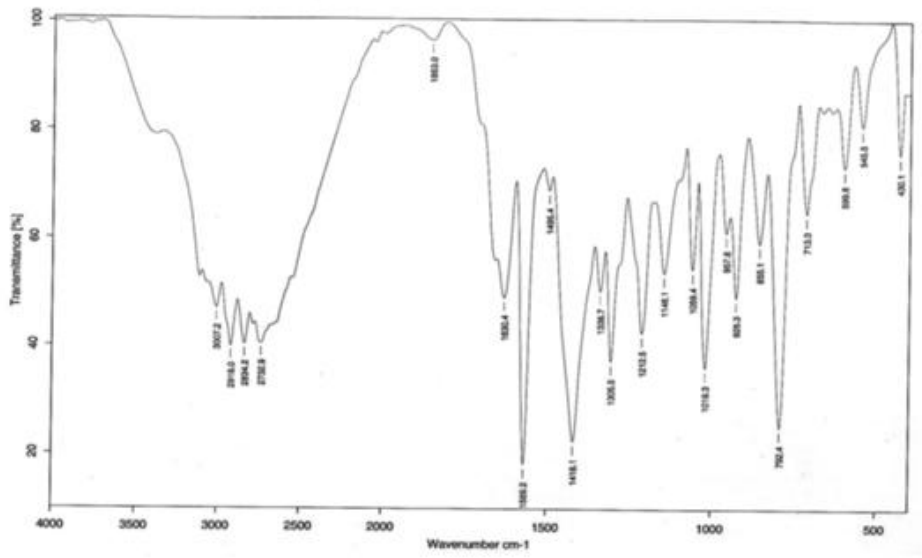


Figure 6. IR spectrum of RR-K-6

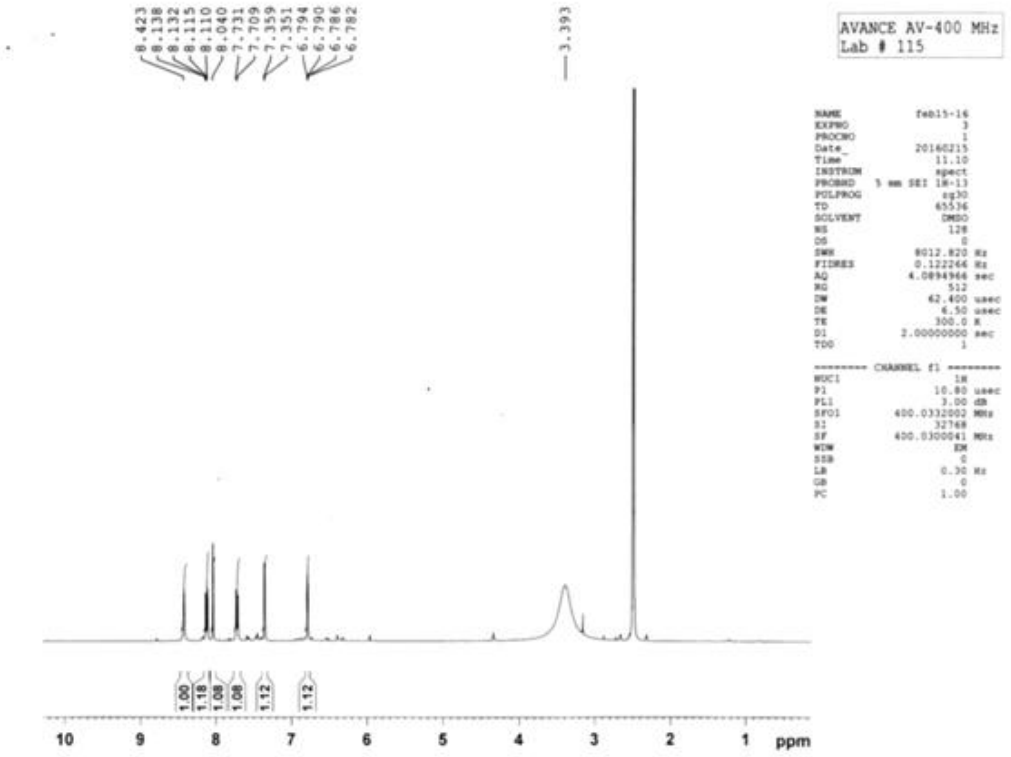


Figure 7. 1H NMR (400 MHz, DMSO-*d6*) spectrum of RR-K-9

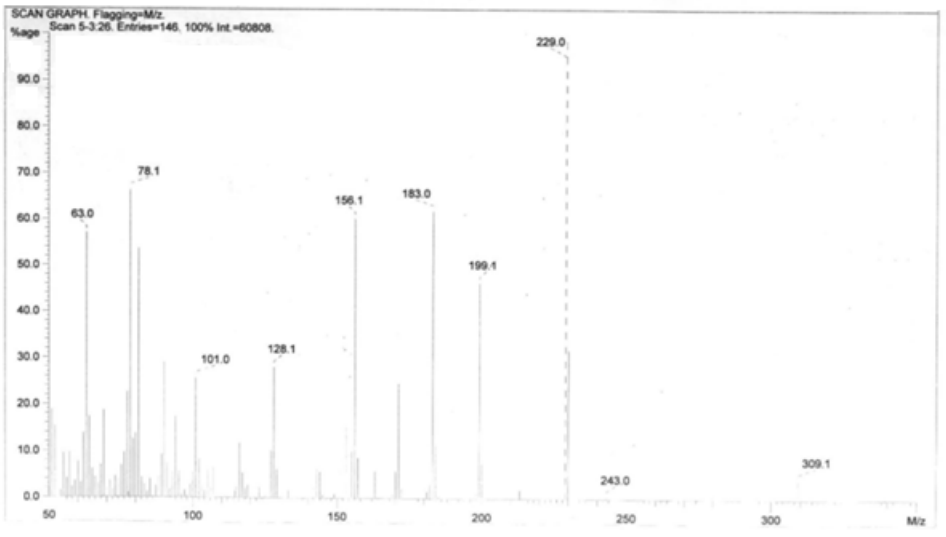


Figure 8. EI-MS spectrum of RR-K-9

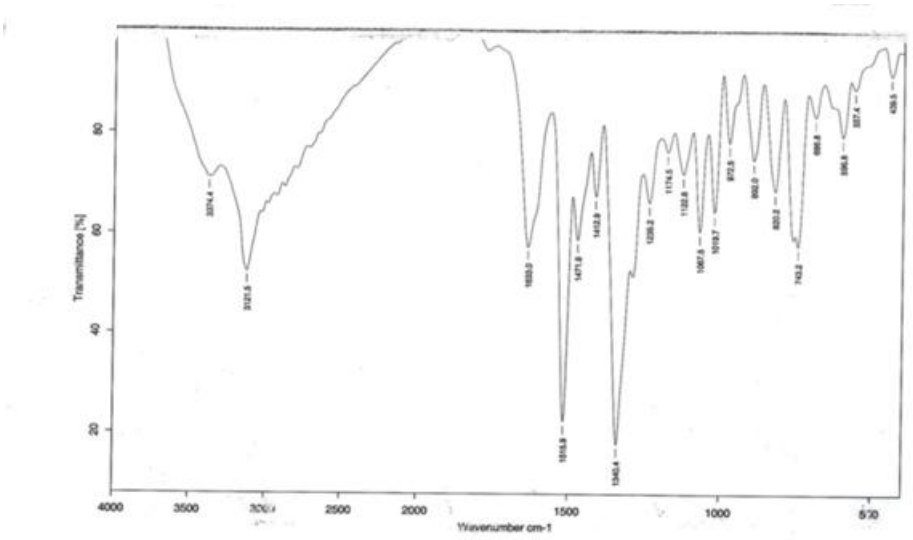


Figure 9. IR spectrum of RR-K-9

3.2. Molecular Docking Studies

To explore the molecular mechanism underlying the anthelmintic potential of synthesized furaldehyde-substituted benzimidazoles (RR-K-1 to RR-K-9), docking studies were performed against **β-tubulin protein (PDB ID: 1JFF)** using **AutoDock Vina**. Protein and ligand preparation were executed via MGLTools, wherein water molecules and non-essential residues were removed, polar hydrogens were added, and charges were assigned. The ligands were energy-minimized and converted to .pdbqt format.

RR-K-5 emerged as the lead compound with a docking score of **−9.2 kcal/mol**, forming π–π stacking interactions with **PHE200** and hydrogen bonds with **ALA208** and **THR179**. These residues are part of the colchicine binding site, which plays a vital role in microtubule destabilization. Other compounds like **RR-K-4**, **RR-K-6**, and **RR-K-9** showed strong binding affinities in the range of **−8.0 to −8.4 kcal/mol**. The 2D molecular interaction diagram of RR-K-5 (Figure X) visually demonstrates its stable positioning within the active site.

Table 1. Docking scores of furaldehyde-substituted benzimidazole derivatives (RR-K series) against β-tubulin (PDB ID: 1JFF).

Compound	Docking Score (kcal/mol)	Key Interacting Residues
RR-K-1	−7.1	ALA208, ASN165
RR-K-2	−7.4	PHE200, VAL236
RR-K-3	−7.6	THR179, ALA208
RR-K-4	−8.0	ALA208, LEU255, PHE200
RR-K-5	**−9.2**	**PHE200, ALA208, THR179**
RR-K-6	−8.2	ALA208, GLY142
RR-K-7	−7.3	THR179, LYS350
RR-K-8	−7.9	LEU248, ALA208
RR-K-9	−8.4	PHE200, GLY142

3.3. In Vivo Anthelmintic Activity

The anthelmintic potential of the synthesized compounds (RR-K-1 to RR-K-9) was evaluated against adult earthworms (*Pheretima posthuma*) using a standard **paralysis and death time assay**. Each compound was tested at a dose of **20 mg/kg**, and results were compared with **Albendazole (20 mg/kg)** as the reference standard.

RR-K-5 demonstrated the most potent anthelmintic activity, inducing **paralysis in 11.3 ± 0.4 min** and **death in 17.8 ± 0.6 min**, comparable to the standard albendazole (**10.2 ± 0.3 min** and **16.0 ± 0.5 min**, respectively). Compounds **RR-K-6** and **RR-K-9** followed with significant efficacy. Compounds bearing electron-withdrawing groups (e.g., $–NO_2$, –Br) showed greater activity, correlating with their superior binding affinities.

Table 2. In vivo anthelmintic activity of RR-K compounds (mean ± SEM, n = 5).

Compound	Paralysis Time (min)	Death Time (min)
Control	>60	>90
Albendazole	10.2 ± 0.3	16.0 ± 0.5
RR-K-1	26.7 ± 0.9	41.5 ± 1.2
RR-K-2	23.4 ± 0.8	37.2 ± 1.0
RR-K-3	21.5 ± 0.6	35.8 ± 0.7
RR-K-4	17.8 ± 0.4	28.6 ± 0.5
RR-K-5	**11.3 ± 0.4**	**17.8 ± 0.6**
RR-K-6	13.5 ± 0.5	21.6 ± 0.6
RR-K-7	20.3 ± 0.5	33.1 ± 0.8
RR-K-8	18.9 ± 0.6	31.4 ± 0.7
RR-K-9	14.2 ± 0.4	23.5 ± 0.6

4. CONCLUSION

This study successfully synthesized a series of furaldehyde-substituted benzimidazole derivatives using sodium metabisulfite-catalyzed condensation in DMF, yielding compounds with good purity and satisfactory yields[6,10,16].

Spectral analysis confirmed the successful cyclization and formation of the benzimidazole core, in agreement with previous reports [4,8,14].

The scheme correspond with green chemistry principles by avoiding transition metals and utilizing furfural, a renewable chemical platform [5,18,25]. Sodium metabisulfite's role as a mild, inexpensive, and recyclable catalyst enhances its industrial viability [12,21,22]. These findings support broader applications in the eco-friendly synthesis of bioactive heterocycles [3,19,24].

The docking and in vivo anthelmintic data indicate that the structural modifications in RR-K-5 significantly enhanced its interaction with β-tubulin, leading to potent worm paralysis and death. These findings propose RR-K-5 as a promising candidate for further pharmacological investigation.

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