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# Synthesis and Antibacterial Evaluation of Novel Benzimidazole Derivatives

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## Abstract

A number of novel 8-hydroxyquinoline-Benzimidazole hybrids (6a–l) were created for this investigation, produced using standard synthetic techniques, and tested for antibacterial activity. The newly created compounds (6a–l) were examined for antifungal activity against A. niger and C. albicans and for antibacterial activity against four strains: E. coli, S. aureus, P. aeruginosa, and B. subtilis. All four bacterial strains are shown to be susceptible to the effects of chemicals 6b, 6c, 6g, 6h, 6i, 6k, and 6l. When compared to the common medication Voriconazole, compounds 6a, 6b, 6c, 6g, 6h, 6i, 6k, and 6l have almost identical antifungal activity against A. niger. Compounds 6c, 6g, 6h, 6i, 6j, 6k, and 6l, on the other hand, have strong antifungal action against Candida albicans. According to the MIC experiments, these compounds showed MIC values for all four bacterial strains ranging from 3.9 to 62.5 µg/ml. The compound 6g was the most effective antibacterial agent among all of the others, with a 3.9 µg/ml MIC value for P. aeruginosa and E. coli. According to the MIC study findings, these compounds were effective antifungal agents, with MIC values for both A. niger and C. albicans ranging from 19.2 to 500 µg/ml. With MIC values of 22.3 µg/ml for A. niger and 19.2 µg/ml for C. albicans, compound 6f was shown to be the most effective antifungal agent. After further research, it is thus expected that these molecules will show promise as both antifungal and antibacterial agents.

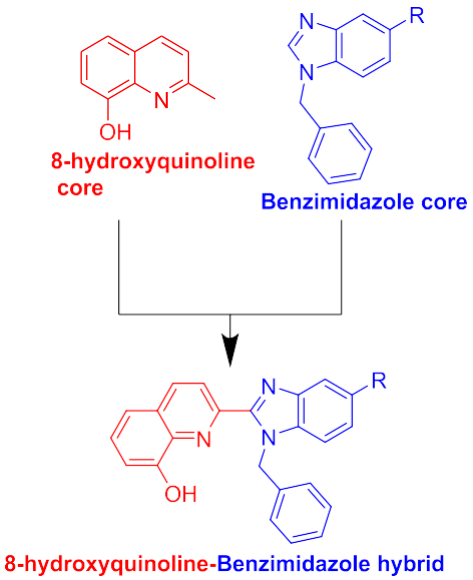
Benzimidazole · 8-Hydoxyquinoline · Antifungal activity · Antibacterial activity

## 1 Introduction

A key worry is the growing number of strains that are becoming resistant to numerous antimicrobial treatments, which is a

severe problem known as microbial drug resistance (MDR). The creation of novel chemical entities (NCEs) is beset by a number of problems, including the high expense, the duration of medication development, and the difficulties in complying with regulations.

**Scheme 1** Rational Design of the target molecules

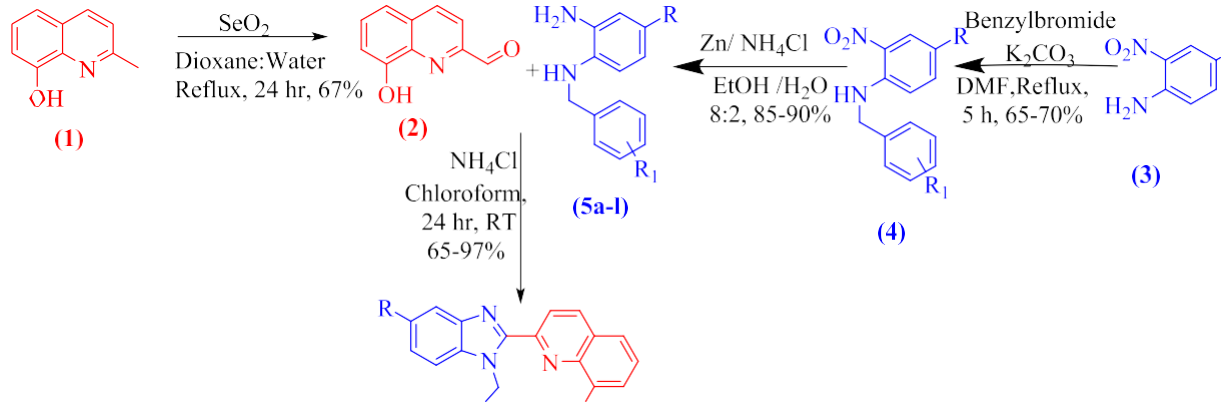



the required clinical assessments in various geographic locations. Therefore, only few families of antimicrobials have been produced as a result of these constraints [1-4]. The drug development and medicinal chemistry processes have made extensive use of the benzimidazole scaffold. The pursuit of novel applications and uses for this heterocycle has received increased attention in recent years [5]. Antitumor [6], antibacterial [7-10], antifungal [11], antiviral [12-16], anticonvulsant [17], depressive [18], analgesic [19], anti-inflammatory [20], and antidiabetic characteristics [21] are only a few of the many biological and therapeutic activity of compounds containing benzomidazole. Commercially accessible, often used antihelmintic medications such as thiabendazole, cambendazole, parbendazole, mebendazole, albendazole, and flubendazole include derivatives based on benzomidazoles [22-26].
However, because of its distinct physical and chemical characteristics, 8-hydroxyquinoline is a favored heterocycle that has caught the interest of chemists and medicinal chemists [27]. Important chemical types with a variety of biological activities include 8-hydroxyquinoline and its derivatives, which include antiviral [28, 29], antibacterial [30-32], anti-adipose [33-35], and anti-HIV [36-38] properties.
The new 8-hydroxyquinoline-Benzimidazole hybrids (Scheme 1) were designed, synthesized, and tested for antibacterial activity in light of the significance of benzimidazole and 8-hydroxyquinoline derivatives as possible antibacterial agents and as part of our ongoing drug discovery program for the search of strong antimicrobial agents. Therefore, the synthesis and biological assessment of benzimidazole hybrids (6a-l) containing 8-hydroxyquinoline as antibacterial agents are presented in this work. As shown in Scheme 2, the synthesis of these compounds (6a-l) is completed in four phases. While the spectrum data were shown in the experimental section, the freshly synthesized compounds were characterized using IR, 1H-NMR, 13C-NMR, and mass spectroscopy methods. The ascribed structures are shown in Table 1. The antibacterial activity of the compounds was tested.

## 2 Methods and materials

### 2.1 General

All the reagents and solvents were procured from commercial suppliers and were used without further purification. Thin layer chromatography (TLC) was performed on MERCK pre-coated silica gel 60-F254 (0.5 mm) aluminium plates. Visualization of the TLC plates was done under UV light 254 nm and 280 nm. $^{1}H$ and $^{13}C$ NMR spectra were recorded




**Scheme 2** The synthesis of 8-hydroxyquinoline containing benzimidazole hybrids (**6a–l**)

**Table 1** The antibacterial activity of newly synthesized 8-hydroxyquinoline containing benzimidazole hybrids (**6a–l**)

| Code of compounds | Conc. (µg/ml) | Zone of inhibition (mm) | | | |
|---|---|---|---|---|---|
| | | *S. aureus* | *B. subtilis* | *E. coli* | *P. aeruginosa* |
| **6a** | **100** | **20.2** | **19.3** | **20.1** | **24.3** |
| | **200** | **21.5** | **20.5** | **19.0** | **21.4** |
| **6b** | **100** | **20.0** | **19.4** | **21.2** | **28.4** |
| | **200** | **22.2** | **20.4** | **23.4** | **27.7** |
| **6c** | **100** | **20.2** | **19.2** | **23.5** | **29.4** |
| | **200** | **20.4** | **20.3** | **24.1** | **30.7** |
| 6d | 100 | 15.1 | 11.4 | 23.2 | 19.3 |
| | 200 | 17.2 | 19.2 | 24.4 | 21.5 |
| 6e | 100 | 18.1 | 15.5 | 14.8 | 20.4 |
| | 200 | 19.7 | 18.2 | 21.3 | 26.7 |
| 6f | 100 | 18.1 | 18.3 | 22.5 | 30.2 |
| | 200 | 20.4 | 18.3 | 21.2 | 31.4 |
| 6g | **100** | **23.2** | **20.4** | **25.4** | **30.5** |
| | **200** | **23.4** | **21.8** | **26.7** | **33.4** |
| 6h | **100** | **22.8** | **20.2** | **26** | **31.5** |
| | **200** | **23.9** | **21.8** | **26.8** | **32** |
| **6i** | **100** | **21.2** | **18.5** | **24.4** | **24.2** |
| | **200** | **22.3** | **19.3** | **23.5** | **26.1** |
| 6j | 100 | 21.5 | 19.5 | 22.1 | 27.2 |
| | 200 | 19.7 | 20.3 | 22.4 | 26.1 |
| **6k** | **100** | **18.4** | **19.5** | **21.5** | **29.5** |
| | **200** | **19.2** | **20.1** | **23.2** | **30.2** |
| **6l** | **100** | **20.7** | **18.4** | **22.5** | **28.4** |
| | **200** | **21.6** | **19.2** | **24.5** | **29.7** |
| **Ciprofloxacin** | **100** | **23.2** | **21.5** | **26.3** | **32.1** |
| | **200** | **24.4** | **22.4** | **27.6** | **33.4** |

on Bruker avance III AV500 MHz using DMSO-d6 as solvent with tetramethyl silane (TMS) as the internal standard. Chemical shifts (δ) for 1H and 13C were reported in parts per million (ppm) downfield from TMS. Spin multiplicities were described as s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constant (J) values were reported in hertz (Hz). HR-MS were determined with Agilent QTOF mass spectrometer 6540. All the purifications were performed using silica gel (230–400) on Biotage isolera one flash chromatography. The reactions were carried under nitrogen positive pressure using freshly distilled anhydrous solvents. Melting points were determined on Stuart MP2 melting point apparatus.

## 2.2 Experimental

### 2.2.1 Preparation of 8-hydroxy-2-quinolincarbaldehyde (2): 8-hydroxy-2-quinoline

Under reflux conditions, 8-hydroxy-2-methylquinoline (3 g, 31.4 mmol) and selenium dioxide (2.5 g, 37.6 mmol) were oxidized in a combination of dioxane (100 ml) and water (2 ml) to produce carbabehyde. This intermediate was then purified using column chromatography silica gel (100–200). 67% yield.

### 2.2.2 N-benzylbenzene1,2-diamine Preparation (5a-l)

Alkylation of 2-nitroamine (1 eq.0.0020 mmol) with benzylbromide (1.2 eq.0.0020 mmol) in the presence of K2CO3 (1.5 eq.0.0020 mmol) in DMF (10 ml) under reflux for 5 hours and allowed to stir at 80 °C until the reaction was completed, as observed by the TLC, produced substituted N-benzyl-2-nitroaniline. Following completion, ethylacetate (3 × 20 ml) was used to extract the reaction mixture after it had been diluted with 15 ml of water. A second step reduction was performed using N-benzyl-2-nitroaniline (1 eq.) in the presence of Zn (1 eq.) and ammonium chloride (5 eq.) in an ethanol (8 ml)/water (2 ml) mixture under reflux for 1 h at 80 °C until the reaction was completed, which was monitored by the TLC. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Ethylacetate and water were used to remove the reaction mixture after the reaction was complete. The product was then used as such for the following process after the organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum.

### 2.2.3 General protocol for 6a-l synthesis

For five minutes at room temperature, 8-Hydroxy-2-quinolinecarbaldehyde (2) (1 mmol) was added to a stirred solution of substituted 1, 2-diamine (5a–l) (1 mmol) and NH4Cl (4 mmol) in CHCl3 (5 ml). They kept stirring for four hours. Following the conclusion of the reaction (TLC, eluent Hexane / ethyl acetate 30 / 70), the organic layer was cleaned with water (10 ml) and the solvent was extracted using ethyl acetate (20 ml) under decreased pressure. After the layers were separated, sodium sulfate was used to dry the organic layer. The crude product was processed to column chromatography using petroleum ether = EtOAc (9:1) after the solvent was extracted under reduced pressure. This produced products (6a–l) as a solid in a 94% yield. These synthetic compounds' (6a–l) spectral data are provided here, and the corresponding spectra are included as Supplementary Figs. 1–48 in the supplemental file as supporting documentation.

### 2.2.2 Spectral data for newly synthesized compounds (6a–l)

2-(1-benzyl-1H-benzo[d]imidazol-2-yl)quinolin-8-ol (6a): Melting point- 149–150 °C; Yield- 91%; Appearance- pale yellow crystalline solid; IR ($cm^{-1}$) 3420,3053,2926,1718,1718.,1430,1366.,1270,1204,743; $^1$H-NMR: (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.6 Hz, 1H), 8.33 (d, *J* = 8.6 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.49–7.34 (m, 8H), 7.26 (d, *J* = 5.5 Hz, 2H), 7.09 (d, *J* = 7.0 Hz, 1H), 6.86 (s, 1H), 6.01 (s, 2H); $^{13}$C-NMR: (126 MHz, $CDCl_3$) δ 152.17, 141.27, 137.38, 137.30, 136.70, 129.38, 129.03, 128.33, 127.96, 125.50, 124.68, 124.63, 123.76, 123.74, 122.49, 120.18, 118.05, 111.17, 110.50, 49.38; HRMS (ESI):calcd for $C_{23}H_{17}N_3O[M + H]^+$. 352.1452, found: 352.1452.

2-(1-(3-methylbenzyl)–1H-benzo[d]imidazol-2-yl)quinolin-8-ol (6b): Melting point: 151–152.6 °C; Yield: 84%; Appearance: Pale yellow crystalline solid; IR ($cm^{-1}$) 3057, 2918, 2721, 2631, 1600, 1582, 1429, 1372, 836, 745; $^1$H-NMR: (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.6 Hz, 1H), 8.32 (d, *J* = 8.6 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.43–7.34 (m, 4H), 7.33–7.29 (m, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.10 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.06 (s, 2H), 6.93 (s, 1H), 5.96 (s, 2H), 2.32 (s, 3H); $^{13}$C-NMR: (126 MHz, $CDCl_3$) δ 152.47, 150.21, 147.19, 141.58, 139.22, 137.26, 137.19, 137.06, 136.97, 129.21, 128.81, 128.60, 128.24, 126.09, 124.38, 123.38, 122.56, 122.46, 120.42, 117.99, 111.09, 110.45, 49.31, 21.53; HRMS (ESI): calcd for $C_{24}H_{19}N_3O[M + H]^+$. 366.1613, found: 366.1613.

2-(1-benzyl-5-chloro-1H-benzo[d]imidazol-2-yl)quinolin-8-ol (6c): Melting point: 213.3–214.9 °C; Yield: 76%; Appearance: light yellow crystalline solid; IR: ($cm^{-1}$): 3061, 2919, 2851, 2636, 1613, 1561, 1426, 1368, 1060, 928., 787, 754; $^1$H-NMR: (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.7 Hz, 1H), 8.32 (d, *J* = 8.6 Hz, 1H), 7.93 (s, 1H), 7.49–7.35 (m, 5H), 7.33–7.27 (m, 2H), 7.23 (d, *J* = 7.3 Hz, 2H), 7.11–7.08 (m, 1H), 6.82 (s, 1H), 5.97 (s, 2H); $^{13}$C- NMR: (126 MHz, $CDCl_3$) δ 152.31, 151.28, 146.86, 143.40, 137.35, 137.24, 136.58, 135.59, 129.41, 129.03, 128.99, 128.32, 128.02, 125.44, 124.83, 122.43, 120.20, 118.07, 111.19, 49.42; HRMS (ESI): calcd for $C_{23}H_{16}ClN_3O[M + H]^+$. 386.0916, found: 386.1058.

2-(5-methyl-1-(3-methylbenzyl)−1H-benzo[d]imidazol-2yl)quinolin-8-ol (6d): Melting point- 195.6-196.2 °C; Yield-77%; Appearance-brown yellow crystalline solid; IR-($cm^1$) 3426, 3050, 2918, 1599, 1499, 1442, 1194, 922, 754, 565; $^1$H-NMR- (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.6hz, 1H), 8.24 (d, *J* = 8.6hz, 1H), 7.84 (d, *J* = 0.7 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.29 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.26 −7.17 (m, 3H), 7.10 (d, *J* = 7.6hz, 1H), 7.02 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.96 (d, *J* = 13.7 Hz, 2H), 6.81 (s, 1H), 5.84 (s,2H), 2.25 (s, 3H); $^{13}$C-NMR- (126 MHz, $CDCl_3$) δ 152.51, 151.22, 146.80, 143.31, 139.33, 137.31, 137.26, 136.58, 135.66, 129.29, 129.01, 128.93, 128.74, 128.31, 126.01, 124.80, 122.48, 122.42, 120.15, 118.03, 111.30, 49.42, 21.53; HRMS (ESI): calcd for $C_{24}H_{18}ClN_3O[M + H]^+$. 400.1214, found: 400.1214.

2-(1-benzyl-5-methyl-1H-benzo[d]imidazol-2-yl)quinolin-8-ol (6e): Melting point: 175.2- 176 °C; Yield: 94%; Appearance: Brown yellow crystalline solid; IR: ($cm^{-1}$) 3008,2920,2853,2631,1725,1562,1431,1362,1352,1326,1272,1731,1033, 840,709; $^1$H- NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.6 Hz, 1H), 8.29 (d, *J* = 8.6 Hz, 1H), 7.73 (s, 1H), 7.40 (ddd, *J* = 27.3, 15.4, 7.9 Hz, 6H), 7.25 (dd, *J* = 11.1, 5.5 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.85 (s, 1H), 5.96 (s, 2H), 2.53 (s, 3H); $^{13}$C- NMR (126 MHz, $CDCl_3$) δ 152.29, 150.03, 137.22, 135.18, 133.23, 129.30, 128.72, 128.17, 127.84, 126.13, 125.50, 122.45, 120.10, 118.07, 111.03, 109.88, 49.21, 21.68; HRMS (ESI) calcd for $C_{24}H_{19}N_3O[M + H]^+$. 366.15, found: 366.1605.

2-(5-methyl-1-(3-methylbenzyl)−1H-benzo[d]imidazol-2-yl)quinolin-8-ol (6f ): Melting point 174-175.9 °C; Yield 97%: Appearance Orange yellow crystalline solid: IR ($cm^{-1}$) 3413,2892,1722,1599,1571,1497,1443,1196,842,791,75 7,570; $^1$H- NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.6 Hz, 1H), 8.28 (d, *J* = 8.7 Hz, 1H), 7.73 (s, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.29 (ddd, *J* = 15.1, 12.1, 5.9 Hz, 1H), 7.20-7.13 (m, 1H), 7.08 (dt, *J* = 21.8, 5.8 Hz, 1H), 6.93 (s, 1H), 5.90 (s, 1H), 2.53 (s, 1H), 2.31 (s, 1H); $^{13}$C- NMR (126 MHz, $CDCl_3$) δ 152.39, 150.04, 147.22, 142.79, 139.18, 137.25, 137.11, 137.09, 135.19, 133.19, 129.18, 128.71, 128.54, 128.18, 126.07, 126.02, 122.55, 122.44, 120.02, 117.97, 111.04, 109.95, 49.29, 21.68, 21.53; HRMS (ESI) calcd for $C_{25}H_{21}N_3O[M + H]^+$. 379.16, found: 380.1769.

2-(1-(3,5-dimethylbenzyl)−5-methyl-1H-benzo[d]imidazol-2-yl)quinolin-8-ol (6g): Melting point: 190.5-191.4 °C; Yield: 84%; Appearance: cream white crystalline solid; IR: ($cm^{-1}$) 3006,2919,2851,1711,1600,1429,1366,1274,835,7 49.12; $^1$H-NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.6 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 7.76 (s, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.37-7.33 (m, 1H), 7.31-7.25 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.12-7.08 (m, 1H), 7.04 (s, 1H), 6.98 (s, 1H), 6.85 (s, 1H), 5.88 (s, 1H), 2.53 (s, 1H), 2.27 (s, 1H); $^{13}$C- NMR (126 MHz, $CDCl_3$) δ 152.59, 149.63, 139.09, 137.36, 137.21, 136.78, 134.95, 129.49, 128.91, 128.29, 126.28, 123.16, 122.44, 119.61, 117.92, 111.18, 110.14, 49.40, 21.65, 21.36; HRMS (ESI) calcd for $C_{26}H_{23}N_3O[M + H]^+$. 394.18, found: 394.1917.

2-(1-(3,5-dimethylbenzyl)−1H-benzo[d]imidazol-2-yl)quinolin-8-ol (6h): Melting point: 125.2-126.9 °C; Yield: 85%; Appearance: Light Yellow crystalline solid; IR: ($cm^{-1}$) 3226,3018,1595,1567,1498,1436, 834,726,741,686; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.6 Hz, 1H), 8.32 (d, *J* = 8.7 Hz, 1H), 7.99 (dd, *J* = 5.9, 2.9 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.43-7.34 (m, 4H), 7.11 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.03 (s, 1H), 6.99 (s, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 5.91 (s, 2H), 2.28 (s, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 152.53, 150.08, 139.10, 137.31, 137.22, 136.98, 136.85, 129.57, 128.95, 128.36, 124.46, 123.50, 123.25, 122.48, 120.28, 117.91, 111.16, 110.58, 49.45, 21.31; HRMS (ESI) calcd for $C_{25}H_{21}N_3O[M + H]^+$. 380.16, found: 380.1762.

2-(5-chloro-1-(3,5-dimethylbenzyl)−1H-benzo[d]imidazol-2-yl)quinolin-8-ol (6i): Melting point- 190.5-191.2 °C; Yield-71%; Appearance-Light yellow crystalline solid; IR: ($cm^{-1}$) 3005,2918,2724,1727,1598,1563,1430,1372,1323,1060,841,7 96,746,593; $^1$H-NMR (500 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 8.6, 3.9 Hz, 1H), 8.35 – 8.31 (m, 1H), 7.95 (s, 1H), 7.50 – 7.46 (m, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 1.1 Hz, 2H), 7.11 (d, *J* = 7.6hz, 1H), 7.01 (d, *J* = 13.3 Hz, 2H), 6.82 (s, 2H), 5.90 (s, 2H), 2.28 (s, 6H); $^{13}$C- NMR (126 MHz, $CDCl_3$) δ 169.70, 152.66, 139.32, 137.57, 137.42, 129.79, 129.49, 128.51, 123.07, 122.30, 118.01, 111.66, 111.53, 49.85, 29.76, 21; HRMS (ESI) calcd for $C_{25}H_{2\circ C}lN_3O[M + H]^+$. 414.90, found: 414.1372.

2-(5-methyl-1-(4-methylbenzyl)−1H-benzo[d]imidazol-2-yl)quinolin-8-ol (6j): Melting point- 203.2-204.9 °C; Yield: 88%; Appearance: Orange yellow crystalline solid; IR: ($cm^{1)}$3011,1611,1561,1431,1348,1329,1272,1172,837,795,748,726; $^1$H-NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.6 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 7.75 (s, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.28-7.24 (m, 1H), 7.18 (dd, *J* = 15.1, 8.2 Hz, 1H), 7.11 (dd, *J* = 14.3, 7.8 Hz, 1H), 7.00 (s, 1H), 5.94 (s, 1H), 2.52 (s, 3H), 2.35 (s, 3H); $^{13}$C- NMR (126 MHz, $CDCl_3$) δ 152.39, 137.61, 137.30, 137.28, 134.83, 133.67, 129.98, 128.91, 128.27, 126.33, 125.43, 122.47, 119.68, 117.96, 111.14, 110.14, 49.22, 21.67, 21.14; HRMS (ESI) calcd for $C_{25}H_{21}N_3O[M + H]^+$. 380.18, found: 380.1760.

2-(1-(4-methylbenzyl)−1H-benzo[d]imidazol-2-yl)quinolin-8-ol (6k): Melting point: 186.2-188 °C; Yield: 88%; Appearance: Yellow crystalline solid; IR: ($cm^{-1}$) 3009,2918,2850,1610,1563,1434,1350,1273,1173,841,748,517; $^1$H-NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 8.6 Hz, 1H), 8.33 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.44-7.35 (m, 4H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.13 (dd, *J* = 14.5, 7.8 Hz, 3H), 7.02 (s, 1H), 5.99 (s, 2H), 2.36 (s, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 152.45, 137.78, 137.46, 137.37, 133.38, 133.33, 133.26, 130.05, 129.19, 128.40, 125.44, 124.84, 124.02, 122.48, 119.86, 118.06, 111.31, 110.69, 49.26, 21.20; HRMS (ESI) calcd for $C_{24}H_{19}N_3O[M + H]^+$. 366.18, found: 366.1719.

2-(1-(4-fluorobenzyl)−1H-benzo[d]imidazol-2-yl)quinolin-8-ol (6l): Melting point: 173.6–174.2 °C; Yield: 65%; Appearance: Light yellow crystalline solid; IR: ($cm^{-1}$) 3405,2919,1713,1602,1496,1217,844,747,517; $^1$H-NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.6 Hz, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.57 (dd, *J* = 10.0, 5.8 Hz, 1H), 7.52–7.42 (m, 4H), 7.38–7.30 (m, 3H), 7.25–7.16 (m, 3H), 7.05 (s, 1H), 6.09 (s, 2H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 163.45, 161.41, 152.24, 137.40, 137.24, 136.63, 129.02, 128.30, 127.37, 127.30, 124.64, 123.70, 122.50, 120.41, 118.08, 116.43, 116.29, 111.17, 110.35, 48.77; HRMS (ESI) calcd for $C_{23}H_{16}FN_3O[M+H]^+$. 370.12, found: 370.1359.

### 2.3 Biological evaluation

#### 2.3.1 Antibacterial activity

*Principle* For the treatment of infectious diseases especially those caused by pathogens that is often drug resistant sensitivity testing is used to select the effective antimicrobial agents. Principle For treating infectious diseases, especially those caused by pathogens that are often drug-resistant, sensitivity testing is used to select effective antimicrobial agents.

*Procedure of disk diffusion technique* The test organism was Isolated in pure culture form. The suspension is for activity by growing overnight in culture broth. The antibiotic assay agar or nutrient agar plates were prepared. Then the swab was inoculated for activity growing culture suspension evenly with the help of cotton swab over the surface of agar plate. It was dried for two minutes. Placed the different antibiotic disc on the surface of agar with the help of sterile forceps and gently presto to make proper contact with agar. Incubated the plates at 37 °C for e 24 h. After the incubation observe for growth inhibition zone around each disc, measure the diameter of inhibition zone with the help of scale and determine the effective antibiotics tested comparing with standard chart.

#### 2.3.2 Minimum inhibitory concentration (MIC)

Any compound's minimum inhibitory concentration (MIC) is the lowest concentration at which growth (turbidity on liquid medium) is totally inhibited. The tube dilution technique was used to examine the compounds' in vitro antibacterial properties. After preparing the medium, each sterile tube was filled with sterile broth, and the chemical was added to the first tube. The tubes were serially diluted twice, and the final tube's extra broth was thrown away. Visual comparisons were made between the McFarland standard and a microbial solution of around 1.5 × 108 cells/ml. Standard inoculums were introduced to each tube. The test substances were diluted to obtain concentrations of 500, 250, 125, 62.5, 31.25, 15.625, 7.8, 3.9, 1.95, and µg/ml in order to determine the minimal inhibitory concentrations. The solvent used was 10% DMSO [39]. Every concentration was measured twice, and the average was used as the final result. A control test using infected broth suspended in 10% DMSO was conducted to make sure the solvent had no influence on the growth. After that, it was stored for incubation.

Antimicrobial action Using Mullere Hinton media, the antibacterial properties of the produced compounds were evaluated against B. subtilis, P. aeruginosa, S. aureus, and E. coli. A pH of 7.4 was maintained. For 24 hours, the incubation was conducted at 37 °C. Following a 24-hour incubation period, the tube that showed no microbial growth was designated as the MIC, which was stated in mg/m µg/ml. The MIC values were determined at the conclusion of the incubation phase. Table 3 presented the findings.

Antifungal action Using sabouraud dextrose broth kept at pH 7.4, the antifungal properties of the produced compounds were evaluated against A. niger and C. albicans. For 48 hours, the tubes were incubated at 25 °C. The tube that showed no fungal growth was used to record the MIC, which is stated in µg/ml. Table 4 presented the findings.

## 3 Results and discussion

### 3.1 Chemistry

As shown in Scheme 2, the target compounds (6a–6l) were synthesized in four stages using standard techniques, and the outcomes are shown in Table 1. Eight-Hydroxy-2-quinolinecarbaldehyde was used in the first phase.

The oxidation of 8-hydroxy-2-methylquinoline (1) with selenium dioxide produced (2). 37 The N-benzyl-2-nitroanilines (4) are obtained in the second stage by refluxing benzyl bromide in DMF with nitroaniline (3) for five hours while potassium carbonate is present. This process is known as N-benzylation. Next, ammonium chloride was used to convert N-benzyl-2-nitroanilines (4) to their equivalent amines, N-benzyl-2-aminoanilines (5a–l). In order to get the end product, which is 8-hydroxyquinoline containing benzimidazole derivatives (6a–l), in good to excellent yield, the N-benzyl-2-aminoanilines (5a–l) were cyclized with 8-hydroxyquinoline-2-carbaldehyde (2) using ammonium chloride at room temperature for 24 hours. 38 These compounds' structures are shown in Figure 1, and their spectra are provided as supporting data in supplemental Figures 1 through 48 in the supplemental file. The compounds' 1H-NMR spectra showed a singlet between δ 6.70 and 6.80 ppm, which is caused by the hydroxyl 1H proton of quinoline, and a singlet at δ 5.80 to 6.00, which is the distinctive peak of the methylene 2H of the benzoimidazole-linked benzyl carbon. The quinoline ring 1H doublet is represented by the distinct doublet δ7.00–7.20 ppm, whereas benzene 2H is responsible for the peak between δ7.25 and 7.30. The aromatic protons of the benzimidazole ring are represented by the multiplet between δ 7.40 and 7.50 ppm, the benzimidazole proton by the doublet between δ 7.90 and 8.10 ppm, and the quinoline proton by the distinct doublet at δ 8.30 to 8.40 ppm and another doublet around δ 8.60 to 8.70 ppm. The compounds' 13C-NMR spectra showed a range of signals, with the aromatic carbons of the benzimidazole and quinoline rings appearing between δ 111.7 and 124.68 ppm. Two carbons in the 1-benzene ring are represented by the signals at δ 127 and δ 128 ppm. The tertiary carbon of the quinoline ring is responsible for the signal at around δ 129 ppm. The amine of the quinoline ring's adjacent carbon is represented by the signal at δ 136 ppm, while the tertiary 2 carbon of the benzimidazole ring is responsible for the peak at δ 137 ppm. The hydroxyl group-attached carbon is represented by the peak at δ 138 ppm, and the tertiary carbon of the quinoline ring attached to the benzimidazole ring is represented by the peak at δ 152 ppm. These compounds' IR spectra revealed unique bands at around 3053 cm−1, 1580 cm−1, and 1270 cm−1, which are caused by the methylene group, C=N, and hydroxyl bond.

### 3.2 Antimicrobial activity

*Antibacterial activity* The newly synthesized compounds (6a-l) were tested for their antibacterial activity against *E. coli*, *S. aureus*, *P. aeruginosa* and *B. subtilis* at 100 and 200 µg/ml concentration. The Ciprofloxacin was used as standard drug.

The results of the antimicrobial activity (zone of inhibition (mm)) of newly synthesized derivatives (**6a–l**) have revealed that they exhibited moderate to good activity. It is noteworthy to note that the compounds **6b, 6c, 6g, 6h, 6i, 6k and 6l** from this series were found to be most active against all 4 bacterial strains at a concentration of 100 and 200 µg/ml when, compared to standard drug. The results of the antimicrobial activity were summarised in Table 1 (zone of inhibition).

*Antifungal activity* The antifungal activity of these compounds (**6a–l**) was tested against *A. niger* and *C. albicans* at a concentration of 100 and 200 µg/ml and the obtained results were summaries in the Table 2. The results of the assay showed that compounds **6a, 6b, 6c, 6g, 6h, 6i, 6k** and **6l** from this series are almost as active as standard drug voriconazole against A. niger, whereas in the case of C. albicans compounds **6c, 6g, 6h, 6i, 6j, 6k** and **6l** were found to be the most active when compared to the standard drug used.

### 3.3 Minimum inhibitory concentration (MIC)

*Antibacterial activity* From the results of the MIC studies as shown in Table 3 revealed that these compounds are good antibacterial agents. The compound **6a & 6l** were exhibiting the 7.8 µg/ml MIC value for *E. coli and P. aeruginosa*. The compound **6b** was exhibiting the 7.8 µg/ml MIC for ***S. aureus*** *and* 3.9 µg/ml *P. aeruginosa*. In the case of **6c** the MIC values were found to be the 7.8 µg/ml MIC for *B. subtilis and* 3.9 µg/ml *P. aeruginosa*. Similarly, the compound **6g** was showing the 3.9 µg/ml MIC value for *E. coli and P. aeruginosa*. The **6h & 6k** were exhibiting the

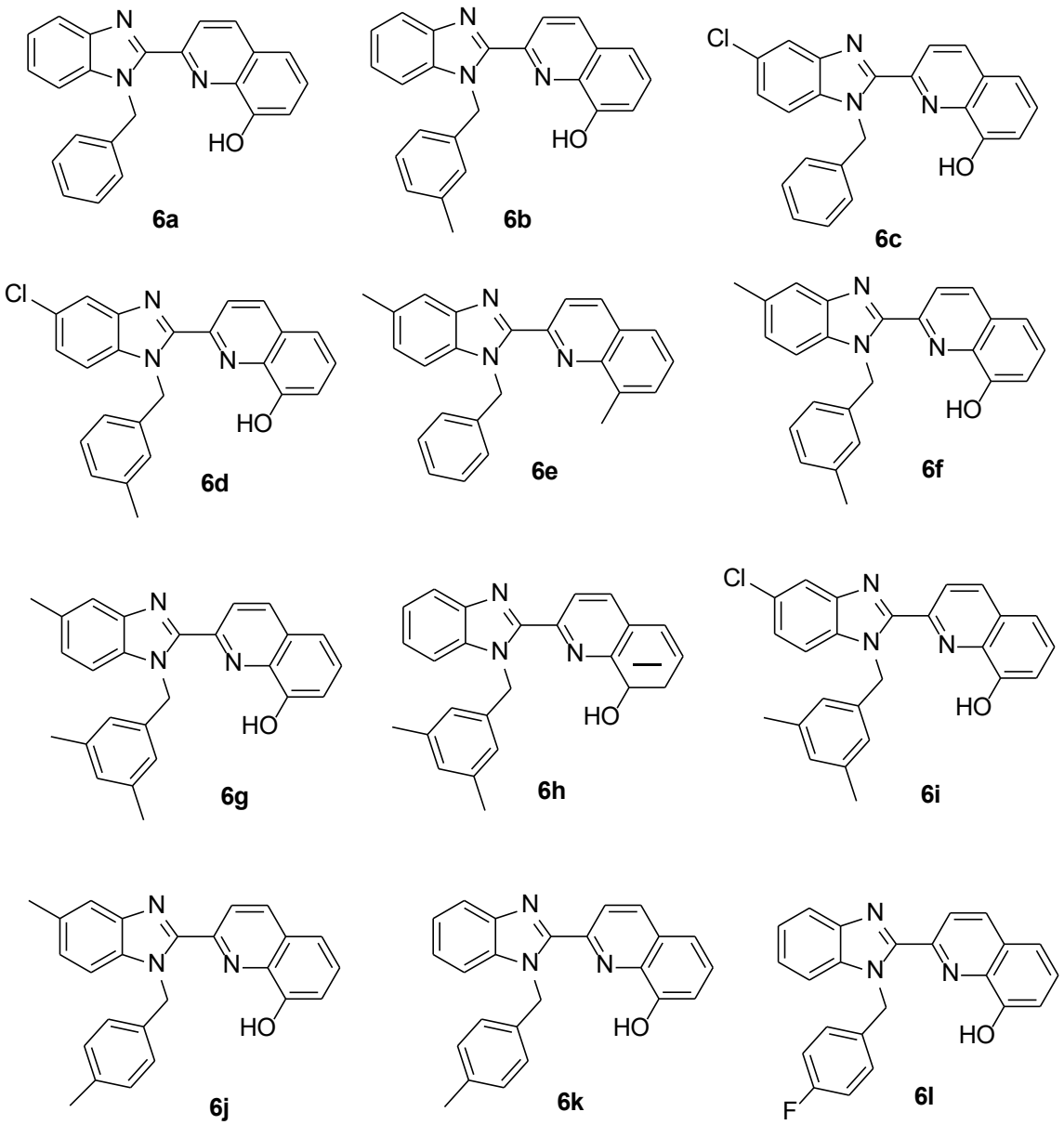



**Fig. 1** The structures of newly synthesized 8-hydroxyquinoline containing benzimidazole hybrids (**6a–l**)

3.9 µg/ml MIC values for *P. aeruginosa*. The standard drug **Ciprofloxacin** was exhibiting the 1.95 µg/ml MIC value for all the four bacterial strains.

*Antifungal activity* From the results of the MIC studies ilustrate in Table 4 exhibit that these compounds were good antifungal agents. The compound **6e** was exhibiting the 20.1 µg/ml MIC value for *A. niger* and 21.2 µg/ml MIC value ***C. albicans***. The compound **6f** was exhibiting the 22.3 µg/ml MIC value for *A. niger* and 19.2 µg/ml MIC value for ***C. albicans***. The compound **6g** was exhibiting the 62.5 µg/ml MIC values for *A. niger* & ***C. albicans***. Similarly, the compound **6h** was exhibiting the 62.5 µg/ml MIC value for *A. niger* and 31.25 µg/ml MIC value for ***C. albicans***. The standard drug **Voriconazole** was exhibiting the 15.625 µg/ml MIC value for both the fungal strains.

**Table 2** The antifungal activity of newly synthesized 8-hydroxyquinoline containing benzimidazole hybrids (**6a–l**)

| Code of compounds | Conc. (µg/ml) | Zone of inhibition (mm) | |
|---|---|---|---|
| | | *A. niger* | *C. albicans* |
| 6a | 100 | 24.1 | 21.2 |
| | 200 | 23.5 | 20.4 |
| 6b | 100 | 20.3 | 20.4 |
| | 200 | 22.6 | 22.5 |
| 6c | 100 | 24.2 | 19.2 |
| | 200 | 26.4 | 20.5 |
| 6d | 100 | 22.7 | 18.1 |
| | 200 | 25.3 | 19.4 |
| 6e | 100 | 20.1 | 21.2 |
| | 200 | 24.2 | 20.8 |
| 6f | 100 | 22.3 | 19.2 |
| | 200 | 25.4 | 20.5 |
| 6g | **100** | **27.5** | **23.7** |
| | **200** | **30.1** | **26.2** |
| 6h | **100** | **27.8** | **23.2** |
| | **200** | **28.9** | **25.4** |
| 6i | 100 | 23.1 | 21.3 |
| | 200 | 21.6 | 23.5 |
| 6j | 100 | 21.3 | 22.5 |
| | 200 | 20.7 | 20.2 |
| 6k | 100 | 19.8 | 19.0 |
| | 200 | 18.6 | 20.2 |
| 6l | 100 | 20.7 | 18.4 |
| | 200 | 21.2 | 20.2 |
| **Voriconazole** | **100** | **28.1** | **24.5** |
| | **200** | **30.2** | **26.7** |

**Table 3** The Minimum inhibitory concentration (MIC) of newly synthesized 8-hydroxyquinoline containing benzimidazole hybrids (**6a-l**) in µg/ml

| Code | *S. aureus* | *B. subtilis* | *E. coli* | *P. aeruginosa* |
|---|---|---|---|---|
| **6a** | **15.625** | **15.625** | **7.8** | **7.8** |
| **6b** | **7.8** | **15.625** | **15.625** | **3.9** |
| **6c** | **15.625** | **7.8** | **15.625** | **3.9** |
| 6d | 62.5 | 62.5 | 15.625 | 62.5 |
| 6e | 125 | 62.5 | 62.5 | 62.5 |
| 6f | 31.25 | 31.25 | 15.625 | **3.9** |
| 6g | **15.625** | **15.625** | **3.9** | **3.9** |
| 6h | **15.625** | **15.625** | **15.625** | **3.9** |
| **6i** | 31.25 | 31.25 | **15.625** | **15.625** |
| 6j | 31.25 | 31.25 | 31.25 | **15.625** |
| **6k** | **15.625** | **15.625** | **7.8** | **3.9** |
| **6l** | **15.625** | **31.25** | **7.8** | **7.8** |
| **Ciprofloxacin** | **1.95** | **1.95** | **1.95** | **1.95** |

## 4 Conclusion

In conclusion we can say a series of new 8-hydroxyquinoline-Benzimidazole hybrids (**6a–l**) were designed, synthesized (**6a–l**) by using conventional synthetic methods and tested for their antimicrobial activity. These newly synthesized compounds (**6a–l**) were assayed for their antibacterial activity against *E. coli*, *S. aureus*, *P. aeruginosa* and *B. subtilis* and for antifungal activity were tested against *A. niger* and *C. albicans*. The compounds **6b, 6c, 6g, 6h, 6i, 6k and 6l** were

**Table 4** The Minimum inhibitory concentration (MIC) of newly synthesized 8-hydroxyquinoline containing benzimidazole hybrids (**6a–l**) in µg/ml

| Code | *A. niger* | *C. albicans* |
|---|---|---|
| 6a | 125 | 250 |
| 6b | 125 | 250 |
| 6c | 125 | 250 |
| 6d | 250 | 500 |
| 6e | **20.1**<br>**24.2** | **21.2**<br>**20.8** |
| 6f | **22.3**<br>**25.4** | **19.2**<br>**20.5** |
| 6g | **62.5** | **62.5** |
| 6h | **62.5** | **31.25** |
| 6i | 250 | 250 |
| 6j | 500 | 500 |
| 6k | 500 | 500 |
| 6l | 250 | 500 |
| **Voriconazole** | **15.625** | **15.625** |

found to be active against all 4 bacterial strains. The compounds **6k** and **6l** showed almost same antifungal activity when compared to standard drug voriconazole against *A. niger*, whereas in the case of *C. albicans* compounds **6c**, **6g**, **6h**, **6i**, **6j**, **6k** and **6l** showed the best antifungal activity. The MIC studies revealed that these compounds were showing the MIC values between 3.9 and 62.5 µg/ml for all the four bacterial strains. Among all the compounds, the compound **6g** was showing the 3.9 µg/ml MIC value for *E. coli and P. aeruginosa* and found to be most potent compound antibacterial agent. Similarly, from the results of the MIC studies exhibit that these compounds were good antifungal agents and showing the MIC values ranging between 19.2 and 500 µg/ml for both *A. niger* and *C. albicans*. The compound **6f** was emerged as most potent antifungal agent by exhibiting the 22.3 µg/ml MIC value for *A. niger* and 19.2 µg/ml MIC value for *C. albicans*. Thus, it is anticipated that these compound will emerged as promising potential antimicrobial agents on further investigation.

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