Synthesis and antimicrobial activity of metal complexes from 2-(1’/2’-hydroxynaphthyl)benzoxazoles

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Abstract
Synthesis and antimicrobial activity of new metal [Mg(II), Fe(II), Co(II), Ni(II), Zn(II) and Cd(II)] complexes from 2-(1’/2’-hydroxynaphthyl)benzoxazoles have been described. Some of the metal complexes show significant antifungal activity (MIC <3.12 µg/ml). Further, 2-(1’/2’-hydroxynaphthyl)benzoxazoles exhibit excited-state intramolecular proton transfer mechanism that has been studied using absorbance and fluorescence spectroscopy.

Keywords: Benzoxazoles, 2-(1’/2’-hydroxynaphthyl)benzoxazoles, metal complexes, antimicrobial activity

Introduction

The excited-state intramolecular proton transfer (ESIPT) of 2-(2’-hydroxyphenyl)benzoxazoles (HBOs) has been studied under physiological conditions using absorbance and steady-state emission spectroscopy and inhibition of ESIPT via metal coordination showed a significant wavelength shift. HBOs exhibit fluorescent and luminescent properties and good thermal and photo stabilities and are excellent materials for plastic scintillation applications and some of their metal complexes are of interest for the organic light emitting diode (OLED) technology. It has also been proposed that HBO behave as structural mimic of DNA base pair for which tautomerism may be initiated at a defined time and position within duplex DNA. HBO moiety is also present in a number of synthetic metal ion chelators. A natural product bis(benzoxazole) (UK-1) also having this moiety has been reported to possess anticancer activity and the metal ion binding studies of UK-1 indicates that it is capable of binding a variety of biologically important metal ions. Recently, we have also demonstrated the metal-mediated DNA binding of UK-1 by ESI-MS that it forms complexes with a variety of metal ions. The numerous applications of HBO promoted to undertake the synthesis of 2-(1’/2’-hydroxynaphthyl)benzoxazoles by replacing the 2’-hydroxyphenyl moiety in HBO with 1’/2’-hydroxynaphthyl moiety and to study
the effect of metal ion binding as well as for evaluation of in vitro antimicrobial activity of metal complexes.

Results and Discussion

The reaction of 2-aminophenol (1) with 1-hydroxynaphthaldehyde (2) in presence of iodobenzene diacetate (IBD) resulted in 2-(1’-hydroxynaphthyl)benzoxazole (4) via the intermediacy of 3 (Scheme 1) in one pot and in 70% yield which was purified by column chromatography. All the physical and spectroscopic (UV, IR, NMR) data were in consonance with the structure.

\[
\begin{align*}
\text{NH}_2 & \quad \text{OH} \\
\text{OHH} & \quad \text{O} \\
\text{N} & \quad \text{OH OH} \\
\text{O} & \quad \text{N} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

\[\text{CH}_3\text{OH} \quad \text{reflux} \]

2-(1’-Hydroxynaphthyl)benzoxazoles (4) exhibit excited-state intramolecular proton transfer (ESIPT) process similar to 2-(2’-hydroxyphenyl)benzoxazole which has widespread implications (Scheme 2). The absorption and fluorescence peaks of 4 are at 365 and 468 nm, respectively. The large difference in absorption and emission spectra is expected due to an excited-state intramolecular proton transfer. The ESIPT process is very fast and occurs in excited-state enol tautomer that undergoes an intramolecular proton transfer reaction with the neighboring hydrogen-bonded nitrogen atom giving rise to the excited keto tautomer which then emits a strongly Strokes-shifted fluorescence.

\[
\begin{align*}
\text{N} & \quad \text{=} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{MX}_2 & \quad \text{CH}_3\text{OH, reflux} \\
X & \quad \text{= OAc, NO}_3
\end{align*}
\]

Scheme 1

5a; M = Mg  
5b; M = Fe  
5c; M = Co  
5d; M = Ni  
5e; M = Zn  
5f; M = Cd
Further, the reaction of 2-aminophenol (1) with 2-hydroxynaphthaldehyde in presence of IBD afforded 2-(2'-hydroxynaphthyl)benzoxazole (6) which was purified by column chromatography. All the physical and spectroscopic (UV, IR, NMR) data were in consonance with the structure. The absorption and fluorescence peaks of 6 are at 373 and 443 nm, respectively. The large difference in absorption and emission spectra is again expected due to an excited-state intramolecular proton transfer.

In an alternate method, 4 and 6 were also obtained by one step reaction of 1 and 1-hydroxynaphthoic acid and 2-hydroxynaphthoic acid, respectively in presence of polyphosphoric acid in good yields.

Furthermore, we examined the reactions of 4 and 6 with metal [Mg(II), Fe(II), Co(II), Ni(II), Zn(II) and Cd(II)] salts in 1:2 ratio that generated new metal complexes 5 and 7, respectively.
(Schemes 1 and 2). The structures of new metal complexes were established through elemental analysis, UV, IR and mass spectral studies. The absorption and fluorescence values of metal complexes (5 and 7) indicate the influence of metal cation binding on the proton transfer process (Table 1). The chelation of metal cations competes with protonation of the ligand donor atoms. The proton transfer is disrupted by coordination of the metal ion, but the red-shift tautomer emission did not disappear in favour of normal emission, instead, the complexation led to a change in both the absorption and emission spectra (Table 1).

The IR spectra of 5 and 7 are also in complete agreement with their structures. There was sharp modification between the IR spectra of the metal complexes and the ligands. Most of the bands changed their pattern in the region probably due to coordination of the oxygen atom of OH group and nitrogen atom of the ligand to metal ions (vide experimental). The matrix-assisted laser desorption ionization (MALDI) mass spectra supported the structures of the metal complexes.

Table 1. The UV and fluorescence emission data of ligand and metal complexes

<table>
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<th>Ligand/Complexes</th>
<th>Metal</th>
<th>$\lambda_{\text{abs}}$ max (nm)</th>
<th>$\lambda_{\text{flu}}$ max (nm)</th>
<th>Compound</th>
<th>Metal</th>
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<td>-</td>
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<td>502</td>
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The complexation of biologically important metals with 2-(1′/2′-hydroxynaphthyl)benzoxazoles was further explored with the evaluation of their antimicrobial activity. The new ligands (4 and 6) and their metal complexes (5 and 7) were evaluated for in vitro antibacterial activity against Gram-positive Bacillus subtilis [MTCC 2063], Staphylococcus aureus [MTCC 2901] and Gram-negative Escherichia coli [MTCC 1652] and in vitro antifungal activity against Aspergillus ficuum [MTCC 8184], Aspergillus parasiticus [MTCC 8189], Candida albicans [MTCC 183] and Aspergillus niger [MTCC 1344]. Double strength nutrient broth-I.P. and Sabouraud dextrose broth-I.P.\textsuperscript{10} were employed for bacterial and fungal growth, respectively. Minimum Inhibitory Concentrations (MIC) were determined by means of standard serial dilution method\textsuperscript{11} and are presented in Table 2. All the ligands/complexes exhibited appreciable in vitro activity against the tested strains.
Table 2. The in vitro antimicrobial activity of metal complexes (MIC in µg/ml)

<table>
<thead>
<tr>
<th>Compd</th>
<th>Antibacterial activity</th>
<th>Antifungal activity</th>
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<td>E. coli</td>
</tr>
<tr>
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<td>5e</td>
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<td>7f</td>
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<td>50</td>
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</table>

# The MIC of standard drugs for antibacterial activity (Tetracycline, Chloramphenicol, Kanamycin, Cefazoline sodium and Cefotaxime) and antifungal activity (Cycloheximide, Carbendazim and Fluconazole) were found to be <3.12 µg/ml.

Table 2 indicates that metal complex 5c, 5e and 7c-7e showed good antibacterial activity against *Bacillus subtilis* and *Escherichia coli*, respectively. The metal complex 5c also displayed good antibacterial activity against *Staphylococcus aureus*. Further, the antifungal activity of metal complex 7d was found to be significant against *Aspergillus ficuum*, while the ligand 6 and its metal complexes 7b-7f showed similar antifungal activity against *Aspergillus parasiticus*. Further, the antifungal activity of metal complex 5a was found to be significant against *Candida albicans* among others. Finally, the metal complex 5f was the only one to display better antifungal activity against *Aspergillus niger*. Most of the metal complexes showed better activity than their respective ligands (4 and 6). These results indicate that the increase in the size of the transition metal ions from iron to cadmium has no substantial effect on the antimicrobial activity except the nickel complex (7d) that possesses appreciable antifungal activity against *Aspergillus ficuum*. Interestingly the magnesium complex (5a) was found to exhibit significant antifungal activity against *Candida albicans*. It was also noticed that all the compounds, ligands and metal complexes were more active as antifungal than as antibacterial.

In conclusion, we have synthesized new ligands and their metal complexes and evaluated their antimicrobial activity. The results clearly showed that the magnesium complex (5a) and the nickel complex (7d) possess significant antifungal activity against *Candida albicans* and *Aspergillus ficuum*. Further, it guides us to design and synthesize the analogs of
bis(benzoazoles), a natural product by substituting 1/2-hydroxynaphthyl moiety in place of 2-hydroxyphenyl moiety and to study their metal mediated binding studies.

**Experimental Section**

The melting points were determined in open capillaries and are uncorrected. The UV (methanol) and florescence spectra (solid) were recorded on Cary 5000 and Fluoromax G (SPEX) spectrophotometer. The FTIR spectra were obtained in KBr on Perkin Elmer Spectrum RX1 instruments and are reported in cm\(^{-1}\). \(^1\)H and \(^{13}\)C NMR spectra were recorded on Bruker Avance II 400 MHz and 100 MHz NMR spectrometer, respectively in CDCl\(_3\) and are expressed as ppm with respect to TMS. Elemental analysis was carried out on Perkin Elmer 2400 instrument. The mass spectra were recorded on Voyager Elite MALDI-TOF instrument. Iodobenzene diacetate and metal salts [magnesium(II) nitrate, iron(II) nitrate, cobalt(II) nitrate, nickel(II) nitrate, zinc(II) acetate and cadmium(II) acetate] were purchased from Aldrich and were used without further purification. All the solvents were purified using standard procedures. The new ligands (4 and 6) have been made utilizing literature procures.\(^{12,13}\)

**2-(1’-Hydroxynaphthyl)benzoxazole (4)**

A mixture of 2-aminophenol (3.27 g, 0.03 mmol) and 1-hydroxynaphthaldehyde (5.16 g, 0.03 mmol) were refluxed in methanol (40 ml) for 2 h. The reaction mixture was cooled to room temperature and IBD (9.66 g, 0.033 mmol) was added and stirred for 1 h. The solvent was distilled off and the residue was purified by column chromatography using hexane to afford 4, yield 70%; m.p. 218°C; UV (CH\(_3\)OH) \(\lambda\): 365, 349, 321, 308, 285, 270, 261, 243, 221, 203 nm; FTIR (KBr) \(\nu\): 1635, 1579, 1552, 1498, 1454, 1409, 1331, 1291, 1250, 1147, 1125, 1071, 949, 883, 809, 747, 722, 660 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 12.56 (br s, 1H), 8.53 (dd, \(J = 7.8, 1.1\) Hz, 1H), 8.03 (d, \(J = 8.7\) Hz, 1H), 7.83 (dd, \(J = 7.2, 1.2\) Hz, 1H), 7.78-7.75 (m, 1H), 7.66-7.57 (m, 3H), 7.46 (d, \(J = 8.7\) Hz, 1H), 7.42-7.39 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\): 163.8, 157.2, 149.2, 140.2, 136.1, 128.7, 127.7, 125.9, 125.1, 125.0, 124.9, 123.8, 123.3, 119.3, 119.0, 110.7, 103.8; Mass Calcd. for C\(_{17}\)H\(_{11}\)NO\(_2\) 261.0789. Found 261.0797 (100); Anal. Calcd. for C\(_{17}\)H\(_{11}\)NO\(_2\): C, 78.15; H, 4.24; N, 5.36%. Found: C, 78.14; H, 3.95; N, 5.55%.

Similarly, 2-(2’-hydroxynaphthyl)benzoxazole (6) was obtained in 60% yield, m.p. 150-152°C; UV (CH\(_3\)OH) \(\lambda\): 373, 357, 319, 306, 253, 245, 227, 203 nm; FTIR (KBr) \(\nu\): 3428, 1617, 1535, 1459, 1420, 1378, 1336, 1289, 1257, 1207, 1181, 1125, 1009, 971, 892, 808, 747, 725, 658; \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 13.35 (br s, 1H, OH), 9.10 (dd, \(J = 8.7, 0.6\) Hz, 1H), 7.89 (d, \(J = 8.96\) Hz, 1H), 7.82-7.63 (m, 4H), 7.43-7.40 (m, 3H), 7.32 (d, \(J = 8.9\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\): 164.8, 161.1, 148.9, 138.5, 134.9, 130.9, 129.2, 128.6, 128.4, 125.3, 125.2, 124.6, 123.8, 119.4, 118.8, 110.8, 102.5; Mass Calcd. for C\(_{17}\)H\(_{11}\)NO\(_2\) 261.0789. Found 261.0797 (100); Anal. Calcd. for C\(_{17}\)H\(_{11}\)NO\(_2\): C, 78.15; H, 4.24; N, 5.36%. Found: C, 78.25; H, 3.91; N, 5.47%.

In an alternate method\(^{13}\) 2-aminophenol (3.27 g, 0.03 mmol) and 1-hydroxynaphthoic acid/2-hydroxynaphthoic acid (5.16 g, 0.03 mmol) were heated in presence of polyphosphoric acid
(100g) at 180°C for 6 h under nitrogen atmosphere. The reaction mixture was cooled to room
temperature and poured in water to afford 4 and 6, in 67% and 69% yields, respectively which
were purified by column chromatography using hexane as eluent.

Metal complexes

**General procedure**: To a solution of 4/6 (261 mg, 1 mmol) in methanol (15 ml) was added
a few drops of 10% aq. sodium hydroxide and a solution of metal salt (0.5 mmol) in methanol (5
ml). The reaction mixture was refluxed for 24 h and cooled. The product thus separated was
filtered, washed with water and dried to give 5a-5f and 7a-7f.

**Metal complexes of 2-(1'-hydroxynaphthyl)benzoxazoles (5a-5f)**

5a; Colourless powder, yield 40%; m.p. >360°C; UV (CH3OH) λ : 321, 307, 298, 283, 271, 261,
222 nm; FTIR (KBr) ν: 3413, 1610, 1562, 1543, 1497, 1459, 1412, 1384, 1330, 1285, 1250,
1208, 1146, 1077, 1004, 953, 889, 790, 739 cm⁻¹; Anal. Calcd for C34H20MgN2O4: C, 74.95; H,
3.70; N, 5.14%. Found: C, 74.77; H, 3.56; N, 5.31%.

5b; Green powder, yield 47%; m.p. >360°C; UV (CH3OH) λ : 366, 349, 286 nm; FTIR (KBr) ν:
3411, 1602, 1561, 1533, 1490, 1455, 1411, 1383, 1309, 1256, 1228, 1149, 1085, 1004, 979, 889,
809, 757, 741 cm⁻¹; Anal. Calcd for C34H20FeN2O4: C, 70.85; H, 3.50; N, 4.86%. Found: C,
70.67; H, 3.27; N, 4.83%.

5c; Light brown powder, yield 39%; m.p. >360°C; UV (CH3OH) λ : 392, 367, 350, 298, 287,
225 nm; FTIR (KBr) ν: 1607, 1557, 1534, 1487, 1458, 1449, 1420, 1384, 1333, 1301, 1255,
1191, 1147, 1087, 1001, 977, 906, 887, 873, 791, 755, 736 cm⁻¹; Anal. Calcd for C34H20CoN2O4:
C, 70.47; H, 3.48; N, 4.83%. Found: C, 70.36; H, 3.26; N, 5.14%.

5d; Light brown powder, yield 40%; m.p. >360°C; UV (CH3OH) λ : 415, 393, 366, 349, 321,
300, 285, 270, 265, 225 nm; FTIR (KBr) ν: 3435, 1636, 1609, 1575, 1543, 1494, 1459, 1420,
1383, 1311, 1251, 1196, 1152, 1072, 935, 884, 810, 789, 760 cm⁻¹; Anal. Calcd for C34H20NiO4:
C, 70.50; H, 3.48; N, 4.84%. Found: C, 70.37; H, 3.34; N, 5.01%.

5e; Yellow powder, yield 39%; m.p. >360°C; UV (CH3OH) λ : 366, 321, 297, 285 nm; FTIR
(KBr) ν: 1608, 1557, 1534 1489, 1458, 1423, 1333, 1299, 1253, 1209, 1191, 1147, 1087, 1001,
980, 887, 791, 735, 674 cm⁻¹; Anal. Calcd for C34H20Zn: C, 69.70; H, 3.44; N, 4.78%. Found:
C, 69.46; H, 3.57; N, 4.92%.

5f; Yellow powder, yield 46%; m.p. >360°C; UV (CH3OH) λ : 350, 337, 257, 241, 219 nm;
FTIR (KBr) ν: 3401, 1609, 1560, 1539, 1493, 1448, 1409, 1327, 1286, 1246, 1232, 1195, 1143,
1078, 958, 791, 742 cm⁻¹; Anal. Calcd for C34H20CdN2O4: C, 64.52; H, 3.18; N, 4.43%. Found:
C, 64.61; H, 3.02; N, 4.24%.

**Metal complexes of 2-(2'-hydroxynaphthyl)benzoxazoles (7a-7f)**

7a; Colourless powder, yield 36%; m.p. >360°C; UV (CH3OH) λ : 373, 357, 319, 305, 253, 244,
233, 219, 213, 209 nm; FTIR (KBr) ν: 3436, 1619, 1539, 1455, 1426, 1383, 1308, 1258, 1208,
1177, 1142, 1007, 985, 893, 822, 739 cm⁻¹; Anal. Calcd for C34H20MgN2O4: C, 74.95; H, 3.70;
N, 5.14%. Found: C, 74.83; H, 3.59; N, 5.30%.
7b: Green powder, yield 37%; m.p. >360°C; UV (CH3OH) \( \lambda \): 356, 319, 305, 254, 217 nm; FTIR (KBr) v: 3431, 1597, 1515, 1448, 1421, 1383, 1259, 1207, 1175, 1143, 1022, 989, 893, 828, 753 cm\(^{-1}\); Mass calcd. for \( \text{C}_3\text{H}_{20}\text{FeN}_2\text{O}_4 \) 576.0768. Found 576.5782 (100); Anal. Calcd for \( \text{C}_3\text{H}_{20}\text{FeN}_2\text{O}_4 \): C, 70.85; H, 3.50; N, 4.86%. Found: C, 70.65; H, 3.37; N, 4.91%.

7c: Yellow-green colour powder, yield 30%; m.p. >360°C; UV (CH3OH) \( \lambda \): 357, 319, 254, 204 nm; FTIR (KBr) v: 3404, 1618, 1538, 1453, 1424, 1380, 1343, 1308, 1257, 1208, 1178, 1142, 1008, 985, 892, 820, 737 cm\(^{-1}\); Mass calcd. for \( \text{C}_3\text{H}_{20}\text{CoN}_2\text{O}_4 \) 579.0755. Found 579.5481 (100); Anal. Calcd for \( \text{C}_3\text{H}_{20}\text{CoN}_2\text{O}_4 \): C, 70.47; H, 3.48; N, 4.83%. Found: C, 70.60; H, 3.29; N, 4.65%.

7d: Yellow powder, yield 32%; m.p. >360°C; UV (CH3OH) \( \lambda \): 373, 357, 319, 305, 253, 245, 225, 202 nm; FTIR (KBr) v: 1618, 1537, 1452, 1377, 1342, 1309, 1257, 1208, 1179, 1143, 1010, 985, 893, 820, 737 cm\(^{-1}\); Mass calcd. for \( \text{C}_3\text{H}_{20}\text{NiN}_2\text{O}_4 \) 578.0771. Found 576.6033 (100); Anal. Calcd for \( \text{C}_3\text{H}_{20}\text{NiN}_2\text{O}_4 \): C, 70.50; H, 3.48; N, 4.84%. Found: C, 70.29; H, 3.34; N, 4.61%.

7e: Yellow powder, yield 38%; m.p. >360°C; UV (CH3OH) \( \lambda \): 403, 317, 261 nm; FTIR (KBr) v: 3406, 1618, 1536, 1452, 1422, 1376, 1342, 1305, 1255, 1207, 1174, 1141, 1006, 983, 892, 820, 736 cm\(^{-1}\); Mass calcd. for \( \text{C}_3\text{H}_{20}\text{ZnN}_2\text{O}_4 \) 584.0715. Found 584.4229 (100); Anal. Calcd for \( \text{C}_3\text{H}_{20}\text{ZnN}_2\text{O}_4 \): C, 69.70; H, 3.44; N, 4.78%. Found: C, 69.56; H, 3.57; N, 4.92%.

7f: Yellow powder, yield 43%; m.p. >360°C; UV (CH3OH) \( \lambda \): 400, 319, 261 nm; FTIR (KBr) v: 3406, 1618, 1536, 1452, 1422, 1376, 1342, 1305, 1255, 1207, 1174, 1141, 1006, 983, 892, 820, 736 cm\(^{-1}\); Mass calcd. for \( \text{C}_3\text{H}_{20}\text{CdN}_2\text{O}_4 \) 634.0466. Found 634.4252 (100); Anal. Calcd for \( \text{C}_3\text{H}_{20}\text{CdN}_2\text{O}_4 \): C, 64.52; H, 3.18; N, 4.43%. Found: C, 64.61; H, 3.39; N, 4.24%.

**Biological studies**

The *in vitro* antibacterial and antifungal activity of 2-(1’/2’-hydroxynaphthyl)benzoxazoles (4 and 6) and their metal complexes (5a-5f and 7a-7f) were carried out against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus Aspergillus ficium*, *Aspergillus parasiticus*, *Candida albicans* and *Aspergillus niger* using serial dilution technique in double strength nutrient broth-I.P. and Sabouraud dextrose broth-I.P. as a medium. The ligands and metal complexes were dissolved in DMSO to give a concentration of 100 μg/ml (stock solution).

**Antibacterial assay**

A 24 h fresh cultures were obtained by inoculation of respective bacteria in double strength nutrient broth-I.P. followed by incubation at 37±1°C. The stock solution of ligands (4 and 6) and their metal complexes (5a-5f and 7a-7f) was serially diluted in a tube containing 1 ml of sterile double strength nutrient broth-I.P. to get a concentration of 100 to 3.12 μg/ml and then inoculated with 100 μl of suspension of respective organisms in sterile saline (*B. subtilis*, *E. coli* and *S. aureus*). The inoculated tubes were incubated at 37±1°C for 24 h and minimum inhibitory concentrations (MIC) were determined. From the observed MIC values, the exact MIC values were determined by making suitable dilution of stock solution.
Antifungal assay
The antifungal activity of 4, 5a-5f, 6 and 7a-7f against the fungal species A. ficcum, A. parasiticus, C. albicans and A. niger was determined by serial dilution method similar to Antibacterial assay using Sabouraud dextrose broth-I.P. following the incubation condition of 25±1°C for a period of 7 days, except C. albicans (37±1°C for a period of 36 h).

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References