Asian Journal of Chemistry Vol. 20, No. 2 (2008), 1588-1592

Synthesis and Antimicrobial Activity of Some Metal Complexes Derived from 2-(2'-Hydroxyphenyl)benzoxazole

ANIL KUMAR and DEVINDER KUMAR*
Department of Chemistry, Guru Jambheshwar University of Science and Technology, Hisar-125001, India
Fax: (91)(1662)276240; Tel: (91)(1662)263152; E-mail: dk_ic@yahoo.com

Synthesis, antibacterial and antifungal activity of metal complexes derived from 2-(2'-hydroxyphenyl)benzoxazole has been described.

Key Words: Synthesis, Metal complexes, Antimicrobial activity, 2-(2'-Hydroxyphenyl)benzoxazole.

INTRODUCTION

The excited-state intramolecular proton transfer (ESIPT) of 2-(2'-hydroxyphenyl)benzoxazole derivatives has been studied under physiological conditions using absorbance and steady-state emission spectroscopy and inhibition of ESIPT *via* metal coordination shows a significant wavelength shift[1]. The 2-(2'-hydroxyphenyl)benzoxazoles (HBO) are chemically and photochemically stable compounds, excellent candidates for plastic scintillation applications[2] and some of their metal complexes are of interest for the organic light emitting diode (OLED) technology[3-5]. 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[6]. The 2-(2'-hydroxyphenyl)benzoxazole moiety is also present in a number of synthetic metal ion chelators[7,8]. A natural product *bis*(benzoxazole) (UK-1) also having 2-(2'-hydroxyphenyl)benzoxazole 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[9]. 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[10]. The numerous applications of benzoxazoles promoted to undertake the synthesis of metal complexes of 2-(2'-hydroxyphenyl)benzoxazole for studying their antimicrobial activity.

EXPERIMENTAL

The UV spectra were recorded on Cary 5000 spectrophotometer. The FTIR spectra were recorded on Perkin Elmer instrument in KBr. The melting points were taken in open capillaries and are uncorrected. The elemental analysis was obtained on Perkin 2400 instrument. DSC, TGA and AAS of the compounds were scanned on TA instrument (Q 10), Perkin Elmer Pyris1 and GBC +932 instruments, respectively.

Iodobenzene diacetate and metal salts *viz.*, zinc(II) acetate, cobalt(II) nitrate, nickel(II) nitrate, cadmium(II) acetate, iron(II) nitrate and magnesium(II) nitrate were purchased from Aldrich and were used as such. All the solvents were purified using standard procedures.

2-(2'-Hydroxyphenyl)benzoxazoles (4): A mixture of 2-aminophenol (1.0 g, 9.42 mmol) and 2-hydroxybenzoic acid (1.3 g, 9.42 mmol) were stirred for 20 min and heated in polyphosphoric acid in an oil bath at 180 °C for 5 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature and poured into ice. The product so obtained was filtered, dried and purified by column chromatography using hexane, m.p. 124 °C, yield 80 %.

In an alternate method, 2-aminophenol (218 mg, 2 mmol) and 2-hydroxybenzaldehyde (244 mg, 2 mmol) were refluxed in methanol (25 mL) for 2 h. The reaction mixture was cooled to room temperature and IBD (758 mg, 2.2 mmol) was added and stirred for 1 h. The solvent was evaporated and the residue was purified by column chromatography using hexane to afford **4** in 60 % yields.

General procedure: To a solution of **4** (211 mg, 0.1 mmol) in methanol (10 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 little methanol and dried.

In case of the metal complexes **6a-6d** (Zn^{2+}, Co^{2+}, Ni^{2+}, Cd^{2+}) the yields were 40-45 % and the melting points were >360 °C. The UV, IR and other TGA data were in consonance with those reported in literature[11].

6e: Yield 38 %; m.p. >360 °C; UV: 319, 292, 285, 273, 204 nm; IR: 3431, 1597, 1515, 1448, 1421, 1383, 1259, 1207 cm^{-1}. [Found: C, 69.89, H, 3.71, N, 6.56 % $C_{26}H_{16}N_2O_4Mg$ requires C, 70.22, H, 3.63, N, 6.30 %].

6f: Yield 42 %; m.p. >360 °C; UV: 318, 292, 284, 281, 273, 209 nm; IR: 3436, 1619, 1539, 1455, 1426, 1383, 1308, 1258, 1208 cm^{-1}. [Found: C, 65.18, H, 3.52, N, 6.16 % $C_{26}H_{16}N_2O_4Fe$ requires C, 65.57, H, 3.39, N, 5.88 %].

Biological studies: Using serial dilution technique in double strength nutrient broth-I.P. and Sabouraud dextrose broth-I.P. as a medium carried out the *in vitro* antibacterial and antifungal activity of the synthesized metal

complexes of 2-(2'-hydroxyphenyl) benzoxazole against *S. aureus, B. subtilis* and *E. coli, A. ficcum, A. parasiticus, C. albicans* and *A. niger*. The complexes were dissolved in DMSO to give a concentration of 10 µg/mL (stock solution).

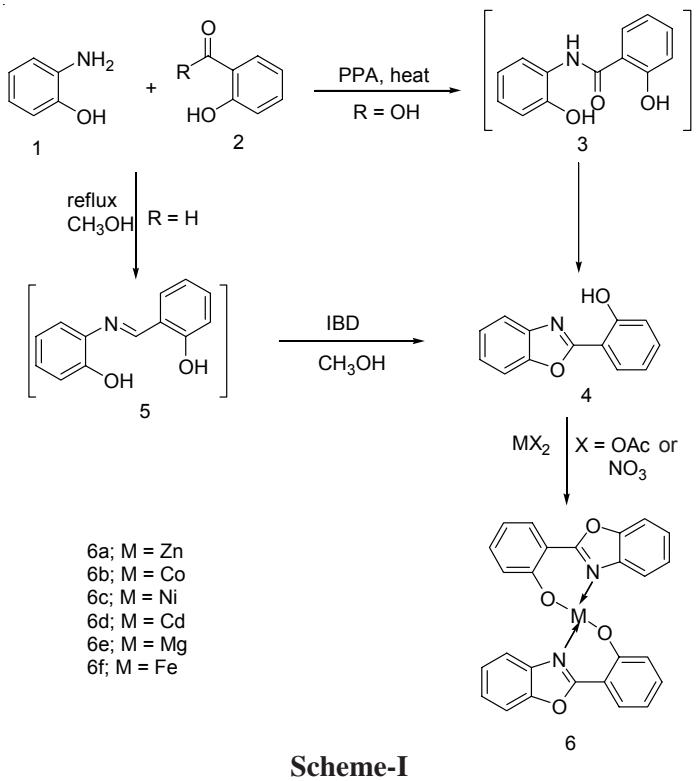
Antibacterial assay: A 24 h fresh cultures were obtained by inoculation of respective bacteria in double strength nutrient broth-I.P. followed by incubation at 37 ± 1 °C. The stock solution of synthesized metal complexes was serially diluted in tube containing 1 mL of sterile double strength nutrient broth-I.P. to get a concentration of 50 to 3.12 µg/mL and then inoculated with 100 µL of suspension of respective organisms to sterile saline (*S. aureus, B. subtilis* and *E. coli*). The inoculated tubes were incubated at 37 ± 1 °C for 24 h and minimum inhibitory concentrations (MIC) were determined in mg/mL. From the observed MIC values, the exact MIC values were determined by making suitable solution of stock solution.

Antifungal assay: The antifungal activity of metal complexes **6a-6d** against the fungal species *A. ficcum, A. parasiticus, Candida albicans* and *Aspergillus 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 d, except *C. albicans* (37 ± 1 °C for a period of 36 h).

RESULTS AND DISCUSSION

The reaction of 2-aminophenol (**1**) with 2-hydroxybenzoic acid (**2**, R = OH) in polyphosphoric acid[12] resulted in 2-(2'-hydroxyphenyl)benzoxazoles (**4**) *via* the intermediacy of **3**. In an alternate method, **1** was treated with 2-hydroxybenzaldehyde (**2**, R = H) in presence of iodobenzene diacetate (IBD)[13] again *via* the intermediacy of **5**. Both the route afforded **4** in one pot without the isolation of intermediates (**3, 5**) and in good yield which was purified by column chromatography. All the physical and spectroscopic data were in consonance with the structure. Further, reaction of **4** with metal (Zn^{2+}, Co^{2+}, Ni^{2+}, Cd^{2+}, Mg^{2+}, Fe^{2+}) salts generated the metal complexes (**6**) in good yields (**Scheme-I**).

The metal complexes **6a-6d** has been described previously with no biological activity, whereas **6e-6f** has been synthesized as iron and magnesium finds applications in biological systems. The structure assignment was supported by UV and IR studies. The DSC of **6e** indicated that at onset temperatures of 285.2, 323.2 and 388.5 °C, the heat flow was 24.9, 22.5 and 61.3 J/g, respectively. Further, the TGA of **6e** showed the weight loss of 81.7 % at a temperature of 698.1 °C thereby suggesting its good thermal stability. The DSC of **6d** indicated that at onset temperatures of 121.2 and 467.2 °C the heat flow was 8.4 and 49.3 J/g, respectively. Further the TGA of **6d** showed the weight loss of 81.3 % at a temperature of 699.4 °C thereby suggesting its good thermal stability.



Scheme-I

The metal complexes **6a-6f** were evaluated for *in vitro* antibacterial activity against Gram-positive *Staphylococcus aureus* [MTCC 2901], *Bacillus subtilis* [MTCC 2063] and Gram-negative *Escherichia coli* [MTCC 1652] and *in vitro* antifungal activity against *Aspergillus ficcum* [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.11 were employed for bacterial and fungal growth, respectively. Minimum inhibitory concentrations (MIC) were determined by means of standard serial dilution[14] and are presented in Table-1. All the compounds exhibited appreciable *in vitro* activity against the tested strains.

Table-1 indicates that metal complex **6a-6d, 6b-6c** and **6d** showed significant antibacterial activity against *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus*, respectively. Further, the antifungal activity of metal complex **6d** was found to be more prominent against *Aspergillus ficcum* among others. However, the metal complexes **6a-6d, 6b-6c** and **6b** were found to display better antifungal activity against *Aspergillus parasiticus, Candida albicans* and *Aspergillus niger*, respectively. Most of the metal complexes showed better activity than the ligand (**4**).

TABLE-1
in vitro ANTIMICROBIAL ACTIVITY OF **4** AND **6a-6f** AND STANDARD DRUG (MIC in µg/mL)

Compd.	Antibacterial activity*			Antifungal activity*			
	BS	EC	SA	AF	AP	CA	AN
4	25.0	25.0	50.0	6.25	50.0	6.25	12.5
6a	12.5	12.5	25.0	6.25	6.25	12.5	12.5
6b	12.5	6.25	50.0	6.25	6.25	6.25	6.25
6c	12.5	6.25	50.0	6.25	6.25	6.25	12.5
6d	12.5	12.5	12.5	3.12	6.25	12.5	12.5
6e	25.0	12.5	25.0	12.5	12.5	12.5	12.5
6f	50.0	12.5	25.0	6.25	12.5	12.5	12.5

BS = *B. subtilis*; EC = *E. coli*; SA = *S. aureus*; AF = *A. ficuum*;
AP = *A. parasiticus*; CA = *C. albicans*; AN = *A. niger*
*The MIC of standard drug for antibacterial activity (tetracycline, chloramphenicol, kanamycin, cefazoline sodium and cefotaxime) and antifungal activity (cycloheximide, kemistin and fluconazole) was found to < 3.12 µg/mL.

ACKNOWLEDGEMENTS

The authors are thankful to UGC, New Delhi for financial support and Dr. B. Narasimhan, Department of Pharmaceutical Sciences, Guru Jambeshwar University of Science & Technology, Hisar for helpful discussions.

REFERENCES

1. M.M. Henary and C.J. Fahrni, *J. Phys. Chem. A*, **106**, 5210 (2002).
2. A. Pla-Dalmau, *J. Org. Chem.*, **60**, 5468 (1995).
3. S. Sakio, S. Miyaoka, S. Kaneko, T. Fujii and T. Takai, Japan Patent 2,001,125,292 (2001).
4. S.Q. Shi, Tw Patent 401,453 (2000).
5. N. Nakamura and K. Miyairi, Eur. Patent, 0,801,518 (1997).
6. A.K. Ogawa, O.K. Abou-Zied, V. Tsui, R. Jimenez, D.A. Case and F.E. Romesberg, *J. Am. Chem. Soc.*, **122**, 9917 (2000).
7. H.R. Hoveyda, S.J. Rettig and C. Orwig, *Inorg. Chem.*, **32**, 4909 (1993).
8. K. Tanaka, T. Kumagai, H. Aoki, M. Deguchi and S. Iwata, *J. Org. Chem.*, **66**, 7328 (2001).
9. D. Kumar, M.R. Jacob, M.B. Reynold and S.M. Kerwin, *Bioorg. Med. Chem.*, **10**, 3997 (2002).
10. M.L. Reyzer, J.S. Brodbelt, S.M. Kerwin and D. Kumar, *Nucleic Acid Res.*, **29**, e103 (2001).
11. F.S. Rodembusch, F.R. Brand, D.S. Correa, J.C. Pocos, M. Martinelli and V. Stefani, *Mat. Chem. Phys.*, **92**, 389 (2005).
12. L.F. Campo, D.S. Correa, M.A. Araujo and V. Stefani, *Macromol. Rapid Commun.*, **21**, 832 (2000).
13. R.S. Varma, R.K. Saini and O. Prakash, *Tetrahedron Lett.*, **38**, 2621 (1997).
14. Pharmacopoeia of India; Ministry of Health Department: Govt. of India: New Delhi, Vol-II, pp. A-88 (1996).

(*Received*: 10 May 2007; *Accepted*: 15 October 2007) AJC-6011