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Synthesis, Characterization and Antimicrobial Activity of Methylquinolino[3,2-b][1,5]benzodiazepine and Methylquinolino[3,2-b][1,5]benzoxazepine and its Various Metal Complexes

B. BASAVARAJU*, H.S. BHOJYA NAIK[#] and M.C. PRABHAKARA[#]

*Department of Biotechnology,
GM Institute of Technology, Davangere-577 006,
Karnataka, India. Phone: (08192) 233377, Fax: (08192) 233344
e-mail: basavaraju_b@yahoo.co.in

[#]Department of PG studies and Research in Industrial Chemistry,
School of Chemical Sciences, Kuvempu University, Shankaraghatta-577 451, Shimoga,
Karnataka, India. Phone: (08282) 256303, e-mail: hsb_naik@rediffmail.com

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Abstract: 2-Chloro-6-methylquinoline-3-carbaldehyde was condensed with *o*-Phenylenediammine and 2-aminophenol in presence of potassium iodide. The resulting Methylquinolino[3,2-b][1,5]benzodiazepine (MQBD) and Methylquinolino[3,2-b][1,5]benzoxazepine (MQBO) were characterized by elemental analysis and spectral studies. The metal chelates *viz* Pd(II), Rh(III) and Ru(III) of ligands were prepared and characterized by metal-ligand (M:L) ratio, UV-Visible, IR, ¹H NMR spectroscopes and magnetic properties. The antibacterial and antifungal activity of MQBD, MQBO and its metal complexes were screened against various bacteria and fungi. The results show that all these samples are good antimicrobial agents.

Keywords: 2-Chloro-6-methylquinoline-3-carbaldehyde, Antimicrobial activity, Methylquinolino[3,2-b][1,5]benzodiazepine, Methylquinolino[3,2-b][1,5]benzoxazepine, quinoline.

Introduction

The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties. The 8-(diethylamino)hexylamino-6-methoxy-4-methylquinoline is highly effective against the protozoan parasite *Trypanosoma cruzi*, which is the agent of Chagas' disease¹. The centipede, *Scolopendra Subspines mutilans* L. which is

found to contain 3,8-dihydroxyquinoline called *Jineol* has been prescribed for tetanus, childhood convulsions and acute heart attack². Cryptolepine (5-methyl-5H-indolo[3,2-b]quinoline) displays a plenty of pharmacological effects, such as antimuscarinic, noradrenergic receptor antagonistic, antihypertensive, vasodilative, antithrombotic, antipyretic and anti-inflammatory properties³⁻⁵. Quinoline containing drugs particularly 4-aminoquinolines, have a long and successful history as antimalarials^{6,7}.

Experimental

Materials

All the chemicals used in the present study are of AR grade. 2-Chloro-6-methylquinoline-3-carbaldehyde (Sigma-Aldrich Chemie, Germany), 2-aminophenol (S.D.Fine Chem Ltd, India) and *o*-Phenylenediamine (S.D.Fine Chem Ltd, India) were used.

Measurements

The IR spectra of ligand and its metal complexes were recorded on a SHIMADZU FTIR-8400S spectrometer with KBr pellets in the region 250-4000 cm^{-1} . JEOL 60 MHz spectrometer was used for recording the proton NMR spectra employing TMS as internal reference and DMSO-d_6 as solvent. UV-visible spectra were measured on a SHIMADZU double beam spectrophotometer using $\text{N,N'$ -dimethylformamide as a solvent at 10^{-3} M concentration.

Antibacterial activity

Antibacterial activity of ligands and its complexes were studied against Gram positive bacteria *S. aureus* and Gram negative bacteria *P. aeruginosa* by employing paper disc method⁸. The streptomycin (100 mg) was used as a standard. For each concentration, the mean diameter of inhibition zone developed (mm) was calculated.

Antifungal activity

The antifungal studies of ligands and its complexes were tested on the fungal strains namely, *C. albicans*, *A. flavus* and *A. niger* in the growth media by using Batemann poisoned food technique⁹. The average percentage inhibition was calculated by using the reported method¹⁰.

Synthesis of Methylquinolino[3,2-b][1,5]benzodiazepine(MQBD)

The mixture of 2-Chloro-6-methylquinoline-3-carbaldehyde (1.569 g, 5 mmol) dissolved in small amount of acetic acid and *o*-Phenylenediamine (0.541 g, 5 mmol) was taken in a 100 ml borosil beaker and a pinch of potassium iodide was then added. The whole mixture was made into slurry and was irradiated by placing the beaker in a microwave oven for about 10 minutes. The product obtained was poured into ice-cold water, the solid separated was filtered, dried and recrystallized (Scheme 1).

Scheme-1. Preparation of Methylquinolino[3,2-b][1,5]benzodiazepine(MQBD)

Synthesis of Methylquinolino[3,2-b][1,5]benzoxazepine(MQBO)

The mixture of 2-aminophenol (0.11 g, 1 mmol), KOH (0.057 g, 1 mmol) and 2 ml of DMSO were taken in a 100 ml borosil beaker. 2-Chloro-6-methylquinoline-3-carbaldehyde (1 mmol, 0.314 g) and a pinch of KI were then added. The mixture was irradiated for about two minutes in a microwave oven. The product was then hydrolyzed by pouring into ice-cold water. The final product separated as a solid on acidification with dilute HCl was then filtered, dried and purified (Scheme 2).

Scheme 2. Preparation of Methylquinolino[3,2-b][1,5]benzoxazepine(MQBO)

General procedure for the preparation of Pd(II) complexes

The complexes were prepared by mixing an ethanolic solution of the metal dichloride with the corresponding ligand in hot ethanol in a 1:1 molar ratio. The resultant solution was refluxed at 110 °C for three hours. When the corresponding metal complex precipitated, it was filtered, washed several times with ethanol and dried under reduced pressure.

General procedure for the preparation of Rh(III) complexes

The complexes were prepared by refluxing the rhodium(III)chloride trihydrate (5 mmol) and the corresponding ligand (10 mmol) in ethanol (75 ml) for 2-3 hours. When the metal complex precipitated, it was filtered, washed several times with hot water, warm ethanol and dried at 110-130 °C.

General procedure for the preparation of Ru(III) complexes

A mixture containing $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (2.5 mmol) and corresponding ligand (5 mmol) was refluxed in methanol for 5 hours. The solution was cooled to room temperature. After evaporation of the solvent, the solid was collected, washed with methanol and dried under suction.

Results and Discussion

Stoichiometry

The complexes are microcrystalline coloured powder, whose melting points are higher than the pure ligand. They are stable at room temperature and are insoluble in common organic solvents. The elemental analysis data show that they are of the types $[\text{ML}_2\text{Cl}_2]$ where $\text{M}=\text{Rh(III)}$ or Ru(III) and $[\text{PdLCl}_2]$ where $\text{L}=\text{MQBD}$ or MQBO . Palladium(II) and Ruthenium(III) complexes are brown to brownish red and rhodium(III) complexes are reddish.

Molar conductivity

The molar conductance values of all the complexes were determined in 10^{-3} M DMF and are tabulated in Table 1. The conductivity values of Pd(II) complexes are in the range 28.5-29.2 mhos $\text{cm}^2 \text{mol}^{-1}$ indicating the non-electrolytic nature of the complexes¹¹. The molar conductance values of rhodium(III) and ruthenium(III) complexes were found to be quite

low (17.5-25.4 mhos $\text{cm}^2 \text{mol}^{-1}$), showing that these complexes have covalent behaviour. The observed very small conductance values show that practically no interaction occurs between the solvent and the dissolved complex. Thus the chloride ions in all these complexes are coordinated to metal ion and are not present outside the coordination sphere¹². This is consistent with the stoichiometry assumed for the complexes on the basis of analytical data.

Magnetic moments

The room temperature magnetic values (Table 1) shows that the Pd(II) complexes are diamagnetic showing square planar geometry. The octahedral Rh(III) complexes are paramagnetic and magnetic moment values are found to be in the range 1.84-1.86 BM¹³. The magnetic susceptibility data indicates that the Ru(III) complexes are paramagnetic with one unpaired electron. The values are in the range 1.78-1.85 BM that is lower than the predicted value of 2.1 BM. This low value may be due to low symmetry ligand fields or electron delocalization. This observed value is very close to the spin only value for one unpaired electron¹⁴. This suggests the low spin d^5 configuration for ruthenium(III) ion in an octahedral environment

Table 1. Physical constants of ligands and its complexes

Compound	Yield %	Found (Calcd) %					Molar conductivity mhos $\text{cm}^2 \text{mol}^{-1}$	Magnetic moment μ_{eff} BM	Mol.wt. found (Calcd)
		C	H	N	M	Cl			
MQBD	74	78.89 (78.74)	5.25 (5.05)	16.35 (16.20)	--	--	--	--	256.21 (259.30)
MQBO	76	78.65 (78.44)	4.83 (4.65)	11.01 (10.76)	--	--	--	--	257.26 (260.29)
[Pd(MQBD)Cl ₂]	81	46.76 (45.78)	3.00 (3.12)	9.62 (9.59)	24.37 (24.52)	16.24 (16.12)	28.5	--	432.59 (436.63)
[Pd(MQBO)Cl ₂]	77	46.66 (45.75)	2.76 (2.81)	6.40 (6.38)	24.32 (25.12)	16.20 (16.32)	29.2	--	435.68 (437.62)
[Rh(MQBD) ₂ Cl ₂]	82	58.98 (57.88)	3.78 (3.68)	12.14 (12.32)	14.86 (13.68)	10.24 (10.32)	17.5	1.86	689.36 (692.42)
[Rh(MQBO) ₂ Cl ₂]	82	58.81 (57.98)	3.48 (3.38)	8.07 (8.12)	14.82 (14.25)	10.21 (10.31)	19.2	1.84	690.98 (694.39)
[Ru(MQBD) ₂ Cl ₂]	79	59.13 (58.25)	3.79 (3.85)	12.17 (12.24)	14.64 (14.58)	10.27 (10.38)	21.5	1.85	688.84 (690.59)
[Ru(MQBO) ₂ Cl ₂]	72	58.96 (58.85)	3.49 (3.59)	8.09 (8.12)	14.59 (14.25)	10.24 (10.38)	25.4	1.78	690.14 (692.55)

Spectral study

The electronic spectrum of Pd(II) complexes gave three bands at 16600, 21300 and 30300 cm^{-1} due to $^1\text{A}_{1g} \rightarrow ^1\text{A}_{2g}$ (ν_1), $^1\text{A}_{1g} \rightarrow ^1\text{B}_{1g}$ (ν_2) and $^1\text{A}_{1g} \rightarrow ^1\text{E}_{1g}$ (ν_3) transitions, respectively in a square planar configuration¹³. In Rh(III) complexes, the observed electronic bands around 16600, 19400 and 22300 cm^{-1} are due to the transitions $^1\text{A}_{1g} \rightarrow ^3\text{T}_{1g}$, $^1\text{A}_{1g} \rightarrow ^1\text{T}_{1g}$ and $^1\text{A}_{1g} \rightarrow ^1\text{T}_{2g}$, respectively in an octahedral structure around Rh(III)¹³. The UV-Visible spectra Ru(III) complexes showed that the complexes exhibit octahedral absorption bands in the region 24800-24570 cm^{-1} . Only charge transfer bands, which masked the weak (spin forbidden as well as spin allowed) bands due to d-d transitions in the visible region. The bands in the range 24800-24570 cm^{-1} may be attributed to $^1\text{A}_{1g} \rightarrow ^1\text{T}_{1g}$ charge transfer transitions¹⁵. All the Ru(III) complexes show absorption band ca. 37000 cm^{-1} corresponding to charge transfer transitions.

IR Spectra

The ligand MQBD shows bands at 1662 cm^{-1} and 3332 cm^{-1} due to $\nu(\text{C}=\text{N})$ and $\nu(\text{NH})$ vibrations respectively¹⁶. These bands are shifting in the complexes indicates the coordination of nitrogen atom of quinoline and azepine moiety with the metal ions. The IR spectra of MQBO showed absorption bands at 1025 cm^{-1} and 1653 cm^{-1} for $\nu(\text{COC})$, $\nu(\text{C}=\text{N})$ respectively¹⁷. The negative shift of these bands in the complexes indicates the sites of coordination are nitrogen and oxygen atoms quinoline and azepine rings, respectively. The important IR spectral data are shown in Table 2.

Table 2. The IR and ^1H NMR spectral data of ligands and complexes.

Compound	Infrared spectral data					^1H NMR spectral data δ , ppm
	$\nu(\text{C}=\text{N})$	$\nu(\text{NH})$	$\nu(\text{COC})$	$\nu \text{ M-N}$	$\nu \text{ M-X}$	
MQBD	1662	3332	--	--	--	10.80 (s, 1H, NH), 8.6 (s, 1H, H-C=N), 7.1-8.2 (m, 11H, Ar-H), 2.7 (s, 3H, CH_3)
MQBO	1653	--	1025	--	--	8.4 (s, 1H, H-C=N), 7.3-8.0 (m, 11H, Ar-H), 2.6 (s, 3H, CH_3)
[Pd(MQBD) Cl_2]	1620	3304	--	406	310	10.85 (s, 1H, NH), 8.4 (s, 1H, H-C=N), 7.2-7.8 (m, 9H, Ar-H)
[Pd(MQBO) Cl_2]	1614	--	996	398	306	8.3 (s, 1H, H-C=N), 7.1-8.0 (m, 9H, Ar-H)
[Rh(MQBD) $_2\text{Cl}_2$]	1636	3294	--	408	340	10.9 (s, 1H, NH), 8.4 (s, 1H, H-C=N), 7.2-7.8 (m, 9H, Ar-H)
[Rh(MQBO) $_2\text{Cl}_2$]	1618	--	1004	400	335	8.3 (s, 1H, H-C=N), 7.1-8.0 (m, 9H, Ar-H)
[Ru(MQBD) $_2\text{Cl}_2$]	1624	3310	--	404	318	10.8 (s, 1H, NH), 8.4 (s, 1H, H-C=N), 7.2-7.8 (m, 9H, Ar-H)
[Ru(MQBO) $_2\text{Cl}_2$]	1624	--	998	402	316	8.3 (s, 1H, H-C=N), 7.1-8.0 (m, 9H, Ar-H)

¹H NMR spectra

All the compounds show the ¹H NMR signals for different kinds of protons at their respective positions. The data are shown in Table 2. The ¹H NMR spectra of the ligand MQBD exhibit a singlets at 10.80 δ (s, N-H) and 8.6 δ (s, H-C=N). The ¹H NMR spectra of complexes slightly changed compared to those of the corresponding ligand, and the signals appeared downfield, as expected, due to the coordination of nitrogen atoms to the metal ion¹⁸⁻²⁰. ¹H NMR spectrum of MQBO ligand showed signals at δ 8.4 (s, 1H, H-C=N), 7.3-8.0 (m, 11H, Ar-H) and 2.6 (s, 3H, CH₃). In the spectra of complexes, all signals remained at same position except the signal of H-C=N. This is probably due to the coordinating effect of the azepine oxygen atom.

Antibacterial Activity

The comparison of inhibition zone values for the metal complexes (Table 3) reveals that the antimicrobial activity could be mainly due to the structure of the complexes and also the oxidation state of the metal ions. These results must be directly related to the greater biological activity exhibited by the square planar Pd(II) complexes compared to the octahedral Rh(III) and Ru(III) complexes.

Table 3. Inhibition zone of bacterial growth (mm)

Compound	<i>P.aeruginosa</i>			<i>S.aureus</i>		
	0.1 %	0.2 %	0.3 %	0.1 %	0.2 %	0.3 %
MQBD	1.2	1.6	2.8	1.4	1.8	3.0
MQBO	1.1	2.0	3.0	1.3	1.6	2.9
[Pd(MQBD)Cl ₂]	2.3	2.8	4.5	2.4	3.2	5.2
[Rh(MQBD) ₂ Cl ₂]	1.5	1.9	3.2	1.6	2.1	3.4
[Ru(MQBD) ₂ Cl ₂]	1.3	1.9	3.0	1.6	2.1	3.3
[Pd(MQBO)Cl ₂]	1.9	3.2	4.3	2.2	3.0	4.7
[Rh(MQBO) ₂ Cl ₂]	1.4	2.4	3.4	1.5	2.0	3.2
[Ru(MQBO) ₂ Cl ₂]	1.4	2.4	3.3	1.4	1.9	3.1

A possible explanation for the high toxicity of metal complexes can be explained as follows. The increase in the activity of metal complexes may be due to effect of metal ions on the normal cell process. The polarity of metal ion is considerably reduced on chelation which is mainly because of partial sharing of its positive charge with a donor groups and possibly π -electron delocalization over the whole molecule. Such molecule increases the lipophilic character of the metal complexes which probably leads to break down of permeability barrier of the cells resulting in interference with normal cell process²¹. Better activities of the metal complexes as compared to free ligand could also be understood in terms of chelation theory²², which explains that a decrease in polarizability of the metal could enhance the lipophilicity of the complexes.

Antifungal activity

The percentage inhibition values of fungicidal growth are recorded in Table 4. The screening data clearly shows that the complexes were more toxic than their parent ligand under identical experimental conditions and as the concentration of the complexes increases the inhibition of the fungal growth increases.

Table 4. Percentage inhibition of fungicidal growth.

Compound	<i>C. albicans</i>			<i>A. niger</i>			<i>A. flavus</i>		
	0.1%	0.2%	0.3%	0.1%	0.2%	0.3%	0.1%	0.2%	0.3%
MQBD	11.2	13.8	18.3	10.3	13.4	20.2	9.8	13.1	24.2
MQBO	10.3	12.9	16.9	8.8	11.9	18.6	7.8	11.8	22.3
[Pd(MQBD)Cl ₂]	13.6	21.5	30.5	13.5	17.2	23.5	12.6	15.6	27.8
[Rh(MQBD) ₂ Cl ₂]	11.5	14.4	21.8	10.8	13.9	20.9	10.4	13.2	24.9
[Ru(MQBD) ₂ Cl ₂]	11.4	14.2	21.5	10.7	13.8	20.8	10.3	13.1	24.8
[Pd(MQBO)Cl ₂]	12.4	20.0	29.5	12.3	15.2	21.3	10.5	14.6	25.6
[Rh(MQBO) ₂ Cl ₂]	10.9	14.1	21.2	9.5	12.6	19.1	8.4	12.6	23.0
[Ru(MQBO) ₂ Cl ₂]	10.8	13.8	20.3	9.3	12.4	18.9	8.3	12.5	22.9

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