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Transition Metal Complexes of Methyl-quinolino[3,2-b][1,5]benzodiazepine and Methylquinolino [3,2-b][1,5]benzoxazepine: Synthesis, Characterisation and Antimicrobial Studies

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Abstract: The synthesis and characterisation of title complexes of the ligand Methylquinolino[3,2-b][1,5]benzodiazepine (MQBD) and Methyl-quinolino[3,2-b][1,5]benzoxazepine (MQBO) are reported. The complexes have been characterized by elemental analysis, molar conductance, magnetic studies, IR, ^{1}H NMR and UV-visible studies. They have the stoichiometry $[ML_2Cl_2]$ where M=Co(II)/Ni(II), L=MQBD/MQBO and $[MLCl_2]$ where M=Zn(II)/Cd(II), L=MQBD/MQBO. The antibacterial and antifungal activity of the metal complexes has been investigated.

Keywords: Antimicrobial activity, magnetic moment, quinoline, Methylquinolino[3,2-b][1,5]benzodiazepine and Methylquinolino[3,2-b][1,5]benzoxazepine

Introduction

Quinoline derivatives represent the major class of heterocycles, and a number of preparations have been known from the late 1980s. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties. The 8-(diethylaminohexylamino)-6-methoxy-4-methyl-quinoline is highly effective against the protozoan parasite *Trypanosoma cruzy*, which is the agent of Chagas' disease[1] and the 2-(2-methylquinolin-4-ylamino)-N-phenylacetamide is more active than the standard antileishmanial drug sodium antimony gluconate[2]. The centipede, *Scolopendra Subspines*

mutilalns L. which is found to contain 3,8-dihydroxyquinoline called *Jineol* has been prescribed for tetanus, childhood convulsions and acute heart attack[3]. 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 properties. Neocryptolepine and cryptolepine derivatives reveal antiplasmodial and antitrypanosomal and first of all, cytotoxic activities[4-6]. Quinoline containing drugs particularly 4-aminoquinolines, have a long and successful history as antimalarials[7,8].

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*-Phenylenediammine (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 MH_Z 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 N,N'-dimethylformamide as a solvent at 10^{-3} M concentration.

Antibacterial activity

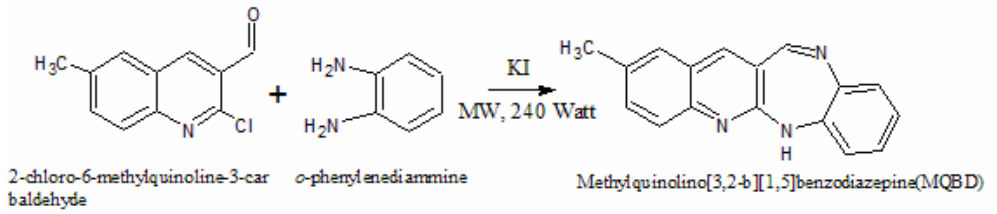
Antibacterial activity of ligands and its complexes were studied against Gram positive bacteria *S. aureus* and Gram negative bacteria *P. aerugenosa* by employing paper disc method[9]. The streptomycin (100 mg) was used as a standard. For each concentration, the mean diameter of inhibition zone developed (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 technique[10]. The average percentage inhibition was calculated by using the reported method[11].

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

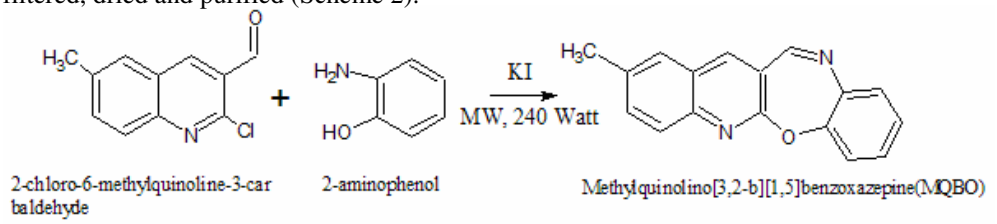
The mixture of 2-Chloro-6-methylquinoline-3-carbaldehyde (1.569 g, 5 mmo1) dissolved in small amount of acetic acid and *o*-Phenylenediammine (0.541 g, 5 mmol) was taken in a 100 ml borosil beaker and a pinch of potassium iodide was then added. The whole mixture was made into slurry and was irradiated 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, 1mmol), 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)

Cobalt(II) and Nickel(II) complex of MQBD and MQBO

The hot solution (0.5 mmol, 50 ml) of metal(II) chloride was slowly added to 50 ml of hot ethanolic solution of the ligand (1.0 mmol) with continuous stirring. The reaction mixture was warmed on a water bath at 60-70 ^{o}C for about 2 hours. The precipitate obtained was filtered, washed several times with absolute alcohol, finally with ether and dried.

Cadmium (II) and Zinc (II) complexes of MQBD and MQBO

The ethanolic solution of divalent metal salt (2.5 mmol) was added to a solution of the ligand (2.5 mmol) in ethanol (10 ml). The reaction was stirred for 24 h at room temperature. The solid formed was filtered and dried under vacuum.

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 $[ML_2Cl_2]$ where M=Co(II)/ Ni(II), L=MQBD/MQBO and $[MLCl_2]$ where M=Zn(II)/Cd(II); L=MQBD/MQBO. Low molar conductance values (14.45-27.4 mhos cm^2 mol^{-1}) of these complexes indicate their non-electrolytic nature (Table 1).

Magnetic moments

The room temperature magnetic moment value (Table 1) support octahedral geometry for Co(II) and Ni(II) complexes[12, 13]. The Zn(II) and Cd(II) complexes are diamagnetic due to non availability of unpaired electrons[14].

Spectral study

The octahedral Co(II) complexes exhibit three bands at 13380-14368 cm^{-1}, 14480-15020 cm^{-1} and 16484-16490 cm^{-1} pertaining to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (ν_1), $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ (ν_2) and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ (ν_3) transitions, respectively[15]. The absorption spectra of Ni(II) complexes show two bands at 12618-16253 cm^{-1} and 23266-28021 cm^{-1} due to $^3A_{2g(F)} \rightarrow {}^3T_{1g(F)}$ (ν_2) and $^3A_{2g(F)} \rightarrow {}^3T_{1g(P)}$ (ν_3) transitions respectively supporting the octahedral stereochemistry[16]. The absorption spectra of Zn(II) and Cd(II) complexes show no bands due to d-d transition. This phenomenon is natural as there is no possibility of transition due

to non availability of empty d-orbital[17]. By considering spectral data, the tetrahedral[18] and square planar geometry[19] have been proposed for Cd(II) and Zn(II) complexes, respectively.

Table 1. Physical constants of ligands and its complexes.

Compound	Yield %	Found (Calcd) %					Molar conductivity mhos cm^2 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)
$[Co(MQBD)_2Cl_2]$	82	60.27 (62.98)	4.23 (4.04)	13.01 (12.96)	9.20 (9.09)	11.21 (10.93)	22.4	4.84	645.35 (648.44)
$[Ni(MQBD)_2Cl_2]$	75	64.4 (63.0)	4.2 (4.0)	13.0 (12.9)	8.9 (9.0)	11.1 (10.9)	23.4	2.99	642.89 (648.21)
$[Cd(MQBD)Cl_2]$	82	42.89 (46.31)	2.86 (2.96)	9.58 (9.48)	26.41 (25.40)	16.15 (16.02)	14.52	--	439.87 (442.62)
$[Zn(MQBD)Cl_2]$	75	55.38 (57.61)	3.35 (3.31)	10.72 (10.62)	16.61 (16.53)	17.86 (17.92)	15.25	--	392.35 (395.60)
$[Co(MQBO)_2Cl_2]$	82	60.68 (62.78)	3.68 (3.72)	8.75 (8.61)	8.96 (9.06)	11.01 (10.90)	22.5	4.87	646.54 (650.41)
$[Ni(MQBO)_2Cl_2]$	80	60.2 (62.8)	3.5 (3.7)	8.8 (8.6)	9.1 (9.0)	11.1 (10.9)	27.4	3.12	645.89 (650.17)
$[Cd(MQBO)Cl_2]$	82	43.31 (46.03)	2.81 (2.73)	6.28 (6.31)	25.36 (25.34)	15.83 (15.98)	14.45	--	440.24 (443.60)
$[Zn(MQBO)Cl_2]$	72	49.52 (51.48)	3.10 (3.05)	7.16 (7.06)	16.58 (16.49)	17.56 (17.88)	24.56	--	393.54 (396.58)

IR Spectra

The ligand MQBD shows bands at 1662 cm^{-1} and 3332 cm^{-1} due to ν(C=N) and ν(NH) vibrations respectively[20]. 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 ν(COC), ν(C=N) respectively[21]. 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.

^{1}H NMR spectra

All the compounds show the ^{1}H NMR signals for different kinds of protons at their respective positions. The data are shown in Table 2. The ^{1}H 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 ion[22-24]. ^{1}H 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, CH_3). 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.

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

Compound	Infrared spectral data					^{1}H NMR spectral data
	ν(C=N)	ν(NH)	ν(COC)	ν M-N	ν M-X	δ, ppm
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)
$[Co(MQBD)_2Cl_2]$	1616	3318	--	438	352	10.95 (s, 1H, NH), 8.4 (s, 1H, H-C=N), 7.2-8.8 (m, 9H, Ar-H)
$[Co(MQBO)_2Cl_2]$	1614	--	996	454	364	8.3 (s, 1H, H-C=N), 7.5-8.9 (m, 9H, Ar-H)
$[Ni(MQBD)_2Cl_2]$	1622	3312	--	468	252	10.90 (s, 1H, NH), 8.4 (s, 1H, H-C=N), 7.2-8.8 (m, 9H, Ar-H)
$[Ni(MQBO)_2Cl_2]$	1630	--	994	450	260	8.1 (s, 1H, H-C=N), 7.5-8.9 (m, 9H, Ar-H)
$[Cd(MQBD)Cl_2]$	1612	3300	--	432	348	10.85 (s, 1H, NH), 8.3 (s, 1H, H-C=N), 7.2-7.8 (m, 9H, Ar-H)
$[Cd(MQBO)Cl_2]$	1610	--	996	430	362	8.2 (s, 1H, H-C=N), 7.1-8.0 (m, 9H, Ar-H)
$[Zn(MQBD)Cl_2]$	1624	2990	--	428	348	10.90 (s, 1H, NH), 8.1 (s, 1H, H-C=N), 7.2-7.8 (m, 9H, Ar-H)
$[Zn(MQBO)Cl_2]$	1614	--	1002	430	350	8.0 (s, 1H, H-C=N), 7.5-8.9 (m, 9H, Ar-H)

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 Zn(II) complexes compared to the tetrahedral Cd(II) and octahedral Co(II), Ni(II) complexes.

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 liphophilic character of the metal complexes which probably leads to break down of permeability barrier of the cells resulting in interference with normal cell process[25]. Better activities of the metal complexes as compared to free ligand could also be understood in terms of chelation theory[26], which explains that a decrease in polarizability of the metal could enhance the liphophilicity of the complexes.

Table 3. Inhibition zone of bacterial growth (mm)

Compound	*P.aerugenosa*			*S.aureus*		
	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
$[Zn(MQBD)Cl_2]$	2.2	2.7	4.3	2.3	3.1	5.1
$[Cd(MQBD)Cl_2]$	1.8	2.4	3.9	2.0	2.8	4.3
$[Co(MQBD)_2Cl_2]$	1.6	2.0	3.4	1.7	2.3	3.6
$[Ni(MQBD)_2Cl_2]$	1.5	2.0	3.2	1.7	2.2	3.5
$[Zn(MQBO)Cl_2]$	1.8	3.2	4.2	2.1	2.9	4.3
$[Cd(MQBO)Cl_2]$	1.6	2.9	3.7	2.0	2.6	3.9
$[Co(MQBO)_2Cl_2]$	1.5	2.6	3.5	1.6	2.2	3.4
$[Ni(MQBO)_2Cl_2]$	1.5	2.5	3.5	1.6	2.1	3.3

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	*C. albicans*			*A. niger*			*A. flavus*		
	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
$[Zn(MQBD)Cl_2]$	13.2	20.5	29.6	13.2	16.9	23.2	12.4	15.2	27.5
$[Cd(MQBD)Cl_2]$	12.9	18.5	25.6	12.1	16.0	22.4	11.3	14.3	26.3
$[Co(MQBD)_2Cl_2]$	12.7	15.9	23.0	11.3	14.5	21.5	10.6	13.6	25.2
$[Ni(MQBD)_2Cl_2]$	11.6	15.2	22.1	11.0	14.3	21.3	10.5	13.5	25.1
$[Zn(MQBO)Cl_2]$	12.3	19.8	28.5	11.5	14.9	21.1	10.2	14.4	25.3
$[Cd(MQBO)Cl_2]$	11.8	17.8	25.2	10.5	14.1	20.1	9.1	13.5	24.6
$[Co(MQBO)_2Cl_2]$	11.1	15.6	22.0	9.8	13.0	19.3	8.6	12.9	23.4
$[Ni(MQBO)_2Cl_2]$	11.1	14.9	21.5	9.7	12.9	19.2	8.5	12.8	23.2

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