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Sanjay R Kale
Postgraduate Department of Chemistry, Tuljaram Chaturchand College, Baramati, Maharashtra, India

Monali R Nanaware
Postgraduate Department of Chemistry, Tuljaram Chaturchand College, Baramati, Maharashtra, India

Rahul S Bhondwe
Postgraduate Department of Chemistry, Tuljaram Chaturchand College, Baramati, Maharashtra, India

Correspondence
Sanjay R Kale
Postgraduate Department of Chemistry, Tuljaram Chaturchand College, Baramati, Maharashtra, India

Synthesis, UV-visible and ADME study of transition metal complexes of 8-Hydroxyquinoline

Sanjay R Kale, Monali R Nanaware and Rahul S Bhondwe

Abstract
8-HQ is a small planer molecule with a lipophilic effect and a metal chelating ability. As a result, 8-HQ and its derivatives hold medicinal properties such as anti-neurodegenerative, anticancer, antioxidant, antimicrobial, anti-inflammatory and antidiabetic. Metal (II), (IV) and (VI) coordination compounds of 8-Hydroxyquinoline were synthesized by stoichiometric reaction between metal (II), (IV) and (VI) with 8-Hydroxyquinoline in molar ratio at (1: 1) and (1:2) [M: 8-HQ] [Where, M= Ni^{2+}, Cu^{2+}, Co^{2+}, Mn^{2+}]. Characterized by using UV-Visible and swiss ADME. In the current implementation the UV-Visible analysis showed different peaks at range 200-800 nm with showed different absorbance respectively. SwissADME study is carried out for different medicinal and chemical factors such as water solubility, drug likeness, physicochemical properties, lipophilicity, pharmacokinetics and medicinal chemistry of different compounds.

Keywords: 8-HQ, UV-Vis, Ni complex, Cu complex, Co complex, Mn complex, SwissADME

Introduction
Medicinal inorganic chemistry has generated significant interest in the design of the metal complexes as diagnostic and therapeutic agents. Metal complexes always been considered as versatile composition for various industries such as pharmaceutical, agriculture, sensors, dyes, solar cells, paints and polymers. Metals play important role in the biomedicine for human health. 8-Hydroxyquinoline (8-HQ), also known as oxine or 8-quinolinol, is an alkaloid which exists in plants of Asteraceae and Euphorbiaceous families [1]. It is monoprotic, bidentate agent that consists of two donor atoms, oxygen and nitrogen [2]. 8-HQ, a quinoline derivative originating in plants as well as from synthesis, has been used as a fungicide in agriculture and a preservative in the textile, wood and paper industries. The derivatives of 8-HQ exert different, pharmacologically useful, activities such as antimicrobial, antioxidant, anticancer, antituberculotic activity [7, 8, 9]. There are several metal complexes that are already in use for these purposes and this has encouraged further research on new metallodrugs such as metal- mediated antibiotics and anticancer and antiviral compounds [3]. 8-Hydroxyquinoline (Oxyquinoline) (8Quinolinol) behaves as bidentate through (N and O) and its characterizes organic chelating ligand. It has been found that a majority of the metal complexes with (8-HQ) shows biological activity [4]. 8-Hydroxyquinoline having ability to get bonded with metal ion with its phenolic stable chelates with metals the producing stable metal- ligand complexes [5]. The current implementation of 8-HQ with metal (ll), (lV) and (Vl) complexes such as Ni^{2+}, Cu^{2+}, Co^{2+}, Mn^{2+} the prepared complex study using different chemical- physical methods such as UV-Vis and Swiss ADME [6].

Experimental
Materials and Methods: Nickel (ll) chloride hexa hydrate, Copper (ll) chloride dihydrate, Cobalt (ll) chloride hexahydrate, Manganese (ll) chloride tetra hydrate, and ligand 8-Hydroxyquinoline were used as received. Ethanol and 1:1 ammonia was used directly.

UV-Vis (Ultraviolet spectroscopy): Ultraviolet-visible spectroscopy refers to absorption spectroscopy or reflectance spectroscopy in the ultraviolet –visible spectral region. The quantitative study of ultraviolet –visible spectroscopy to measure the absorbance with selected wavelength range from 200 to 800 nm. All metal complexes are soluble in chloroform.

Weight accurately 0.01 gm dissolve in 10 ml chloroform then filter the ordinary filter paper for remove some impurities. Sample loaded in Shimadzu UV 1800 (Shimadzu, Kyoto, Japan) spectrophotometer. Record the maximum wavelength one by one.

Swiss ADME (Absorption Distribution Metabolism and Excretion): Swiss ADME software (www.swissadme.ch) is a free web tool to evaluate physicochemical properties, pharmacokinetics, drug-likeness, lipophilicity, BBB permeant, skin permeation, bioavailability score and medicinal chemistry friendliness of small molecules.

Synthesis: Preparation of Metal Complexes of metal salts with ligand 8-Hydroxyquinoline. Metal complexes were synthesized by equimolar concentration of 8-Hydroxyquinoline (1 gm) was dissolve in ethyl alcohol and the solution was added to 1.00 gm of respective metal salts ($NiCl_2.6H_2O$, $CuCl_2.2H_2O$, $CoCl_2.6H_2O$, $MnCl_2.4H_2O$. The resultant mixture was stirred on hot plated magnetic stirrer at the temperature 50 to 60 °C. The metal complexes were obtained as precipitates which were filtered ordinary filter paper and dried at room temperature or under IR lamp. The proposed structures and the schematic presentation of the synthesis of metal complexes are presented in Figures 1.

Nickel complex; $[NiC_{18}H_{12}O_2N_2].6H_2O$ (Yield: 0.82g, 71.30%), Elemental analysis, Ni, 16.91; C, 62.31; H, 3.49; O, 9.22; N, 8.07. Nickel plays a role as a cofactor. Divalent metal cation, complex with 8- HQ shows paramagnetic nature.

Copper complex; $[CuC_{18}H_{12}O_2N_2].2H_2O$ (Yield: 2.67g, 97.44%), Elemental analysis, Cu, 18.06; C, 61.45; H, 3.44; O, 9.09; N, 7.96. Copper is the most essential metal for human body. It works with iron to help body form red blood cells. Copper also helps keep blood vessels, nerves, immune system, and bones healthy. Divalent metal cation, complex with 8- HQ shows paramagnetic nature.

Cobalt complex; $[CoC_{18}H_{12}O_2N_2].6H_2O$ (Yield: 2.34g, 72.44%), Elemental analysis, Co, 16.97; C, 62.26; H, 3.48; O, 9.21; N, 8.07. Cobalt metal is the part of Vitamin B-12. This vitamin is essential for making red blood cells. Divalent metal cation, complex with 8-HQ shows paramagnetic nature.

Manganese complex; $[MnC_{18}H_{12}O_2N_2].4H_2O$ (Yield: 1.76g, 71.54%), Elemental analysis, Mn, 16.01; C, 62.99; H, 3.52; O, 9.32; N, 8.16. Manganese metal is an essential nutrient necessary for a variety of metabolic functions including those involved in normal human development, energy metabolism. Divalent metal cation, complex with 8-HQ shows geometry with paramagnetic nature.

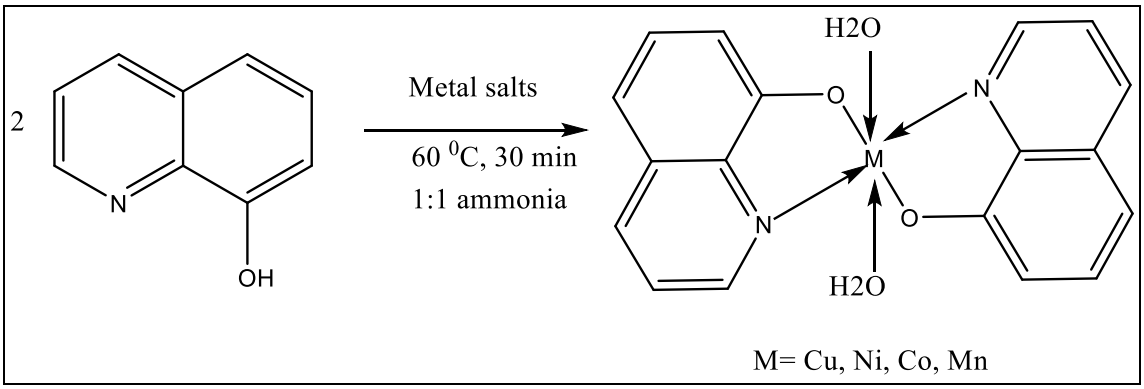

Fig 1: Schematic representation of the synthesis of the complexes.

Result

The qualitative study of Ultra-Violet Visible Spectroscopy to measure the absorbance with selected wavelength range from 200 to 800 nm. All metal complexes are soluble in chloroform. Weight accurately 0.01 gm dissolve in 10 ml chloroform filter the ordinary filter paper. Record the λ_{max} one by one.

Table 1: UV- Visible spectrum Peak Value of prepared Metal complexes

Sr. No	Complex	Wavelength in nm	Absorbance
1	Ni complex	506	0.226
2	Cu complex	336	2.058
3	Co complex	342	2.46
4	Mn complex	398	1.527

The result on prognostic data for Physicochemical properties, Lipophilicity, Water solubility, Pharmacokinetics, Drug likeness and Medicinal chemistry friendliness of prepared 6 metal complexes such as Nickel complex, Copper complex, Cobalt complex, Manganese complex, In table 2, Molecular weight and molecular formula were obtained. Ligand 8-HQ [C_9H_7ON, 145.05 g/mol], Ni complex [$NiC_{18}H_{12}O_2N_2$, 346.99 g/mol], Cu complex [$CuC_{18}H_{12}O_2N_2$, 351.85 g/mol], Co complex [$CoC_{18}H_{12}O_2N_2$, 347.23 g/mol], Mn complex [$MnC_{18}H_{12}O_2N_2$, 343.24 g/mol.

Table 2: General characteristics of Metal complexes

Sr. No.	Compound	Molecular formula	Canonical smiles	Molecular weight (in g/mol)
1	8-HQ	C_9H_7ON	OC1=CC=CC2=C1N=CC=C2	145.05
2	Ni complex	$NiC_{18}H_{12}O_2N_2$	O1C2=CC=CC3=C2[N](=CC=C3)[Ni]11OC2=CC=CC3=C2[N]1=CC=C3	346.99
3	Cu complex	$CuC_{18}H_{12}O_2N_2$	O1C2=CC=CC3=C2[N](=CC=C3)[Cu]11OC2=CC=C2[N]1=CC=C3	351.85
4	Co complex	$CoC_{18}H_{12}O_2N_2$	O1C2=CC=CC3=C2[N](=CC=C3)[Co]11OC2=CC=C2[N]1=CC=C3	347.23
5	Mn complex	$MnC_{18}H_{12}O_2N_2$	O1C2=CC=CC3=C2[N](=CC=C3)[Mn]11OC2=CC=C2[N]1=CC=C3	343.24

In table 3, in case of Lipophilicity, five different parameters such as iLOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT were also obtained. For iLOGP, 8-HQ and respective all metal complexes were 0. For XLOGP3, Ni complex (4.72), Cu complex (4.72), Co complex (4.72) and Mn (4.72) showed lower value. For WLOGP, Ni complex (4.16), Co complex (4.16), Mn complex (4.16) Cu complex (4.15) showed lower value. For MLOGP, Ni complex (1.97), Cu complex (1.97), Co complex (1.97), Mn complex (1.97) showed lower value. For SILICOS-IT, Cu complex (-1.58), Ni complex (-1.61), Co complex (-1.61), Mn complex (-1.63).

Table 3: Lipophilicity of the prepared Metal complexes

Sr. No.	Compound	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log $P_{o/w}$
1	8-HQ	1.65	2.02	1.94	1.19	2.01	1.76
2	Ni	0	4.72	4.16	1.97	-1.61	1.85
3	Cu	0	4.72	4.15	1.97	-1.58	1.85
4	Co	0	4.72	4.16	1.97	-1.61	1.85
5	Mn	0	4.72	4.16	1.97	-1.63	1.84

In table 4, in SwissADME to predict water solubility, first one is the application of the ESOL model. The water solubility data obtained for solubility. E.g., 8-HQ soluble compound; Ni complex, Cu complex, Co complex, Mn complex moderately soluble compound. Second one is application of the Ali. The water solubility data obtained for solubility of compound. e.g., 8-HQ soluble compound, Ni complex, Cu complex, Co complex, Mn complex moderately soluble compound; The third predictor of SwissADME was developed for SILICOS-IT. The water solubility data obtained. e.g., 8-HQ soluble compound; Ni complex, Cu complex, Co complex, Mn complex moderately soluble compound.

Table 4: Water solubility of the prepared Metal complexes

Compound	ESOL				Ali				SILICOS- IT			
	Log S (ESOL)	Solubility		Class	Log S (ESOL)	Solubility		Class	Log S (ESOL)	Solubility		Class
		mg/ml	mol/L			mg/ml	mol/L			mg/ml	mol/L	
8-HQ	-2.69	3.00e-01	2.06e-03	Soluble	-2.34	6.59e-01	4.54e-03	Soluble	-3.10	1.15e-01	7.91e-04	Soluble
Ni	-5.61	8.5e-04	2.46e-06	Moderately soluble	-5.04	3.14e-03	9.04e-06	Moderately soluble	-5.52	1.06e-03	3.05e-06	Moderately soluble
Cu	-5.64	8.09e-04	2.30e-06	Moderately soluble	-5.04	3.18e-03	9.04e-06	Moderately soluble	-5.53	1.04e-03	2.96e-06	Moderately soluble
Co	-5.61	8.53e-04	2.46e-06	Moderately soluble	-5.04	3.14e-03	9.04e-06	Moderately soluble	-5.52	1.06e-03	3.04e-06	Moderately soluble
Mn	-5.59	8.92e-04	2.60e-06	Moderately soluble	-5.04	3.10e-03	9.04e-06	Moderately soluble	-5.50	1.07e-03	3.13e-06	Moderately soluble

Table 5: Pharmacokinetic Parameters of the Prepared Metal complexes

Compound	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2D9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K_P (cm/s)
8-HQ	High	Yes	No	Yes	No	No	No	No	-5.75
Ni	High	Yes	Yes	Yes	No	Yes	Yes	Yes	-5.07
Cu	High	Yes	Yes	Yes	No	Yes	Yes	Yes	-5.10
Co	High	Yes	Yes	Yes	No	Yes	Yes	Yes	-5.07
Mn	High	Yes	Yes	Yes	No	Yes	Yes	Yes	-5.04

In table 5, in SwissADME for pharmacokinetics predictions, the GI absorption rate was high for ligand 8-HQ and respective all complexes. The Blood Brain Barrier (BBB) permeability observed in ligand 8-HQ, Ni complex, Cu complex, Co complex, Mn complex. In case of P-gp substrate, respective all metal complexes showed P-gp substrate but ligand 8-HQ doesn't show. For CYP1A2 inhibitor, ligand 8-HQ and respective all metal complexes showed this inhibitor. The ligand 8-HQ and metal complexes such as Ni complex, Cu complex, Co complex, Mn complex did not show CYP2C19 inhibitor.

For metal complexes Ni complex, Cu complex, Co complex, Mn complex showed CYP2D9 inhibitor while ligand 8-HQ. In case of CYP2D6 and CYP3A4 inhibitors, metal complex such as Ni complex, Cu complex, Co complex, Mn complex showed CYP2D6 and CYP3A4 inhibitor while Ligand 8-HQ, For the skin permeability (Log K_P, cm/s), higher negative values are obtained for ligand 8-HQ (-5.75) followed by Cu complex (-5.10), Ni complex (-5.07), Co complex (-5.07), Mn complex (-5.04).

Table 6: Drug likeness predictions of prepared Metal complexes

Compound	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
8-HQ	Yes; 0 violation	No; 2 violations: MW<160, #atoms<20	Yes	Yes	No; 1 violation: MW<200	0.55
Ni	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
Cu	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
Co	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
Mn	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55

In table 6, for drug likeness predictions, ligand 8-HQ, Ni complex, Cu complex, Co complex, Mn complex were obtained for Lipinski rule as 0 violations except. In case of Ghose filter, Ni complex, Cu complex, Co complex, Mn complex showed Ghose 0 violations while 8-HQ were obtained 2 violations. For the Veber filter, ligand 8-HQ and respective all metal complexes were showed 0 violation. For Egan filter, 0 violations were observed for ligand 8-HQ, Ni complex, Cu complex, Co complex, Mn complex while 1 violation was obtained.

Ni complex, Cu complex, Co complex Mn complex showed 0 violation while 8-HQ were obtained violation as 1. The Bioavailability Score were obtained for studied ligand 8-HQ and for respective all metal complexes (0.55) such as Ni complex, Cu complex, Co complex, Mn complex.

Table 7: Medicinal Chemistry properties of prepared Metal complexes

Compound	Pains	Brenk	Leadlikeness	Synthetic accessibility
8-HQ	0 alert	0 alert	No; 1 violation: MW<250	1.07
Ni	0 alert	0 alert	No; 1 violation: XLOGP3>3.5	3.70
Cu	0 alert	0 alert	No; 2 violations: MW>350, XLOGP3>3.5	3.73
Co	0 alert	0 alert	No; 1 violation: XLOGP3>3.5	4.23
Mn	0 alert	0 alert	No; 1 violation: XLOGP3>3.5	4.10

In table 7, for Medicinal chemistry prediction, the PAINS obtained 0 violation for ligand 8-HQ and respective all metal complex such as Ni complex, Cu complex, Co complex, Mn complex, In leadlikeness were obtained 1 violations for 8-HQ, Ni complex, Co complex, Mn complex while Cu complex were obtained violations as 2. In synthetic accessibility parameter score showed in a following manner as Co complex (4.23), Mn complex (4.10), Cu complex (3.73), Ni complex (3.70) and ligand 8-HQ (1.07).

Conclusion

Based on the obtained results, it is concluded that nickel, copper, cobalt, manganese forms with 8-HQ a complex of square-planner geometry while zirconium and molybdenum forms with 8-HQ a complex of octahedral geometry. The synthesized complexes of metal ions with 8-HQ show good practical yield and high Antioxidant, Antitumor activity, Good bioavailability score, Less toxic complexes.

Conflict of Interest

The authors have no conflicts of interest regarding this investigation.

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