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3-(((8-HYDROXYQUINOLIN-5-YL)AMINO)METHYL)-5-(4-METHOXYPHENYL)-1,3,4-OXADIAZOLE-2(3H)-THIONE (HAMMOT) AND ITS METAL (II) COMPLEXES: SYNTHESIS AND ANTIMICROBIAL STUDY

M F Tank[*1], G D Acharya[2]

[1]*Government Polytechnic, Palanpur-385001(Gujarat), India.*
[2]*Head, Dept. of Chemistry, R.R.Mehta College of Science & C.L.Parikh College of Commerce, Palanpur-385001(Gujarat), India.*
[*]*E-mail: maheshftank@gmail.com*

Abstract
A novel clubbed molecule 3-(((8-hydroxyquinolin-5-yl)amino)methyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole-2(3H)-thione (HAMMOT) was synthesized through Mannich condensation reaction among 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2(3H)-thione, formaldehyde and 5-amino-8-hydroxyquinoline hydrochloride. Then some transition metal (II) complexes of novel ligand (HAMMOT) were prepared using transition metal (II) salts. Novel clubbed molecule (HAMMOT) and its metal (II) complexes were analyzed by spectroscopic techniques and elemental analysis. Furthermore, in vitro antimicrobial activities of all the newly synthesized compounds were measured using agar cup plate method. Novel clubbed molecule and its metal (II) complexes displayed moderate to good antibacterial and antifungal activity.

Keywords 1,3,4-oxadiazole-2(3H)-thione, 5-amino-8-hydroxyquinoline, Mannich condensation, transition metal (II) complexes, spectral studies, antimicrobial activity

Introduction

Novel antimicrobial agents are always in demand due to the worldwide spread of drug-resistant pathogens[I]. Multidrug resistance (MDR) of bacteria is a serious problem threatening the health of people[II]. Therefore, development of antibacterial molecules having new structural characteristic and broad-spectrum of antimicrobial activity against resistant pathogens is required. Clubbed molecules having different pharmacophores may afford good biological activities[III].

Nitrogen heterocycles play an important role in medicinal chemistry due to their diverse pharmacological and biological activities. In medicinal chemistry, the role of 8-hydroxyquinoline derivatives (8HQs) is noteworthy due to their varied biological properties like antiamoebic, antimalarial, antiallergic, antineoplastic, anticancer, antileishmanial and antifungal efficiency[IV-XII]. A series of 8HQ derivatives, such as 5-chloro-7-iodo-8-hydroxyquinoline, or clioquinol (CQ), 5-((4-(prop-2-ynyl)piperazin-1-yl)methyl)quinolin-8-ol, 5-((methyl(prop-2-ynyl)amino)methyl)quinolin-8-ol, and 5-((4-(2-hydroxyethyl)piperazin-1-yl)methyl)quinolin-8-ol have been reported to exert potent

antineurodegenerative effects[XIII]. As a Cu chelator, CQ exerts selective antiangiogenesis activity[XIV] toward breast cancer[XV], prostate cancer[XVI] leukemia, and myeloma[XVII] with less effect on normal cells. Antimicrobial properties like antibacterial[XVIII-XX], antimalarial[XXI-XXIII], antiviral[XXIV], antitubercular[XXV], and antidental plaque activities[XXVI-XXVII] of 8HQ and its derivatives have also been reported. 8HQ has been found to be non-carcinogenic and is employed for in vitro assays as well as genetic toxicity[XXVIII]. 8-Hydroxyquinoline, at concentrations of 10-50 µg/mL, rapidly and selectively inhibits RNA synthesis in fission yeast. Protein synthesis, cell growth and uridine uptake are not immediately affected. The mechanism of inhibition appears to be by chelation of divalent cations required for RNA synthesis. The effects of 8-hydroxyquinoline are remarkably similar to those of the antibiotic lomofungin[XXIX]. Iron bound to the lipophilic chelator (8HQ), results in substantial DNA-strand breakage of cultured human lung cells[XXX]. The Fe-8HQ complex acts as a cytostatic drug[XXXI]. Due to high lipophilicity, 8HQ can penetrate bacterial cell membrane and arrive at metal-binding site of bacterial enzymes. The metal-8HQ complex dissociates into a 1:1 ratio of 8HQ-metal charged complex and 8HQ free ligand[XXXII]. The charged 8HQ metal complex can bind and block the metal-binding sites on bacterial enzymes that offer the antimicrobial activity[XXXIII]. In addition, the dissociated free ligand of 8HQ possesses high chelating ability that could bind metallic prosthetic groups of microbial enzymes thereby leading to the inhibition of enzymatic activity[XXXII]. 8HQ-uracil metal complexes exhibited growth inhibition against many strains of Gram-positive and Gram-negative bacteria including resistant pathogens, such as *S. aureus*, *Enterococcus faecalis*, and *Candida albicans*[XXXIV].Among the groups of tested metal-binding compounds, 8HQ exhibited high antiviral activity with approximately 50-fold higher activity[XXXV].

Like 8HQ, Oxadiazole core also is a fertile source of bioactivity in the field of medicinal chemistry owing to wide-ranging pharmacological and biological activities. A large number of oxadiazole compounds have shown a wide range of antimicrobial activity[XXXVI-XLII]. 1,3,4-oxadiazoles have shown therapeutic values like antimicrobial[XLIII-XLV], antituberculosis[XLV-XLVII,] anticancer[XLVIII], anti-inflammatory[XLIX], anticonvulsant[L], CNS Stimulant[LI], antihypertensive[LII], hypnotic and sedative activities[LIII]. Quinoline-oxadiazole hybrid derivatives have shown potent antibacterial as well as antifungal activities[LIV].

Hence, it was thought of interest to club two different pharmacophores-oxadiazole and 8HQ for enhancement of biological activity. The present communication comprises the synthesis, characterization and antimicrobial study of a novel clubbed molecule 3-(((8-hydroxyquinolin-5-yl)amino)methyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole-2(3H)-thione(HAMMOT) and some transition metal complexes of it.

Methodology

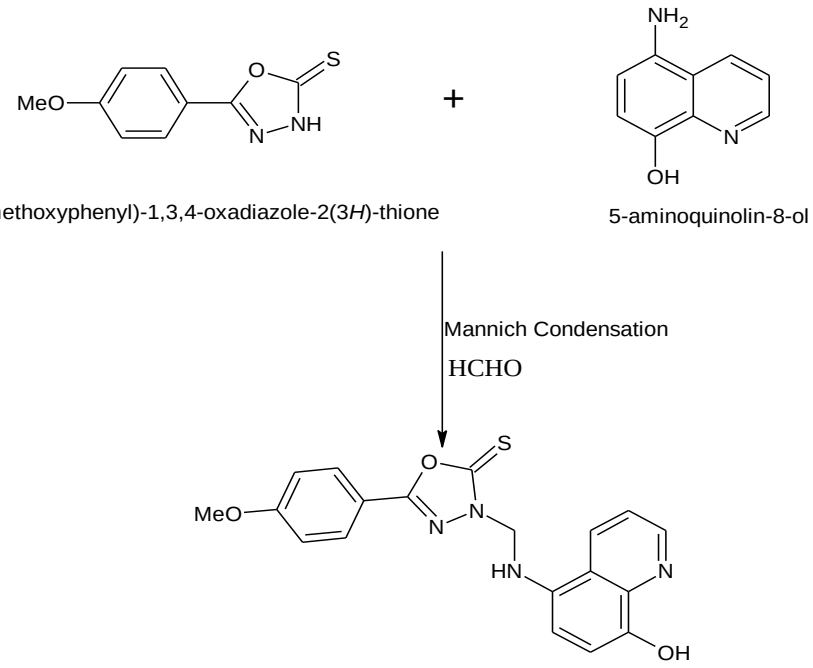
Experimental

Melting points were determined by standard open capillary method and are uncorrected. Elemental analysis was performed with Perkins Elmer (USA) 2400-II CHN analyzer. The FT-IR spectra were recorded on Perkin Elmer Spectrum GX spectrophotometer using KBr pellets. The ^{1}H NMR spectra were recorded on Bruker 400 MHz instrument using DMSO-d6 as solvent and TMS as internal reference standard. Magnetic moments were determined by the Gouy method using mercury tetrathiocyanatocobaltate(II) [$HgCo(NCS)_4$] as calibrant and the diamagnetic correction was made using Pascal's constant. The metal contents of the complexes were analyzed by EDTA titration after decomposing the organic matter with $HClO_4$, H_2SO_4 and HNO_3 (1:1.5:2.5) mixture[LV].

Synthesis of novel clubbed molecule (HAMMOT)

First of all 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2(3H)-thione was prepared as per reported procedures[LVI-LVII]. Then, novel clubbed molecule 3-(((8-hydroxyquinolin-5-

yl)amino)methyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole-2(3H)-thione (HAMMOT) was synthesized through Mannich condensation reaction[LVIII-LIX] of 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2(3H)-thione with formaldehyde and 5-amino-8-hydroxyquinoline hydrochloride (Scheme 1). A mixture of 5-amino-8-hydroxyquinoline hydrochloride (0.01 mol), 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2(3H)-thione (0.01 mol), formaldehyde (0.03 mol) and few drops of concentrated hydrochloric acid in isopropanol (50 mL) was stirred and warmed on the steam bath for about ten hours. End of reaction was monitored by TLC. Then isopropanol was distilled out and water was added to extract product into aqueous layer. Methylene dichloride (50 mL) was charged to extract impurities and aqueous layer basified using 10% NaOH solution and extract product in methylene dichloride (2 X 50 mL). Finally organic layer dried over Na_2SO_4 and distilled out atmospherically and finally apply vacuum to get a product. The physicochemical parameters and characteristic FT-IR frequencies are presented in Tables 1 and 2 respectively.



5-(4-methoxyphenyl)-1,3,4-oxadiazole-2(3*H*)-thione

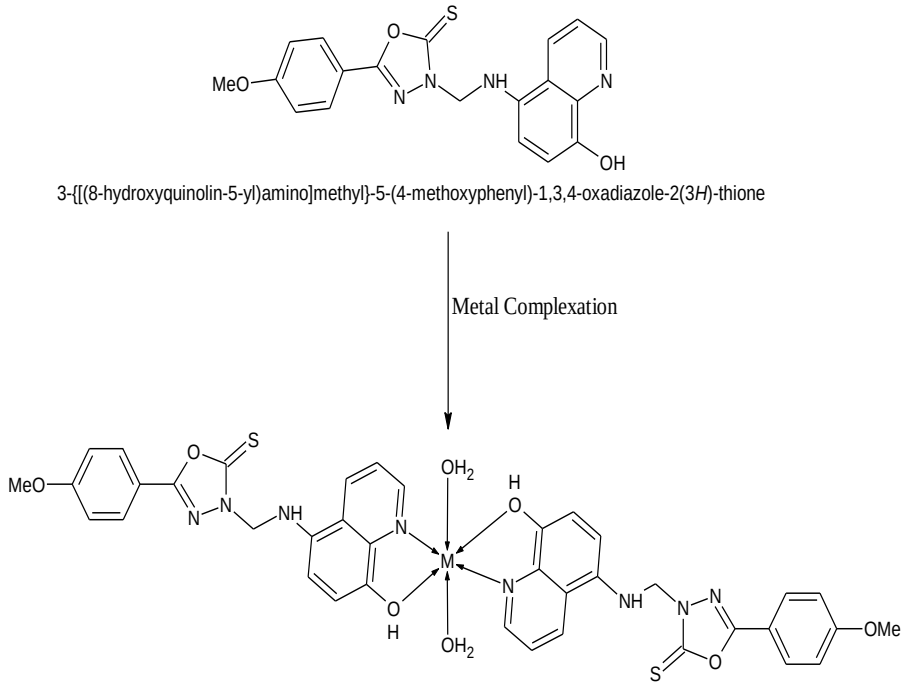
5-aminoquinolin-8-ol

3-{[(8-hydroxyquinolin-5-yl)amino]methyl}-5-(4-methoxyphenyl)-1,3,4-oxadiazole-2(3*H*)-thione

Scheme 1

General procedure for the synthesis of metal complexes

Metal (II) complexes were synthesized using reported procedure[LX]. A hot solution of transition metal (II) salt (2.5 mmol) in 50% aqueous formic acid (2.5 mL) was added drop-wisely with continuous stirring to the hot 20% aqueous formic acid solution (20 mL) of HAMMOT (5 mmol). With the proper adjustment of the pH (~8.5) using 50% NH_4OH solution, the resultant mixture was further digested for 4 hours in the water bath (Scheme 2). The obtained solid product was filtered, washed with hot water, and subsequently with small quantity of ethanol, acetonitrile and dried in a vacuum desiccator. The physicochemical parameters and characteristic FT-IR frequencies of metal (II) complexes are summarized in Tables 1 and 2 respectively.



Scheme 2

***In vitro* evaluation of antibacterial and antifungal activity**

Novel clubbed molecule HAMMOT and its metal (II) complexes were screened for in vitro antimicrobial activity against the representative panel of two Gram-positive and two Gram-negative bacterial strains and two strains of fungi[LXI] taking ciprofloxacin as a reference standard drug. To evaluate antimicrobial activities, agar cup plate method was used. Antibacterial activities were evaluated against Gram-positive bacterial strains: *Staphylococcus aureus, Bacillus subtilis* and Gram-negative bacterial strains: Escherichia coli, *Pseudomonas aeruginosa* at 50 µg/mL concentration. Zone of inhibition was recorded in mm. Antifungal activities were evaluated against fungal strains: *Aspergillus niger* and *Aspergillus flavus* at 1000 ppm concentration. Newly synthesized compounds exhibited moderate to good inhibitory action towards test organisms.

Results and Discussion

The synthesized 3-(((8-hydroxyquinolin-5-yl)amino)methyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole-2(3H)-thione (HAMMOT) appears as colourless crystals. It is partially soluble in acetone, methanol, ethanol and acetonitrile, while it is soluble in polar organic solvents like dimethylformamide (DMF), dimethylsulphoxide (DMSO), organic acids and pyridine. Metal (II) complexes [M(II) $(HAMMOT)_2(H_2O)_2$] have characteristic colour, are stable in air, and are practically insoluble in water, ethanol, methanol, chloroform and hexane.

The FT-IR spectra of HAMMOT and its metal complexes demonstrating all the important stretching and bending vibrations in appropriate region are summarized in Table 2. In the spectrum of HAMMOT the absorption band at 3299 cm^{-1} is due to O-H stretching vibration and the strong band at 1408 cm^{-1} to O-H bending vibration[LXII]. The CH_2 group shows C-H stretching vibration band at 2968 cm^{-1}. The bands at 1596 cm^{-1} for C=N, at 1500 cm^{-1} for C=C and at 1478 cm^{-1} for C-C bond, assigned to the aromatic skeletal stretching vibrations of parent heterocyclic ring[LXII]. The N-H stretching vibrations appeared near 3240 cm^{-1}, while N-H and C-N bending vibrations appeared at 1657 and 1263 cm^{-1}, respectively. However, a

comparison of IR spectra of ligand and its metal (II) coordinated complexes exhibited some significant characteristic differences[LXIII]. One of the considerable differences to be expected was the presence of more broadened band in the region of 2700-3400 cm^{-1} for the chelates. As the oxygen atom of the OH group of the ligand forms a coordination bond with the metal ions, the broadening of this band may be attributed to the presence of coordinated water molecules[LXIV]. The band due to the C=N stretching vibration at around 1596 cm^{-1} was shifted to lower frequency, whereas, the band at 1408 cm^{-1} in the spectrum of HAMMOT assigned to in-plane OH deformation was shifted towards higher frequency in the spectra of the chelates due to the formation of M-O bond[LXV]. This has been further confirmed by the presence of a weak band at 1095 cm^{-1} for C-O-M stretching mode, while bands around ~770 cm^{-1} and ~523 cm^{-1} correspond to the N→M vibration[LXVI]. All these characteristics features of the FT-IR studies unveil the formation of HAMMOT and metal (II) complexes. Structural analysis of the ligand was also carried out with the help of ^{1}H NMR using DMSO-d6 at room temperature. In case of ^{1}H NMR spectrum of HAMMOT exhibited 3.82 (d, 2H, -CH_2-), 5.84 (t, 1H, NH), 6.74-7.92 (m, 8H, Ar-H), 9.00 (dd, 1H, H2 of quinoline), 9.72 (bs, 1H, OH). ^{1}H-NMR spectrum of [Zn(HAMMOT)$_2$] exhibited 3.90 (d, 4H, -CH_2-), 5.82 (t, 2H, NH), 6.58-8.05 (m, 16H, Ar-H), 8.94 (dd, 2H, H2 of quinoline). By comparing the ^{1}H-NMR data of the ligand and the metal complex of Zn(II), it was concluded that, a broad singlet at δ 9.72 ppm due to the OH proton[LXVII] will disappear in the spectrum of Zn(II) complex suggested that this proton has been lost due to coordination of oxygen atom to the metal ion[LXVIII]. The H2 signal of the Zn(II) complex appeared at low magnetic field (δ 9.00) compared to that of ligand (δ 8.94), suggesting the involvement of N1 in the formation of complex. The absorptions of all quinoline protons are slightly downfield shifted; except H7 which is upfield shifted[LXIX] which further indicate the coordination of oxygen atom to metal ion. The results of the magnetic moment value (Table 1) were shown to have octahedral geometry for all the metal complexes.

Table 1 Physicochemical parameters of ligand (HAMMOT) and its metal complexes

Empirical formula of ligand / metal complexes	**Mole. Weight**	**% Yield**	**m.p.** (°C)	**Elemental Analysis calc. % (found %)**					**μ_{eff} B.M. (expected)**
				C	**H**	**N**	**S**	**metal**	
HAMMOT $C_{19}H_{16}N_4O_3S$	380	70	165	60.00 (60.0)	4.21 (4.2)	14.73 (14.7)	8.42 (8.4)	--	--
[Mn(HAMMOT)$_2$(H_2O)$_2$] $C_{38}H_{34}MnN_8O_8S_2$	849	66	>300	53.71 (53.69)	4.00 (3.96)	13.19 (13.15)	7.53 (7.50)	6.47 (6.45)	5.56 (5.2-6.0)
[Co(HAMMOT)$_2$(H_2O)$_2$] $C_{38}H_{34}CoN_8O_8S_2$	853	65	>300	53.45 (53.41)	3.98 (3.94)	13.13 (13.10)	7.50 (7.48)	6.91 (6.88)	4.92 (4.4-5.2)
[Ni(HAMMOT)$_2$(H_2O)$_2$] $C_{38}H_{34}NiN_8O_8S_2$	853	67	>300	53.45 (53.42)	3.98 (3.93)	13.13 (13.10)	7.50 (7.49)	6.91 (6.87)	3.24 (2.9-3.4)
[Cu(HAMMOT)$_2$(H_2O)$_2$] $C_{38}H_{34}CuN_8O_8S_2$	857.5	62	>300	53.17 (53.15)	3.96 (3.93)	13.06 (13.00)	7.46 (7.45)	7.40 (7.38)	1.80 (1.7-2.2)
[Zn(HAMMOT)$_2$(H_2O)$_2$] $C_{38}H_{34}ZnN_8O_8S_2$	859	64	>300	53.08 (53.00)	3.95 (3.94)	13.03 (13.00)	7.45 (7.43)	7.56 (7.50)	diamagnetic

Table 2 FT-IR spectral frequencies of ligand (HAMMOT) and its metal complexes (in cm^{-1})

Compound	**ν(O–H)**	**ν(C=N)**	**ν(N→M)**	**ν(N→M)**	**ν(O→M)**	**ν(C-O-M)**
$[Mn(HAMMOT)_2(H_2O)_2]$	3370(br)	1566	521	768	1423	1091
$[Co(HAMMOT)_2(H_2O)_2]$	3376(br)	1573	522	763	1424	1092
$[Ni(HAMMOT)_2(H_2O)_2]$	3373(br)	1569	518	772	1421	1097
$[Cu(HAMMOT)_2(H_2O)_2]$	3375(br)	1578	524	770	1427	1089
$[Zn(HAMMOT)_2(H_2O)_2]$	3372(br)	1571	521	764	1420	1093
HAMMOT	3299	1596	--	--	--	--

Table 3 Antimicrobial activities of ligand (HAMMOT) and its metal complexes

Compound	**Zone of inhibition (mm)[a]**					
	Antibacterial activity				**Antifungal activity**	
	S.aureus	***B.subtillis***	***E.coli***	***P.aerugionsa***	***A.niger***	***A.flavus***
5AHQ	24	22	26	22	21	19
HAMMOT	31	32.5	29	30	36	33
$[Mn(HAMMOT)_2(H_2O)_2]$	15	13	13	14	12	11
$[Co(HAMMOT)_2(H_2O)_2]$	176	15.5	16	16.5	13	17
$[Ni(HAMMOT)_2(H_2O)_2]$	18.5	17	13	18	15	16
$[Cu(HAMMOT)_2(H_2O)_2]$	22	23.5	22	20	21	20
$[Zn(HAMMOT)_2(H_2O)_2]$	14.5	15	11	11.5	13	14
Ciprofloxacin	28	42	26	35	44	38

[a] : Results are taken in triplicate and average are shown.

Conclusion

The novel clubbed molecule 3-(((8-hydroxyquinolin-5-yl)amino)methyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole-2(3H)-thione (HAMMOT) and its octahedral metal (II) complexes (1:2 metal to ligand ratio) were synthesized and characterized. They showed moderate to good antibacterial and antifungal activities compared to 8-hydroxyquinoline. This might be due to the additive biological effect-lipophilicity of parent molecules and/or due to the metal chelating properties. Among the complexes, Cu(II) complex displayed better activity which was comparable to Ciprofloxacin, but was found less active than HAMMOT.

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