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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF 3-(((8-HYDROXYQUINOLIN-5-YL)AMINO)METHYL)-5-(1-NAPHTHYL)-1,3,4-OXADIAZOLE-2(3H)-THIONE AND ITS OCTAHEDRAL METAL (II) COMPLEXES

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Abstract
Through Mannich condensation reaction of 5-(1-naphthyl)-1,3,4-oxadiazole-2(3H)-thione with formaldehyde and 5-amino-8-hydroxyquinoline hydrochloride (AHQ), a novel hybrid ligand: 3-(((8-hydroxyquinolin-5-yl)amino)methyl)-5-(1-naphthyl)-1,3,4-oxadiazole-2(3H)-thione (HAMNOT) was synthesized. Octahedral metal (II) complexes of newly synthesized hybrid ligand were prepared using various 3d-transition metal (II) salts. Newly synthesized hybrid ligand and its octahedral metal (II) complexes were analyzed and characterized by spectroscopic techniques and elemental analysis. Evaluation for in vitro antimicrobial activities of all the newly synthesized compounds was carried out. Some newly synthesized compounds have shown moderate to good antimicrobial activities.

Keywords 5-(1-naphthyl)-1,3,4-oxadiazole-2(3H)-thione, 8-hydroxyquinoline(oxine), Mannich condensation, octahedral metal (II) complexes, antimicrobial activity

Introduction

World is highly affected because of antimicrobial resistance (AMR) and multidrug resistance (MDR) of bacteria[I]. So quality medicine is essential to address the global threat of antimicrobial resistance and drug-resistant pathogens[II]. A pharmacophore refers to the essential steric and electronic features of a molecule responsible for its biological activity. Hybrid molecules possessing mixed pharmacophores may display good antimicrobial activities[III].

The 8-hydroxyquinoline (8HQ) core is a well-recognized pharmacophore with diverse therapeutic potential, primarily due to its ability to chelate metal ions and interact with biological targets. 8-hydroxyquinoline (oxine) and its oxinates possess important role in medicinal chemistry due to their varied pharmacological and biological activities like antibacterial, antiamoebic, antiviral, antimalarial, antiallergic, antineoplastic, anticancer, antitubercular, antileishmanial and antifungal efficiency[IV-XII]. Oxine 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 8-hydroxyquinoline (oxine) and its derivatives have also been reported. Oxine has been found to be non-carcinogenic and is employed for in vitro assays as well as genetic toxicity. Oxine, at concentrations of 10-50 µg/mL, rapidly and selectively inhibits RNA synthesis in fission yeast. The mechanism of inhibition appears to be by chelation of divalent cations required for RNA synthesis. The effects of oxine are remarkably similar to those of the antibiotic lomofungin. The Fe- oxine complex acts as a cytostatic drug. Because of high lipophilicity, oxine can penetrate bacterial cell membrane and arrive at metal-binding site of bacterial enzymes. The metal- oxine complex dissociates into a 1:1 ratio of oxine -metal charged complex and oxine free ligand. The charged oxine metal complex can bind and block the metal-binding sites on bacterial enzymes that offer the antimicrobial activity. The dissociated free ligand of oxine possesses high chelating ability that could bind metallic prosthetic groups of microbial enzymes thereby leading to the inhibition of enzymatic activity. Oxine-uracil metal complexes displayed growth inhibition against many strains of Gram-positive and Gram-negative bacteria including resistant pathogens, such as *S. aureus*, *Enterococcus faecalis*, and *Candida albicans*[XXVIII-XXXV]. 5-amino-8-hydroxyquinoline is a notable pharmacophore scaffold in medicinal chemistry. Hydroxyl Group (-OH) at position 8 is crucial for hydrogen bonding and metal chelation, which are key to its mechanism of action e.g., inhibiting proteasomes or acting as an ionophore. Amino Group ($-NH_2$) at position 5 acts as a hydrogen bond donor/acceptor and influences the electronic properties and specific interactions with target proteins. The pyridyl nitrogen also acts as a potential protonation site and a metal-binding site, working in concert with the hydroxyl group for chelation.

An oxadiazole is a pharmacophore found in many drugs due to its ability to act as a scaffold, form hydrogen bonds, and exhibit metabolic stability. It is a versatile core structure for designing molecules with diverse activities, including anticancer, antimicrobial, anti-inflammatory, and antidiabetic properties. Different isomers, such as 1,2,4- and 1,3,4-oxadiazole, are used to target a variety of biological mechanisms. The oxadiazole ring is a metabolically stable five-membered heterocycle that provides a rigid framework for attaching other functional groups. Oxadiazole nucleus is a fruitful source of bioactivity in the field of medicinal chemistry owing to broad spectrum pharmacological and biological activities. Series of oxadiazole compounds have displayed a wide range of antimicrobial activities[XXXVI-XLII]. The 2-thioxo-2,3-dihydro-1,3,4-oxadiazole (1,3,4-oxadiazole-2(3H)-thione) structure is a key building block due to its diverse pharmacological properties and ability to act as a bioisostere for other functional groups. The 1,3,4-oxadiazole-2(3H)-thione nucleus remains a vital and highly versatile scaffold in modern medicinal chemistry. Its straightforward synthesis and the ability to readily modify its structure have led to the discovery of numerous derivatives with diverse and potent pharmacological activities. 1,3,4-oxadiazole derivatives 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]. The oxadiazole structure can be decorated with different substituents to tune its properties and target a wide range of enzymes and receptors. Its significance lies in its unique physicochemical properties, which allow it to act as a stable bioisostere for functional groups like esters and amides, enhance molecular rigidity, and facilitate crucial interactions with biological targets. Oxadiazole can be combined with other heterocyclic rings, such as

indole or quinoline, to create hybrid molecules with enhanced biological activity. Quinoline-oxadiazole hybrid derivatives have shown potent antibacterial as well as antifungal activities[LIV]. The 1,3,4-oxadiazole-2(3H)-thione moiety serves as a significant pharmacophore due to its unique chemical properties, including its ability to act as a bioisostere for amides and esters, and its capacity to engage in various non-covalent interactions e.g., hydrogen bonding with biological targets. These features contribute to a wide range of biological activities and favorable pharmacokinetic properties in drug development. The azole ring's inherent lipophilicity helps modulate a drug's ability to cross cell membranes and reach its target, significantly impacting pharmacokinetic properties such as absorption, distribution, metabolism, and excretion.

Therefore, we were interested to accommodate two unlike pharmacophores - 1,3,4-oxadiazole-2(3H)-thione and 5-amino-8-hydroxyquinoline in a single moiety for enrichment of biological activity. This research paper presents the synthesis, characterization and antimicrobial studies of a novel hybrid heterocyclic ligand: 3-(((8-hydroxyquinolin-5-yl)amino)methyl)-5-(1-naphthyl)-1,3,4-oxadiazole-2(3H)-thione (HAMNOT) and its octahedral metal (II) complexes.

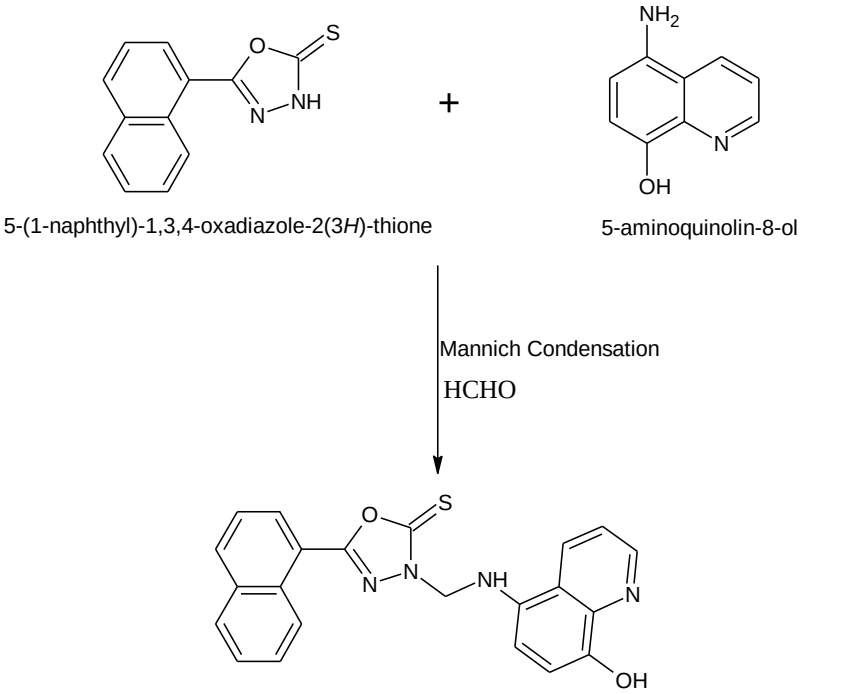
Methodology

Experimental

By standard open capillary method, melting points were determined and are uncorrected. Elemental analysis was performed with Perkins Elmer (USA) 2400-II CHN analyzer. On Perkin Elmer Spectrum GX spectrophotometer, FT-IR spectra were recorded via 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 through the Gouy method using mercury tetrathiocyanatocobaltate(II) [$HgCo(NCS)_4$] as calibrant and the diamagnetic corrections were made using Pascal's constant. The metal contents of the complexes were analyzed by EDTA titration after decomposing the organic matter using $HClO_4$, H_2SO_4 and HNO_3 (1:1.5:2.5) mixture[LV].

Synthesis of novel hybrid molecule (HAMNOT)

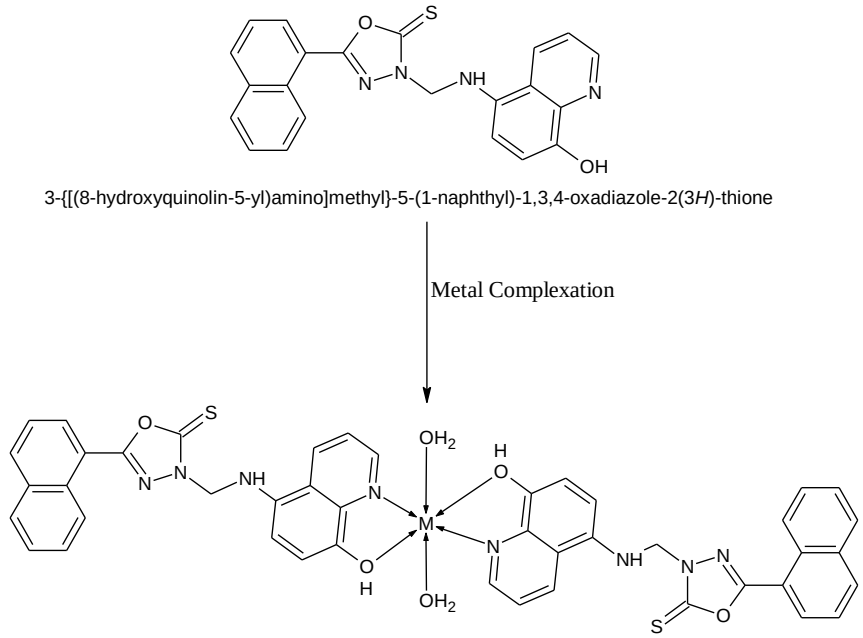
Initially 5-(1-naphthyl)-1,3,4-oxadiazole-2(3H)-thione was prepared as per reported procedures[LVI-LVII]. The primary synthetic route for 5-substituted-1,3,4-oxadiazole-2(3H)-thiones involves the cyclization of an acyl hydrazide with carbon disulfide (CS_2) in a basic alcoholic solution, followed by acidification. Then, hybrid ligand: 3-(((8-hydroxyquinolin-5-yl)amino)methyl)-5-(1-naphthyl)-1,3,4-oxadiazole-2(3H)-thione (HAMNOT) was synthesized by Mannich condensation reaction[LVIII-LIX] of 5-(1-naphthyl)-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-(1-naphthyl)-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 the Mannich reaction was monitored by TLC. Next 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). Lastly organic layer dried over Na_2SO_4 and distilled out atmospherically and applied vacuum to get a product. The physicochemical parameters and characteristic FT-IR frequencies of novel hybrid ligand: 3-(((8-hydroxyquinolin-5-yl)amino)methyl)-5-(1-naphthyl)-1,3,4-oxadiazole-2(3H)-thione (HAMNOT) are presented in Tables 1 and 2 respectively.



Scheme 1

General procedure for the synthesis of metal (II) complexes

Octahedral metal (II) complexes of novel hybrid ligand: 3-(((8-hydroxyquinolin-5-yl)amino)methyl)-5-(1-naphthyl)-1,3,4-oxadiazole-2(3H)-thione (HAMNOT) were synthesized using reported procedures[LX]. A hot solution of 3d-transition metal (II) salt (2.5 mmol) in 50% aqueous formic acid (2.5 mL) was added drop by drop with continuous stirring to the hot 20% aqueous formic acid solution (20 mL) of novel ligand HAMNOT (5 mmol). The resultant mixture was more digested for 4 hours in the water bath with the proper adjustment of the pH (~8.5) using 50% NH_4OH solution (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 octahedral metal (II) complexes of HAMNOT are summarized in Tables 1 and 2 respectively.



Scheme 2

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

Novel hybrid molecule HAMNOT and its octahedral metal (II) complexes were tested 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] using ciprofloxacin as a reference standard drug. To assess 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

Novel hybrid ligand: 3-(((8-hydroxyquinolin-5-yl)amino)methyl)-5-(1-naphthyl)-1,3,4-oxadiazole-2(3H)-thione (HAMNOT) 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. Octahedral metal (II) complexes $[M(II)(HAMNOT)_2(H_2O)_2]$ of HAMNOT have characteristic colour, are stable in air, and are almost insoluble in water, ethanol, methanol, chloroform and hexane.

The Fourier Transform Infrared spectroscopy-FT-IR spectra of HAMNOT and its octahedral metal(II) complexes representing all the significant stretching and bending vibrations are summarized in Table 2. In the FT-IR spectrum of HAMNOT, the absorption band at 3300 cm^{-1} is owing to O-H stretching vibration and the strong band at 1410 cm^{-1} to O-H bending vibration. The bands at 1590 cm^{-1} for C=N, at 1500 cm^{-1} for C=C and at 1477 cm^{-1} for C-C bond, assigned to the aromatic skeletal stretching vibrations of parent heterocyclic ring. The N-H stretching vibrations appeared near 3242 cm^{-1}, while N-H bending vibrations appeared at 1656 and C-N bending vibrations appeared at 1260 cm^{-1}. Comparison of IR spectra of novel

ligand HAMNOT and its octahedral metal (II) complexes have shown some significant characteristic differences[LXII-LXIV]. One of the significant differences to be expected was the occurrence of more broadened band in the region of 2700-3400 cm^{-1} for the chelates. Since 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 ascribed to the presence of coordinated water molecules [LXII-LXIV]. C=N stretching vibration band around at 1590 cm^{-1} shifted to lower frequency and the band at 1410 cm^{-1} in the spectrum of HAMNOT assigned to in-plane OH deformations shifted towards higher frequency in the spectra of the octahedral metal (II) complexes due to the formation of M-O bond[LXV]. This has been further confirmed by the presence of a weak band at 1090 cm^{-1} for C-O-M stretching mode and bands around at 770 cm^{-1} and 520 cm^{-1} correspond to the N→M vibrations[LXVI]. All these characteristic features of the FT-IR studies favor the formation of novel ligand HAMNOT and octahedral metal (II) complexes of it. Structural analysis of the ligand HAMNOT was also carried out with the help of ^{1}H NMR using DMSO-d6 at room temperature. The ^{1}H NMR spectrum of HAMNOT exhibited 3.80 (d, 2H, -CH_2-), 5.83 (t, 1H, NH), 9.00 (dd, 1H, H2 of quinoline), 9.70 (bs, 1H, OH). ^{1}H-NMR spectrum of [Zn(HAMNOT)$_2$] exhibited 3.91 (d, 4H, -CH_2-), 5.81 (t, 2H, NH), 8.92 (dd, 2H, H2 of quinoline). A broad singlet at δ 9.70 ppm due to the OH proton is absent in the spectrum of octahedral metal (II) complex of Zn, suggested that this OH proton has been vanished due to coordination of oxygen atom to the metal ion. The H2 signal of the octahedral metal (II) complex of Zn appeared at low magnetic field (δ 9.00) compared to that of ligand (δ 8.92), suggesting the involvement of N1 in the formation of complex[LXVII-LXIX]. The magnetic moment values (Table 1) favor the octahedral geometry for all the newly synthesized 3d-transition metal(II) complexes.

Table 1 Physicochemical parameters of ligand (HAMNOT) 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**	
HAMNOT $C_{22}H_{16}N_4O_2S$	400	75	180	66.00 (66.0)	4.00 (4.0)	14.00 (14.0)	8.00 (8.0)	--	--
[Cu(HAMNOT)$_2$(H_2O)$_2$] $C_{44}H_{34}N_8O_6S_2Cu$	897.5	70	>300	58.83 (58.80)	3.78 (3.75)	12.47 (12.45)	7.13 (7.10)	7.07 (7.00)	1.73 (1.7-2.2)
[Co(HAMNOT)$_2$(H_2O)$_2$] $C_{44}H_{34}N_8O_6S_2Co$	893	66	>300	59.12 (59.10)	3.80 (3.77)	12.54 (12.50)	7.16 (7.15)	6.60 (6.57)	3.87 (4.4-5.2)
[Ni(HAMNOT)$_2$(H_2O)$_2$] $C_{44}H_{34}N_8O_6S_2Ni$	893	68	>300	59.12 (59.10)	3.80 (3.79)	12.54 (12.51)	7.16 (7.14)	6.60 (6.58)	2.82 (2.9-3.4)
[Mn(HAMNOT)$_2$(H_2O)$_2$] $C_{44}H_{34}N_8O_6S_2Mn$	889	69	>300	59.39 (59.35)	3.82 (3.80)	12.60 (12.58)	7.19 (7.15)	6.18 (6.10)	5.91 (5.2-6.0)
[Zn(HAMNOT)$_2$(H_2O)$_2$] $C_{44}H_{34}N_8O_6S_2Zn$	899	70	>300	58.73 (58.70)	3.78 (3.75)	12.45 (12.40)	7.11 (7.10)	7.23 (7.20)	diamagnetic

Table 2 FT-IR spectral frequencies of ligand (HAMNOT) 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)**
$[Cu(HAMNOT)_2(H_2O)_2]$	3375(br)	1578	524	770	1426	1089
$[Co(HAMNOT)_2(H_2O)_2]$	3385(br)	1569	529	760	1425	1094
$[Ni(HAMNOT)_2(H_2O)_2]$	3370(br)	1565	518	770	1422	1096
$[Mn(HAMNOT)_2(H_2O)_2]$	3365(br)	1563	521	765	1423	1091
$[Zn(HAMNOT)_2(H_2O)_2]$	3380(br)	1575	518	760	1421	1093
HAMNOT	3300	1590	--	--	--	--

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

Compound	**Zone of inhibition (mm)[a]**					
	Antibacterial activity				**Antifungal activity**	
	S.aureus	***B.subtilis***	***E.coli***	***P.aerugionsa***	***A.niger***	***A.flavus***
5AHQ	24	22	26	22	21	19
HAMNOT	13	14	12	10	14	12
$[Cu(HAMNOT)_2(H_2O)_2]$	16	17	15	12	13	11
$[Co(HAMNOT)_2(H_2O)_2]$	8	10	10	14	12	15
$[Ni(HAMNOT)_2(H_2O)_2]$	13	14	9	10	14	13
$[Mn(HAMNOT)_2(H_2O)_2]$	8	8	5	12	17	18
$[Zn(HAMNOT)_2(H_2O)_2]$	17	16	16	21	15	14
Ciprofloxacin	28	42	26	35	44	38

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

Conclusion

The novel hybrid molecule: 3-(((8-hydroxyquinolin-5-yl)amino)methyl)-5-(1-naphthyl)-1,3,4-oxadiazole-2(3H)-thione (HAMNOT) and its octahedral 3d-transition metal (II) complexes (1:2 metal to ligand ratio) were synthesized and characterized. HAMNOT and its octahedral 3d-transition metal (II) complexes displayed moderate to good antibacterial and antifungal activities compared to 5-amino-8-hydroxyquinoline. This might be due to the additive biological effect of core pharmacophores-1,3,4-oxadiazole-2(3H)-thione and 5-amino-8-hydroxyquinoline, and / or due to the metal chelating properties.

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