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Research Article

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Synthesis and antimicrobial activity of novel metal chelates of 2-(8-quinolinol-5-yl)-methyl amino-5-pyridinyl-1,3,4-thiadiazole derivatives

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ABSTRACT

The novel metal chelates of 2-(8-quinolinol-5-yl) –methyl amino-5-pyridinyl-1, 3, 4-thiadiazole derivatives ***(1)*** *has been synthesized and their antimicrobial properties were evaluated. These compounds were synthesized by reaction of 2-(8-quinolinol-5-yl) –methyl amino-5-pyridinyl-1, 3, 4-thiadiazole derivatives* ***(1)*** *with metal acetate and characterized using IR, ^{1}H-NMR and elemental analysis. The synthesized compounds were screened for their in vitro antimicrobial activity against microorganism P. Expansum. B. Thiobromine, Nigras pora Sp. T. roseum, A. Niger, B. megaterium, S. aureus, P. aeruginosa and E. coli. All of the compounds are active against the microorganism in which some are exhibited moderate to good activity, whereas some were less active.*

Keywords: Metal chelates, 5-chloromethyl-8-quinolinol, 5-pyridinyl-1,3,4-thiadiazole, antifungal activity, antibacterial activity

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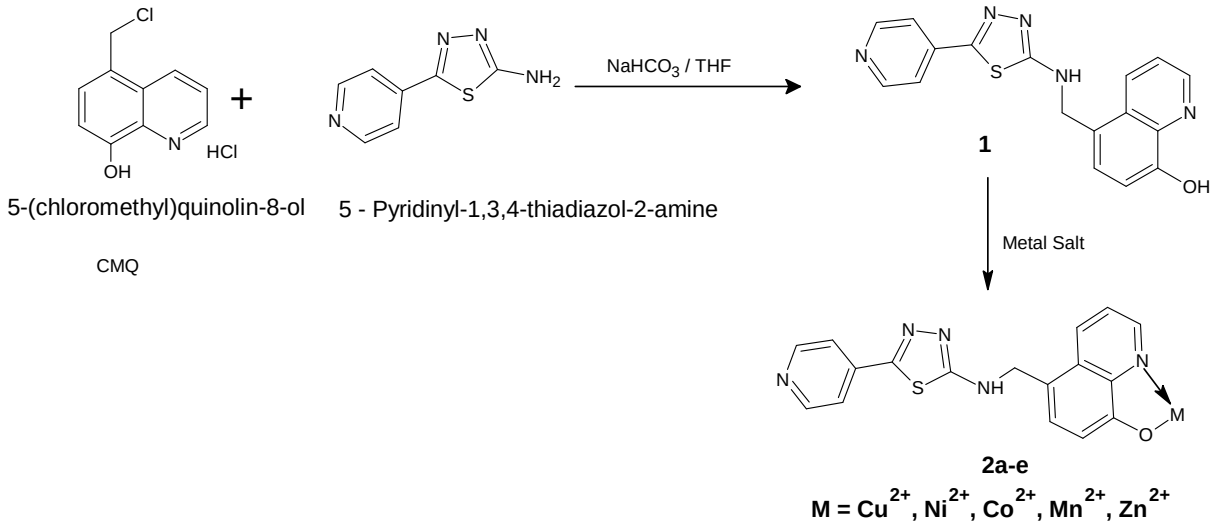
INTRODUCTION

Many classes of thiadiazole compounds, many of which were found to possess an extensive spectrum of pharmacological activity such as antimicrobial activity[1-3], antimycobacterium [4-6], anticonvulsant, antitumor [7], CNS depressants [8], herbicidal [9], antiviral [10], antitrypanosomal activity [11-12] and anti-inflammatory activity[13].

8-quinolinol (8Q) and its derivatives have been introduced as chelating groups [14]. Some 8-hydroxyquinoline derivative has antibacterial and antifungal activity [15], activity against both viral and protozoal infections [16]. 8Q and its metalloquinolates have attracted great interest because their high thermal stability and good electroluminescence properties make them important prototypical electron transport and emitting materials for OLED devices [17-19]. 8Q it self is inactive but exerts activity by virtue of the metal chelates produced in its reaction with metal ions in the medium. These encouraging results led us to design the chelates metal chelates of 2-(8-quinolinol-5-yl) –methyl amino-5-pyridinyl-1, 3, 4-thiadiazole (**1**) which is synthesized by coupling of 5-chloromethyl-8-quinolinol with 5-pyridinyl -1, 3, 4-thiadiazol-2-ylamine in the presence of sodium bicarbonate followed by formation of chelates using metal acetate of different transition metal and screened for their antimicrobial activities..

EXPERIMENTAL SECTION

All the chemicals used were of analytical grade. 8-hydrxyquinoline, hydrochloric acid, formaldehyde, sodium bicarbonate, ethyl alcohol and different metal salt was purchased from the E. Merck (India) Limited, Mumbai. Luria broth and agar- agar were purchased from SRL, India. Acetic acid and EDTA were purchased from Sigma Chemical Co., India. The elemental contents were determined by Thermo Finigen Flash1101 EA (Italy), the metals were determined volumetrically by Vogel's method. Infrared spectra of the synthesized compounds were recorded on Nicolet760 FT-IR spectrometer. NMR spectrum of compound was recorded on 400 MHz NMR spectrophotometer. TMS was used as reference.



5-(chloromethyl)quinolin-8-ol CMQ

5 - Pyridinyl-1,3,4-thiadiazol-2-amine

Scheme-1:- synthesis of metal chelates of 2-(8-quinolinol-5-yl) –methyl amino-5-pyridinyl-1, 3, 4-thiadiazole derivatives

***Synthesis of 2-(8-quinolinol-5-yl) –methyl amino-5-pyridinyl-1, 3, 4-thiadiazole derivatives* 1**

5-chloromethyl-8-quinolinol hydrochloride (2.3 gm, 0.01 mole) and 2-amino-5-pyridinyl-1, 3, 4-thiadiazole (3.35 gm, 0.01 mole) were suspended in acetone (50 ml). Sodium bicarbonate (1.68 gm, 0.02 mole) was added to the reaction mass and warmed for 6 h. Solvent was evaporated and product was collected by filtration further purified by washing with acetone

Synthesis of metal chelates of compound 2a-e

The metal chelates of compound with Cu^{2+}, Ni^{2+}, Co^{2+}, Mn^{+2}, Zn^{2+} and metal ions were prepared in two steps. All the metal chelates were prepared in an identical procedure. The details are given as follows.

Preparation of compound solution

Ligand 2-(8-quinolinol-5-yl) –methyl amino-5-pyridinyl-1, 3, 4-thiadiazole (0.05 mol) was taken in 500 mL beaker and formic acid (85% v/v) was added up to slurry formation. To this slurry, water was added till the complete dissolution of compound. It was diluted to 100 mL.

Table No. 1:- Physical parameter of synthesized compound 2a-e

Sr. No	Chelates	Molecular formula	M. Wt	Yield %	Colour
1	2a	$C_{34}H_{24}N_{10}O_2S_2Cu^{+2}.2H_2O$	767	74	Greenish Blue
2	2b	$C_{34}H_{24}N_{10}O_2S_2Ni^{+2}.2H_2O$	763	75	Greenish
3	2c	$C_{34}H_{24}N_{10}O_2S_2Mn^{+2}.2H_2O$	759	72	Brown
4	2d	$C_{34}H_{24}N_{10}O_2S_2Co^{+2}.2H_2O$	763	80	Blackish
5	2e	$C_{34}H_{24}N_{10}O_2S_2Zn^{+2}.2H_2O$	769	77	Yellow

Synthesis of metal-chelates of 2-(8-quinolinol-5-yl) –methyl amino-5-pyridinyl-1, 3, 4-thiadiazole

In a solution of metal acetate (0.005 mol) in water (100 ml), 20 ml of above mentioned compound solution (*i.e*. containing 0.01 M compound) was added with vigorous stirring at room temperature. The pH was adjusted around 4.5 to 6 for complete precipitation of metal chelate. The precipitates were digested on a boiling water bath. The precipitates of chelate were filtered off, washed by 1:1 mixture of water: ethanol and finally with acetone and dried at 70°C for 24 hours.

Antifungal Activity

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in *vitro*. Plant pathogenic organisms used were *Penicillium expansum, Botrydepladia thiobromine, Nigrospora Ssp, Trichothecium roseum and Aspergillus niger*. The antifungal activity of all the compounds was measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium such a PDA medium contained potato 200 gm., dextrose 20 gm., agar 20 gm., and water 1 liter. Five days old cultures were employed. The compounds to be tested were suspended (1000 ppm) in a PDA medium and autoclaved at 120 ^{0}C for 15 min and at 15 atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below.

$$\text{Percentage of inhibition} = \frac{100\ (X - Y)}{X}$$

Where X = Area of colony in control plate.
Y = Area of colony in test plate.

The fungicidal activity displayed by various compounds is shown in Table: 1.0

Antibacterial Activity

The study has been conducted according to the method adopted by Cruickshank et al**.** Nutrient agar broth was melted in a water bath and cooked to 45 ^{0}C with gentle shaking to bring about uniform cooling. It was inoculated with 0.5-0.6 ml of 24 hour old culture especially and mixed well by gentle shaking before pouring on the sterilized Petri dish (25 ml each). The poured material was allowed to set (1.5 hour) and there after the "cups" was made by punching into the agar surface with a sterile cork borer and soaping out the punched part of agar. Into this "cups" 0.1 ml of test solution (prepared by dissolving 100 ml of sample in 10 ml DMF) was added by sterile micropipette. The plates were noted. The antibacterial stain use are *Bacillus megaterium, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli* activities of all compounds are shown in Table: 3

RESULTS AND DISCUSSION

The toxic effect of all the complexes on fungi is shown in Table 1. The results give the following conclusions. All the complexes are toxic more or less to fungi. The substitution of phenyl rings does not have more effect on the fungicidal activity of complexes. In each series the Cu-complexes have much toxicity. This is expected because the copper salts are mostly used as fungicides. Most of the complexes inhibit the growth of the above organisms which cause decease in many plants. Cu+2 metal complexes are more toxic than others and the order for is $Cu^{+2} > Zn^{+2} > Co^{+2} > Ni^{+2} > Mn^{+2}$.

The IR spectrum of the compound **1** comprises the important bands due to 8-quinolinol. The bands were observed at 1667, 1577, 1508, and 1390 cm^{-1}. The broad band due to -OH group appeared at 3500 cm^{-1}. In this band the inflections are observed at 2989 cm^{-1}.While the latter two might be attributed to asymmetric and symmetric vibration of CH_2 of CMQ. The NMR spectrum of compound in DMSO-d_6 indicates that the singlet of 2H at 3.35 ppm of N-CH_2-Ar group. While the singlet at 5.76 ppm due to -OH group. The aromatic protons are appeared in multiplicity at 7.25 to 7.72 ppm. The melting point is 164°C. Thus the structure of compound is confirmed as shown in Scheme 1.

The metal and C, H, N contents of metal chelates of compound are also consistent with the predicted structure. The results show that the metal: ligand (M: L) ratio for all divalent metal chelate is 1:2.

The diffuse electronic spectrum of Cu^{2+} chelates shows two broad bands at 14970 and 24614 cm^{-1}. The first band shows structures suggesting a distorted octahedral structure for the Cu^{2+} metal chelates. The higher value of the magnetic moment of the Cu^{2+} chelate supports the same. The Co^{2+} metal chelate gives rise to two absorption bands at 24935 and 19897 cm^{-1}, these absorption bands e indicate an octahedral configuration of the Co^{2+} metal chelate. The spectrum of Mn^{2+} polymeric chelate comprised two bands at 18414 cm^{-1} and 23782 cm^{-1}. The spectrum of the metal chelate of Ni^{2+} shows two distinct bands at 22312 and 15716 cm^{-1} suggested the octahedral environment for Ni^{2+} ion.

***Spectral data of 2-(8-quinolinol-5-yl) –methyl amino-5-pyridinyl-1, 3, 4-thiadiazole* 1**

Yield: 83%; colour; yellow solid; m.p. 164 °C; M.F. : $C_{17}H_{13}N_5OS$; M.W. 335; IR (KBr, cm^{-1}): 3400 (N-H), 2920 (C-H), 2850, 1599, 1507, 1450 (C-H Ar); NMR (400 MHz, DMSO-d6): ppm 8.51(d 4H pyridinyl), 7.25-7.72 (m, 5H, Ar-CH), 5.76 (s, 1H, -OH), 3.35 (s, 2H, $-CH_2$); Elemental Analysis (C% ,H% ,N% ,S%), Calculated: 60.89, 3.88, 20.89, 9.55, Found : 60.8 ,3.7,20.8,9.4

Table: 2 Antifungal activity of metal chelates of 2-(8-quinolinol-5-yl) –methyl amino-5-pyridinyl-1, 3, 4-thiadiazole

Compound code	Metal Ion	Zone of inhibition in mm at 1000 ppm (%)				
		P. expansum	*B. thiobromine*	*N. pora.*	*T. roseum*	*A. niger*
1	-	65	62	71	57	59
2a	Cu^{+2}	85	84	80	90	85
2b	Mn^{+2}	67	55	56	55	5
2c	Co^{+2}	73	70	73	68	70
2d	Zn^{+2}	82	82	77	82	80
2e	Ni^{+2}	70	58	60	62	67

Table: 3 Antibacterial activity of metal chelates of 2-(8-quinolinol-5-yl) –methyl amino-5-pyridinyl-1, 3, 4-thiadiazole

Compound code	Metal Ion	Zone of inhibition (in mm)			
		Gram + Ve		*Gram -Ve*	
		B. megaterium	*S. aureus*	*P. aeruginosa*	*E. coli*
1	-	18	17	19	12
2a	$(L\text{-}1)_2\ Cu^{+2}$	21	20	21	18
2b	$(L\text{-}1)_2\ Mn^{+2}$	10	11	12	15
2c	$(L\text{-}1)_2\ Co^{+2}$	17	18	16	15
2d	$(L\text{-}1)_2\ Zn^{+2}$	17	20	17	17
2e	$(L\text{-}1)_2\ Ni^{+2}$	14	12	19	13

CONCLUSION

The complexes were obtained as colored powdered materials and were characterized using IR spectra, electronic spectra, and magnetic measurements. The elemental analyses were in good agreement with the complexes. From the antimicrobial activity data, it is observed that the complexes exhibit higher activity than the free ligands and the metal salt. The increase in antimicrobial activity of the complexes may be due to the metal chelation. From comparative analysis as shown in Table 2 & 3 it is observed that all the metal complexes are more potent biocidal than the ligand. From the results it is clear that Cu^{2+} is highly active among the complexes of the respective metal also Cu^{2+} is most active among all which may be due to combine effect of Cu^{2+} and functional groups on the ligand.

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