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Synthesis, characterization and antibacterial activities of Zn(II) and Cd(II) complexes of a 3-amino-2-phenylquinazolin-4(3H)--one Schiff base

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Abstract: Zn(II) and Cd(II) complexes of a Schiff base derived from 3-amino-2-phenylquinazolin-4(3*H*)-one and 2-(2-formylphenoxy) acetic acid were prepared and characterized by elemental and different spectroscopic (IR, UV–Vis and NMR) analyses. The elemental analysis indicated the formation of the complexes: [ML(AcO)]·H₂O, where M stands for Zn(II) or Cd(II) and L stands for the Schiff base. The molar conductivities of the prepared complexes revealed their non-electrolytic nature. The complexes were also investigated for their antimicrobial activities using the turbidimetric assay method.

Keywords: Zn(II); Cd(II); quinazolin-4(3*H*)-one Schiff base; 2-(2-formylphen-oxy) acetic acid; antibacterial activities.

INTRODUCTION

Schiff bases derived from an amine and aldehydes are an important class of ligands that co-ordinate to metal ions through the azomethine nitrogen.^{1–3} Among the wide variety of nitrogen-containing heterocycles explored for the development of pharmaceutically important molecules, quinazoline is an important compound in medicinal chemistry and subsequently have emerged as an important pharmacophore.⁴ The quinazoline moiety has O and N donor atoms and can act, therefore, as a good chelating agent. Quinazolin-4(3H)-one and its derivatives are versatile nitrogen-containing heterocyclic compounds that have long been known as a promising class of biologically active compounds.⁵ Compounds containing 4(3H)-quinazolinone ring system were reported to possess varied biological activities, such as antibacterial, antifungal, antitubercular, antiviral, anticancer and anticonvulsant activities, depending on the substituents in the ring system.^{6–9}

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The aldehydic precursor 2-(2-formylphenoxy) acetic acid plays an important role in reducing the toxicity of the parent drug and acts as a part of a pro-drug called aconiazide.^{10,11} A survey of the literature^{12–19} revealed that the reaction of quinazoline hydrazide **2** and 2-(2-formylphenoxy) acetic acid has hitherto remained unattended. Therefore, it was thought worthwhile to synthesize a novel quinazoline Schiff base and its complexes with transition metals. Hence, in this work, the synthesis and characterization of the Schiff base ligand derived from quinazolin-4-(3*H*)-one and 2-(2-formylphenoxy) acetic acid and its mononuclear complexes with Zn(II) and Cd(II) ions are reported.

EXPERIMENTAL

Materials and measurements

Pyridine, benzoyl chloride, anthranilic acid, hydrazine hydrate, salicylaldehyde, monochloroacetic acid, cadmium acetate dihydrate and zinc acetate dihydrate were procured from S. D. Fine Chemicals, India. Except monochloroacetic acid (purity 98 %) and hydrazine hydrate (purity 80 %), all the chemicals were of 99 % purity. The spectroscopic grade solvents were also purchased from S. D. Fine Chemicals, India and used without further purification. 2-(2-Formylphenoxy) acetic acid and quinazolin-4(3*H*)-one were prepared by following reported procedures.^{20,21}

The FT-IR spectra of the ligand and metal complexes were recorded in KBr discs in the range 400–4000 cm⁻¹ using a Shimadzu FTIR 8300 spectrophotometer. ¹H- and ¹³C-NMR spectra were recorded on an FT-NMR Bruker Advance II 400 MHz spectrometer with TMS as the internal standard. Mass spectrum of the ligand was recorded employing a ZQMAA225 mass spectrometer using acetonitrile as a solvent. Due to the poor solubility of the synthesized metal complexes in common solvents, their masses were not recorded. The UV–Vis spectra were measured in DMF with a JascoV-530 spectrophotometer. Elemental microanalyses were realized using a CHNOS elemental analyzer (Model 550 Carlo-Erba). The molar conductances of the complexes (1×10⁻³ mol dm⁻³) were measured in DMF with a Systronic-308 conductivity bridge at 25 °C under atmospheric pressure. The melting points of the ligand and the complexes were determined using the open capillary method.

Synthesis of the ligand

The syntheses of 3-amino-2-phenylquinazolin-4(3H)-one was reported earlier.²¹ The synthesis of 3-amino-2-phenylquinazolin-4(3H)-one is shown in Scheme 1. A mixture of 2-phenyl-4H-3,1-benzoxazin-4-one (2.23 g, 0.01 mol), **1**, and hydrazine hydrate (0.5 mL, 0.01 mol) in ethanol was refluxed for 8 h. The excess of solvent was then evaporated and the



Scheme 1. The synthesis of the ligand (LH): 1, 2-phenyl-4H-3,1-benzoxazin-4-one;
2, 3-amino-2-phenylquinazolin-4(3H)-one; 3, the ligand (LH).

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resulting solid 3-amino-2-phenylquinazolin-4(3*H*)-one **2** was filtered off, dried under vacuum and recrystallized from ethanol. Its melting point was 142 $^{\circ}$ C and its yield was 72 %.

Next, a mixture of 3-amino-2-phenylquinazolin-4(3*H*)-one and 2-(2-formylphenoxy) acetic acid in equimolar amount (5 mmol each: 1.18 and 0.90 g, respectively) in absolute ethanol was refluxed for about 5 h. The solution was then cooled and poured into ice-cold water. The resulting white product, $2-\{2-[((4-0x0-2-phenyl-3(4H)-quinazolinyl)imino)-methyl]phenoxy}acetic acid$ **3**was filtered off, washed with dried ethanol and recrystallized from ethanol.

Synthesis of complexes

A solution of 0.5 mmol of metal acetate dihydrate [Zn(II) and Cd(II)]: 0.109 and 0.134 g, respectively) in 15 mL ethanol was added to 0.5 mmol, 0.200 g of the ligand dissolved in 20 mL absolute ethanol. The solution was heated under reflux for about 2 h. The resulting precipitate was filtered off washed with cold dried ethanol and dried under vacuum over fused CaCl₂.

Antibacterial activity

The antibacterial activities of the ligand and its complexes were assayed against the Gram-negative bacteria *Escherichia coli* (K12MTCC302) by the turbidimetric method. The test compounds were dissolved in DMSO (SRL, Extra-pure, India) to prepare stock solutions, which were aseptically filtered through a bacterial membrane. The required volumes of filtrate were transferred to tubes containing a defined volume of nutrient broth to achieve the desired concentration of the compounds. The concentrations of the tested compounds were 25, 50, 100, 200, 300, 400, 600, 800 and 1000 μ g mL⁻¹ and the standard drug for comparison was ampicillin. A loop full of bacteria from a 24 h-old slant culture were transferred to 10 mL of nutrient broth (Himedia M 502) and incubated at 37 °C for 6 h. The tubes in duplicate containing 5 mL nutrient broth were incubated with 0.1 mL of a 6-h liquid culture. The tubes containing the nutrient broth were incubated at 37 °C for 18 h and the relative growths in the tubes were determined turbidimetrically by spectrophotometry.

RESULTS AND DISCUSSION

All the isolated compounds were found to be air-stable and were characterized based on elemental and different spectroscopic analyses, the results of which are given in the Supplementary material to this paper. The metal complexes were insoluble in common organic solvents except in DMF and DMSO.

Molar conductivity

The molar conductivity (Λ_M) of the synthesized complexes were measured at 25 °C and under atmospheric pressure in DMF. The molar conductivities of the complexes (1×10⁻³ mol dm⁻³) indicated that the complexes behave as non-electrolytes in DMF, which suggests that no anion was present outside the coordination sphere as a counter anion of the central metal ion.

Infrared spectra of the Schiff base ligand and its complexes

The comparative IR spectral study of ligand and its complexes revealed the coordination mode of the synthesized ligand during the complex formations. The

weak broad bands at 3084 cm⁻¹ and 3230–3294 cm⁻¹ in the spectrum of the free ligand may be attributed to the -NH stretching and the hydrogen bonded -OH of the carboxylic moiety, respectively. In the complexes the disappearance of these bands followed by a shift of acid carbonyl from 1734.6 to 1684–1690 cm⁻¹ implied deprotonation and subsequent coordination of the oxygen of carbonyl (C=O) group to the metal ions (M^{2+}) . In the spectra of the free ligand and the complexes, the band at 1653.8–1654.8 cm⁻¹ was due to the amide C=O and this band did not change, supporting the fact that the carbonyl oxygen of the amide did not participate in the metallation. The azomethine band at 1602.7 cm^{-1} in the spectrum of the free ligand shifted towards lower frequency range 1590-1597.9 cm⁻¹, which indicated coordination of the N-atom of the azomethine group to M^{2+} . This fact was further supported by concomitant increase in the v_{N-N} stretching frequency from 930 cm⁻¹ towards the range 963–960 cm⁻¹ for free ligand and the complexes, respectively.^{22,23} In addition, the coordination of the ethereal oxygen (>C–O–C<) to M^{2+} was confirmed by the observed frequency increase of the 1215.1 cm⁻¹ band towards the range 1232–1256 cm⁻¹ on complexation. The medium intensity broad bands at 3435 and 3420 cm⁻¹ for the Zn(II) and Cd(II) complexes, respectively, are due to the presence of water molecules in the coordinating sphere.²⁴ Assignment of the proposed coordination sites was further supported by the appearance of medium bands at 592.1 and 594.1 cm^{-1} attributed to v_{M-N} for the Zn(II) and Cd(II) complexes, respectively.^{25,26}

¹H- and ¹³C-NMR spectra

The ¹H- and ¹³C-NMR spectra of the ligand and the Cd(II) complex were recorded in DMSO-d₆. The 2D-NMR spectrum for the ligand was also recorded in order to distinguish the different protons on the phenyl ring of the quinazoline moiety. The ¹H-NMR spectrum of the ligand showed the following signals (δ / / ppm): 4.79 (s), 6.99–8.56 (m), 8.87 (s) and 11.99–12.24 (s); these signals may be assigned to the protons in -O-CH₂-, the aromatic moiety, the azomethine (HC=N) group, -OH (carboxylic proton hydrogen bonded with -N= group) and the free –OH (carboxylic) group, respectively. Since the ¹H-NMR spectrum of the synthesized ligand showed close signals in the δ range 6.99–8.87 ppm, its 2D spectra were recorded. In the 2D spectrum of the ligand, three sets of correlations: the quinazoline protons (H_5-H_8) , the arylidene protons $(H_3''-H_6'')$ and the phenyl protons of the 2-phenyl group $(H_2'-H_4')$, were observed. In the total correlated spectroscopy (TOCSY) spectrum, a distinct set of four cross-peaks was observed, indicating four consecutive protons with δ values of 8.56, 7.95, 7.62 and 6.99 ppm. The atom numbering of the ligand is shown in Fig. 1A. An analysis of the cross-peaks of ¹H–¹H correlation spectroscopy (COSY) spectra (Fig. 1B) revealed the nearest member of each proton. Since the proton at the ortho--position to the amidic group was assumed to be most deshielded (marked as H_5),



Fig. 1. A) Atom numbering of the ligand structure; B) $^{1}H^{-1}H$ COSY spectra of the ligand; C) $^{1}H^{-13}C$ COSY spectra of the ligand.

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all other protons were assigned with respect to this proton (H₅). The sequential assignments were thus at δ values: 8.56 (H₅), 7.61 (H₆), 7.65 (H₇) and 7.27 ppm (H₈). The arylidene protons (H₃"–H₆") and the 2-phenyl protons (H₂'–H₄') were also assigned in similar fashions. The arylidene protons were assigned the following δ values: 7.04 (H₃"), 7.56 (H₄"), 6.99 (H₅") and 7.40 ppm (H₆"), and 2-phenyl protons were assigned the δ values: 7.95 (H₂'), 7.91 (H₃') and 7.93 ppm (H₄'). After the assignment of the entire ¹H-spectrum of the ligand, the ¹H–¹³C COSY spectrum was further analyzed to assign the eleven ¹H–¹³C peaks (Fig. 1C).

In the ¹H-NMR spectrum of the Cd(II) complex the signal due to carboxylic proton had disappeared, which confirmed the involvement of the carboxylic group in the coordination. The shifts in the signal assigned to the azomethine proton and the methylene proton at 8.73 and 4.53 ppm in the complex were indications of the coordination of the nitrogen of the azomethine linkage and ethereal oxygen of the $-O-CH_2$ - linkage to the metal ion. A signal at around 2.45–2.50 ppm was also observed and assigned to methyl protons of the acetate group coordinated to the metal ion. This fact clearly indicated that during complex formation, one proton (carboxylic) of the free ligand was deprotonated and it behaved as a monobasic tridentate ligand. Unfortunately, it was not possible to perform NMR studies on the Zn(II) complex due to its poor solubility in DMSO- d_6 .

Electronic spectra

The electronic spectra of the ligand and its Zn(II) and Cd(II) complexes, recorded in DMF, are shown in Fig. 2. In the electronic spectra, the $n\rightarrow\pi^*$ transition associated with the azomethine group of the ligand was found at 332 nm but was shifted to longer wavelengths for Cd(II) and Zn(II) complexes. These results indicated that the nitrogen atom of azomethine group remained coordinated to the metal ions in the complexes. From the electronic and other spectral data, it could



Fig. 2. UV–Vis spectra of the ligand and its Zn(II) and Cd(II) complexes. 1, LH; 2, Cd(II) complex; 3, Zn(II) complex.

thus be concluded that both the complexes had tetrahedral geometry. The probable structure of the metal complexes is shown in Fig. 3.



Fig. 3. Probable structure of the synthesized metal complexes (M = Cd(II) or Zn(II)).

Antibacterial activities

The ligand and its Zn(II) complex did not show any antibacterial activity against *E. coli* up to 1000 μ g mL⁻¹, whereas the Cd(II) complex showed antibacterial activity at 100 μ g mL⁻¹. Thus, it could be concluded that the incorporation of the 2-(2-formylphenoxy) acetic acid group in the quinazoline molecule quenched the antibacterial activity of the parent quinazoline molecule.

CONCLUSIONS

In this paper, the syntheses and physicochemical characterization of a 3amino-2-phenylquinazolin-4(3*H*)-one Schiff base ligand and its Zn(II) and Cd(II) complexes are described. The antibacterial activities of the synthesized compounds are also described. The results of elemental analysis confirmed a 1:1 ratio of ligand to metal binding. Based on the physical and spectral analyses (IR, UV– –Vis and NMR), tetrahedral geometry was proposed for the complexes of quinazolin-4-(3*H*)-one Schiff base. In the complexes, the azomethine nitrogen, ethereal oxygen and phenoxy oxygen occupied the three coordination sites. The fourth coordination site was occupied by an acetate group and one water molecule of crystallization was present in the complex, as confirmed by elemental analysis. The Zn(II) complex did not show any antibacterial activity, whereas the Cd(II) complex showed marked antibacterial activity. Again, it was found that the incorporation of the 2-(2-formylphenoxy) acetic acid group in the quinazoline molecule quenched the antibacterial activity of the parent quinazoline molecule.

SUPPLEMENTARY MATERIAL

Physical, analytical and spectral data for the ligand and its Zn and Cd complexes are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА, КАРАКТЕРИЗАЦИЈА И АНТИБАКТЕРИЈСКА АКТИВНОСТ КОМПЛЕКСА Zn(II) и Cd(II) са шифовом базом 3-амино-2-фенилхиназолин-4(3*h*)-она

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Описана је синтеза Zn(II) и Cd(II) комплекса са Шифовом базом 3-амино-2-хиназолин-4(3*H*)-она и 2-(2-формилфенокси)-сирћетне киселине као лигандом. Комплекси су окарактерисани помоћу елементалне микроанализе и различитих спектроскопских метода (IR, UV–Vis и NMR). На основу елементалне микроанализе претпостављено је да комплекси имају општу формулу: [ML(AcO)]·H₂O, где је M Zn(II) или Cd(II), а L представља Шифову базу као лиганд. На основу кондуктометријских мерења закључено је да изоловани комплекси представљају неутралне комплексне врсте. Применом турбидиметријских метода испитивана је антимикробна активност изолованих комплекса.

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