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Full Length Research Paper

Synthesis and biological evaluation of some new Schiff bases and their Cu(II) and Mg(II) complexes

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The Schiff base ligands, 4-(pyrrol-2-yl-methylen)amino-1-phenyl-2,3-dimethylpyrazolin-5-one (L1) and 2-hydroxyacetophenon-salcyl hydrazine (L2) have been synthesized by the condensation of 4-aminoantipyrine with pyrrole-2-carboxaldehyde and salicylic acid hydrazide with 2-hydroxyacetophenone, respectively. The Cu(II)and Mg(II) complexes of these ligands have also been obtained. Their structure has been proven using spectral methods such as ultraviolet and visible absorption spectroscopy (UV-VIS), Fourier transform-infrared spectroscopy (FT-IR), ^{1}H-NMR and elemental analysis. The compounds were evaluated for toxicity degree and for their anti-inflammatory activity using carrageenan induces rat paw edema bioassay. All tested compounds are nontoxic at dose of 100 and 200 mg/kg. At dose of 400 mg/kg, the compounds have induced toxic central phenomena and the death occurred at dose of 800 mg/kg. At 8 h after the experiment started, some compounds showed anti-inflammatory effects comparable with the effect of indomethacin used as reference drug. The most active compound was Cu(II) complex (3) at dose of 10 mg/kg.

Key words: Schiff base, ligand, transition metal, toxicity, anti-inflammatory effect.

INTRODUCTION

Compounds with the structure of -C=N- (azomethine group) are known as Schiff bases, which are usually synthesized from the condensation of primary amines with compounds having active carbonyl groups (Ali et al., 2012). The biological activities of Schiff bases have attracted considerable attention to organic and medicinal researchers for many years. Schiff bases are now well known for their importance in biological fields such as anticancer (Qiao et al., 2011), antimicrobial (Venkatesh, 2011; Hussein et al., 2011), anti-inflammatory (Sathe et al., 2001; Pandey et al., 2011), antiviral (Kumar et al., 2009), analgesic (Chinnasamy et al., 2010), pesticidal (Ali et al., 2009), and antioxidant (Vančoa et al., 2004; Harinath et al., 2013) agents. Related to anti-inflammatory effects, it was reported that several Schiff bases with pyrazole, thiazole, thiazoline and benzothiazole moiety and their metal complexes with Cu(II), Ni(II), and Zn(II) (Alam et al., 2012; Geromikaki et al., 2003) posses important anti-inflammatory effects. These compounds inhibit the activity of cyclooxygenase (COX) and 5-lipooxygenase enzymes (Ali et al., 2012; Zhou et al., 2010; Bertolini et al., 2001), and they can also scavenge the free radicals, being known by the implication of the free radicals and oxidative stress in inflammatory diseases (Nirmal et al., 2010; Gaubert et al., 2000). At the same time it was noted that the low levels of magnesium

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are associated with the inflammation and, as a result, a large number of magnesium complexes have been synthesized and their anti-inflammatory effects were studied (Ferré et al., 2010).

Based on the aforementioned applications of Schiff bases, this study presents synthesis, physico-chemical characterization, toxicity degree and anti-inflammatory effects of new Schiff bases and their complexes with Cu(II) and Mg(II).

MATERIALS AND METHODS

Chemistry

All chemicals and solvents have analytical reagent grade and were used as supplied by Merck and Chimopar Bucharest. The melting points were determined with Boetius apparatus and are uncorrected. The IR spectra (KBr pellets) were recorded on a FTS-135 BIO-RAD spectrometer. The ultraviolet and visible absorption spectroscopy (UV-VIS) spectra have been obtained on a UV-VIS spectrophotometer Hewlett-Packard 8453. Elemental analysis (C, H, N) was carried out with an Elemental Vario Analyzer. The quantitative determination of Cu(II) and Mg(II) was performed using the AAS- IN Carl- Zeiss-Jena spectrometer.

4-(pyrrol-2-yl-methylen)amino-1-phenyl-2,3-dimethylpyrazolin-5-one (L1)

The Schiff base L1 was prepared by condensation of 4-aminoantipyrine (0.2 g, 1 mmol) with pyrrole-2-carboxaldehyde (0.095 g, 1 mmol) in methanol (25 ml) using similar methods with the literature (Ziessel, 2001; Mounika et al., 2010). The mixture was heated under reflux for 3 h and then it was left to crystallize at room temperature. After 24 h, a yellow-brown solid was obtained, which was filtered and dried at room temperature. The ligand (L1) is a yellow-brown crystalline powder, stable at room temperature, insoluble in water, soluble in ethanol, methanol, very soluble in acetone and dimethylformamide (DMF). Yield 82.7%; m.p. 194-195°. UV-VIS λ_{max} (DMF) nm (ε, $mol^{-1} \cdot L\ cm^{-1}$): 280 (3.10), 320 (3.27). FT-IR (KBr), cm^{-1}: v_{max} 2970 (CH_3), 1665 (C=O), 1615 (C=N), 1370, 760 (C_6H_5), 496 (>C-NH-C<). ^{1}H-NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 7.15 (d, 3H, CH-pyrrole), 7.26-7.49 (m, 5H, H-Ar), 7.85 (s, 1H, NH), 9.75 (s, 1H, CH=N). Analysis calculated for $C_{16}H_{16}N_4O$: C, 68.48; H, 5.60; N, 19.72. Found: C, 68.55; H, 5.75; N, 19.99.

2-hydroxyacetophenon-salcyl hydrazine (L2)

The Schiff base L2 was prepared by condensation of the salicylic acid hydrazide (0.23 g, 1.5 mmol) with 2-hydroxyacetophenone (0.136 g, 1 mmol) in methanol (20 ml) using similar methods to the literature (Sarika et al., 2009). The mixture was gently heated under reflux for 2 h and afterwards it was left to crystallize at room temperature. After 48 h, the solid was filtered and dried at room temperature. The ligand (L2) is a white crystalline powder, stable at room temperature, insoluble in water, ethanol, benzene, chloroform, soluble in methanol, dimethylsulfoxide (DMSO), DMF. Yield: 63.5%; m.p. 221 -222°C. UV-VIS λ_{max} (DMF) nm (ε, $mol^{-1} \cdot L\ cm^{-1}$): 218 (3.05), 238 (3.25), 300 (3.14). FT-IR (KBr), cm^{-1}: v_{max} 2970 (CH_3), 1675 (C=O amide), 1620 (C=N), 1285 (Ar-OH), 1380, 750 (C_6H_4). ^{1}H-NMR (DMSO-d_6): δ 2.0 (s, 3H, CH_3), 5.45 (s, 1H, NH), 7.35-7.42 (m, 8H, H-Ar), 12.80 (s, 2H, OH). Analysis calculated for $C_{15}H_{14}N_2O_3$: C, 66.52; H, 5.35; N, 10.77. Found: C, 66.66; H, 5.22; N, 10.36.

[Cu(II)-L1]complex (3)

The Cu(II) complex of L1 was synthesized using general procedure (Tiang-Rong et al., 2007). A solution of Cu $(OAc)_2 \cdot H_2O$ (0.04 g, 0.3 mmol) in methanol (25 ml) was added drop wise to a solution of L1 (0.081 g, 0.2 mmol) in methanol (25 ml). The mixture was stirred at room temperature for 4 h and then evaporated at 90°C, until the solution darkened; there were obtained sparkling black micro crystals, which were filtered, washed with a mixture of ethanol-water (1:1, v/v) and then with ethyl ether. The complex 3 is a black crystalline powder that is stable at room temperature, insoluble in water, ethanol, benzene, chloroform, soluble in methanol, DMSO, DMF. Yield: 65.3%; m.p. 352-354°C. UV-VIS λ_{max} (DMF) nm (ε, $mol^{-1} \cdot L\ cm^{-1}$): $7.9 \cdot 10^4$; Ks = $7.1 \cdot 10^5$; solubility (mol/L): $4.48 \cdot 10^{-4}$, 350 nm. FT-IR (KBr), cm^{-1}: v_{max} 2968 (CH_3), 1612 (C=N), 1648 (C=O), 1416, 1453 (CH_3-CO), 1360, 770 (C_6H_5), 518 (Cu(II)-N), 500 (Cu(II)-O). ^{1}H-NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 7.20 (d, 3H, CH-pyrrole), 7.28-7.50 (m, 5H, H-Ar), 9.78 (s, 1H, CH=N). Analysis calculated for Cu($C_{16}H_{15}N_4O$)(OAc): C, 53.38; H, 4.64; N, 13.53; Cu, 15.86. Found: C, 53.66; H, 4.25; N, 13.91, Cu, 16.27.

[Mg(II)-L2]complex (4)

A solution of $MgSO_4 \cdot 7H_2O$ (0.05 g, 0.2 mmol) in water (5 ml) was added drop wise to a solution of L2 (0.059 g, 0.2 mmol) in methanol (25 ml). The reaction mixture was stirred at room temperature for 4 h and after cooling, the resulted solid was filtered and washed three times with mixture of ethanol-water and then with dry ethanol. The compound was recrystallized from dimethylformamide. The complex is a pink crystalline powder that is stable at room temperature, insoluble in water, ethanol, benzene, chloroform, soluble in methanol, DMSO, DMF. Yield: 61.2%; m.p. 420-423°C. UV-VIS λ_{max} (DMF) nm (ε, $mol^{-1} \cdot L\ cm^{-1}$): $6.27 \cdot 10^4$; Ks = $3.2 \cdot 10^3$; solubility: $1.85 \cdot 10^{-5}$, 220, 240, 275, 305. FT-IR (KBr), cm^{-1}: v_{max} 2985 (CH_3), 1650 (C=O), 1595 (C=N), 1055 (C-O), 1370, 740 (C_6H_4), 478 (Mg-O), 515 (Mg-N). ^{1}H-NMR (DMSO-d6): δ 2.20 (s, 3H, CH_3), 7.28-7.52 (m, 8H, H-Ar); Analysis calculated for [Mg($C_{15}H_{11}N_2O_3$)$\cdot 2H_2O$]: C, 57.86; H, 4.86; N, 9.00; Mg, 7.71; Found: C, 58.12; H, 5.24; N, 9.36; Mg, 8.12.

Acute toxicity assay

The acute toxicity of the ligands (1, 2) and their complexes (3, 4) was studied on mice. The animals, weighting 20 to 25 g, were obtained from Central Animal House, University of Medicine and Pharmacy “Grigore T. Popa” Iasi. The animals were kept in polyethylene boxes, in a controlled environment at constant temperature (24 ± 2°C) with a 12 h light-dark cycle and relative humidity of 40 to 70%. They were kept without food for 24 h before the experiment and water was *ad libitum*. Groups of six mice were used and the studies were carried out in accordance with the current guidelines for the veterinary care of laboratory animals (Guide for the Care and Use of Laboratory Animals, 2011; European Directive, 2010) and were performed under the consent of Ethics Committee for Animal Research of ”Grigore T. Popa” University of Medicine and Pharmacy Iasi. Each group was treated p.o. with compounds in 0.5% sodium carboxymethyl cellulose (Na-CMC) (w/v solution). A group of animals treated with Na-CMC (0.5%) was used as control. The symptoms of toxicity and mortality were observed in the following 10 days. The acute toxicity was evaluated using geometrically progressing doses in single administrations (Salga et al., 2012).

Anti-inflammatory activity

The anti-inflammatory activity was determined in male Wistar rats, weighting 180 to 200 g using carrageenan induced rat paw edema method (Winter et al., 1962; Ravishankar et al., 2011). The animals were randomly divided into group of six rats each. The standard drug (indomethacin) and test compounds (L1, L2, [Cu(II)-L1] complex (3) and [Mg(II-L2)] complex (4)) were administered p.o. as a suspension in Na-CMC 0.5%, 1 h before to carrageenan injection. The control group received only 0.5% w/v solution of Na-CMC. The right hind paw edema was induced by sub-plantar injection of 0.2 ml of 2% carrageenan solution in saline (0.9%). The volume of paw edema (ml) was determined using plethysmometric method before and after 1, 2, 4, 6, 8 and 24 h of carrageenan injection. The anti-inflammatory activity was shown as the variation of the volume of inflammation paw edema (ml).

Statistical analysis

The results were analyzed using one-way analysis of variance (ANOVA) and expressed as mean ± standard error of mean (SEM). Values of $P \leq 0.05$ were considered statistically significant.

RESULTS AND DISCUSSION

Chemistry

The synthetic procedure for the synthesis of Schiff bases involved condensation of 4-aminoantipyrine with pyrrole-2-carboxaldehyde in 1:1 molar ratio (L1) (Figure 1a) and condensation of 2-hydroxyacetophenone with salicylic acid hydrazide in 1:1.5 molar ration (L2) (Figure 1b), respectively.

The [Cu(II)-L1] (3) and [Mg(II)-L2] (4) complexes were prepared in good yields from the reaction of ligands (L1, L2) with corresponding metal salts in methanol solution, in 1:1 molar ratio (Figures 2 and 3).

The structure of the ligands and their complexes was proved using spectroscopic methods and elemental analysis. In the UV-VIS spectrum of L1, a large absorption band appears at 280 nm while for its complex with Cu(II) (3) the peak is shifted at 350 nm, due to the ligand's coordination with the metallic ion. The L2 presents three absorption bands at 218, 238 and 300 nm and for its complex with Mg(II) (4), it was observed at four peaks: 220, 240, 275 and 305 nm. The band of 275 nm suggests that L2 is involved in coordination with the Mg(II).

The IR spectrum of the ligand L1 presents a characteristic band at 1615 cm^{-1} which is due to C=N group vibration. The shifting of this group to lower frequency (1612 cm^{-1}) in the spectrum of [Cu(II)-L1] complex (3) suggests the coordination of metal ion through nitrogen atom of azometine group. It is expected that coordination of nitrogen to the metal atom would reduce the electron density in the azomethine bond and thus lower the C=N group absorption. The band at 1665 cm^{-1} attributed to C=O vibration group in the spectrum of L1 is also shifted to lower frequency (1648 cm^{-1}) in the spectrum of its Cu(II) complex, which indicates the involvement of oxygen atom from C=O group in bonding with metal ion. Two new bands, which are not present in the spectrum of L1 appeared in the spectrum of [Cu(II)-L1] complex (3) at 500 and 518 cm^{-1} corresponding to vibration of M-O and M-N groups. The appearance of these bands supports the involvement of N and O atoms in complexation with Cu(II). Other two absorption bands, at 1416 and 1453 cm^{-1}, which were assigned to the vibration frequency of the acetate group with monodentate coordination were observed in the spectrum of the [Cu(II)-L1] complex (3).

In the FT-IR spectrum of [Mg(II)-L2] complex (4), the characteristic band of azometine group (C=N) vibration appeared at 1595 cm^{-1}. This band is shifted towards to the band at 1620 cm^{-1} assigned to the same group in the spectrum of the free ligand (L2).

The lower frequency of the azomethine group in the spectrum of [Mg(II)-L2] (4) supports the coordination of imino nitrogen with Mg(II) ion. The band at 1285 cm^{-1} assigned to the stretching frequency of C-OH (phenolic) observed in the spectrum of L2 disappeared from the spectrum of complex 4. In the spectrum of the [Mg(II)-L2] (4), the bands due to the stretching vibration of the M-O and M-N bonds appeared at 478 and 515 cm^{-1}, respectively.

The ^{1}H-NMR spectra of the complexes, in reference with that of the ligands, present significant changes due to the coordination process. The -NH proton signal of L1 (7.85 ppm) disappears upon complexation with Cu(II) (3). The aromatic protons and the methyl protons do not seem to register significant changes as a result of the coordination process. The ^{1}H-NMR spectrum of the complex (4), comparatively with that of L2, presents significant changes due to the coordination process. The proton signal of N<u>H</u> and O<u>H</u> (5.45 and 12.80 ppm) from ligand disappears upon complexation with Mg(II).

The results of the elemental analysis of ligands 1 and 2 and their complexes (3 and 4) were found to be in good agreement with the values that were theoretically calculated.

Toxicity assay

In order to evaluate the toxicity of the ligands (L1 and L2) and their complexes (3 and 4), several doses of 100, 200, 400 and 800 mg/kg were used. At doses of 100 and 200 mg/kg, all compounds are nontoxic. At dose of 400 mg/kg, L1 and L2 and their complexes have induced central phenomena, which were manifested by shaking and fast breathing. It was also noticed that, in dose of 800 mg/kg, all compounds induced sudden death due to convulsive phenomena.

Anti-inflammatory activity

The results (Table 1) revealed that the tested compounds

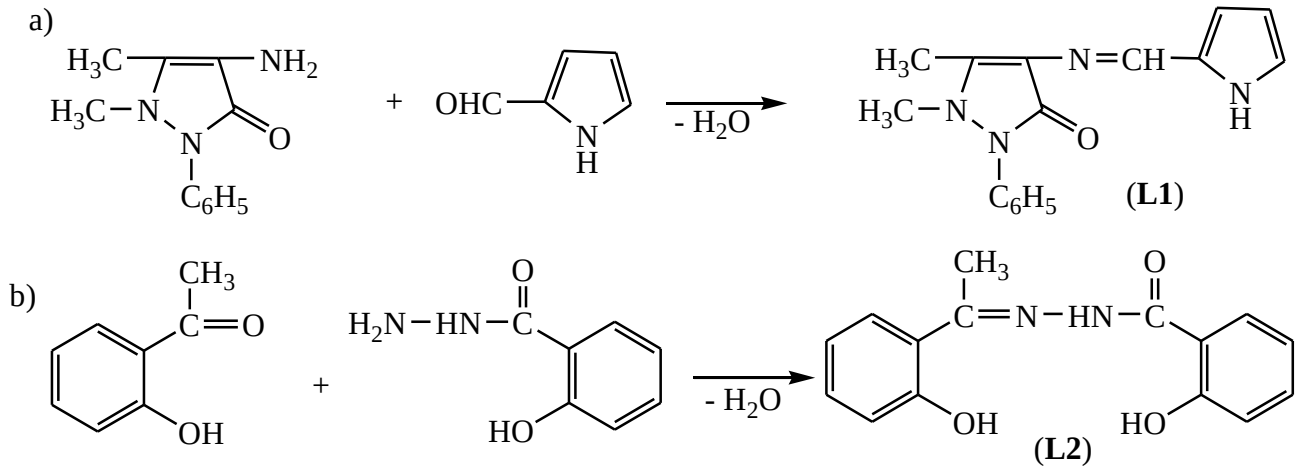

Figure 1. Synthesis of the Schiff bases (L1, L2).

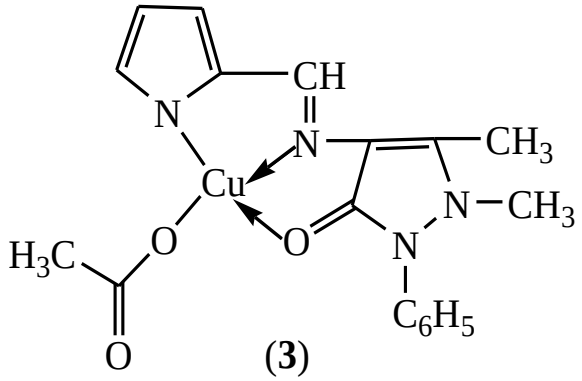

Figure 2. The proposed structure of the [Cu(II)-L1] complex (3).

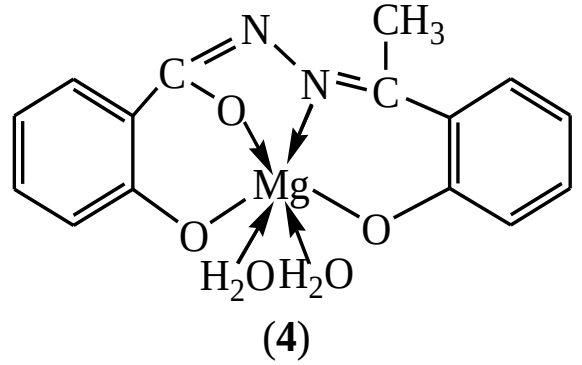

Figure 3. The proposed structure of the Mg(II)-L2] complex (4).

have significantly anti-inflammatory effect in reference with the control group and the effect is comparable with the effect of indomethacin, which was used as a reference drug. The effect starts at 4 h, increases at 6 and 8 h and then begins to decrease. In the group treated with L1 (15 mg/kg), the maximum effect was observed after 8 h, when the volume of paw edema was 30.83±3.62 in reference with the control (38.50±1.80). In the group treated with L2 (5.4 mg/kg), the volume of paw edema was 23.60±7.02 after 8 h, which means that it is 1.3 times more active than L1 and comparable with indomethacin (25.32±3.61).

The [Cu(II)-L1] complex (3) showed a higher effect at a dose of 10 mg/kg than at a dose of 5 mg/kg. At 8 h after the administration of the compound, in dose of 10 mg/kg, the volume of paw edema was 22.50±7.54, which means that it is 1.4 time more active than its ligand L1 (30.83±3.62) and slightly higher than indomethacin (25.32±3.61). In the same conditions, the volume of paw edema was 31.67±9.96 when the complex 3 was administered in dose of 5 mg/kg. At this concentration, the complex is less active than indomethacin but remain active in reference with control (38.50±1.80). The anti-inflammatory effect of the [Mg(II)-2] complex (4) (6 mg/kg) is also important (26.55±3.82) at 8 h in reference with control (38.50±1.80) and comparable with indomethacin (25.32±3.61), but it is slightly lower than its ligand L2 (23.60±7.02).

Conclusions

Conclusively, two new Schiff bases and their Cu(II) and Mg(II) complexes have been synthesized and characterized using spectral methods (UV-VIS, IR, ^{1}H-NMR) and elemental analysis. All tested compounds are not toxic at dose of 100 and 200 mg/kg. At dose of 10 mg/kg, the [Cu(II)-L1] complex (3) was the most active compound in

Table 1. *In vivo* anti-inflammatory activity of the synthesized compounds in carrageenan-induced paw edema.

Compound	Dose (mg/kg)	Paw edema (ml±SME)						
		0	1 h	2 h	4 h	6 h	8 h	24 h
Control	-	18.17±1.02	27.83±0.62	30.17±0.32	35.17±1.06	38.83±2.36	38.50±1.80	23.67±1.18
I	10	22.30±4.05	25.30±2.71	26.90±2.04	25.02±3.21	24.80±2.25	25.32±3.61	24.55±2.77
L1	15	19.50±0.62	28.33±1.42	30.33±0.80	33.83±0.63*	32.00±3.20**	30.83±3.62**	21.83±0.86*
3	5	19.83±0.78	26.83±0.47	28.50±0.80	34.50±0.95	33.33±7.78*	31.67±9.96**	23.50±0.08
3	10	20.67±1.18	29.67±0.86	33.83±1.72	27.17±3.76**	23.67±7.14**	22.50±7.54**	21.33±1.56**
L2	5.4	21.20±2.46	30.80±1.72	31.33±0.96	29.83±4.36**	24.90±6.56**	23.60±7.02**	22.40±1.08
4	6	19.66±0.32	23.66±1.34	27.50±0.94	30.16±1.26**	28.66±2.44**	26.55±3.82**	23.64±4.46

I: Indomethacin; *P<0.05, ** P<0.001 in reference with control group.

reduction of the carrageenan-induced paw edema, its effect being comparable with the effect of indomethacin.

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