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Synthesis, characterization and antimicrobial activities of 1,5-dimethyl-2-phenyl-4-(pyrolidin-2-ylideneamino)-pyrazolidin-3-one and complex with iron(II)

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ABSTRACT

A multifunctional ligand derivative of pyrrolidone has been synthesized by condensation reaction between 4-aminoantipyrine and 2-pyrrolidinone. The ligand and its Iron(II) complex were characterized using physical method and UV and IR techniques. The ligand and Fe(II) complex were tested against broad spectrums of bacterial organisms and the results show that both the ligand and complex were active against various organisms tested.

Capsule Summary: Derivative of pyrrolidone and Iron(II) complex were synthesized and characterized along antimicrobial activities evaluation. Both ligand and complex were active against various organisms tested.

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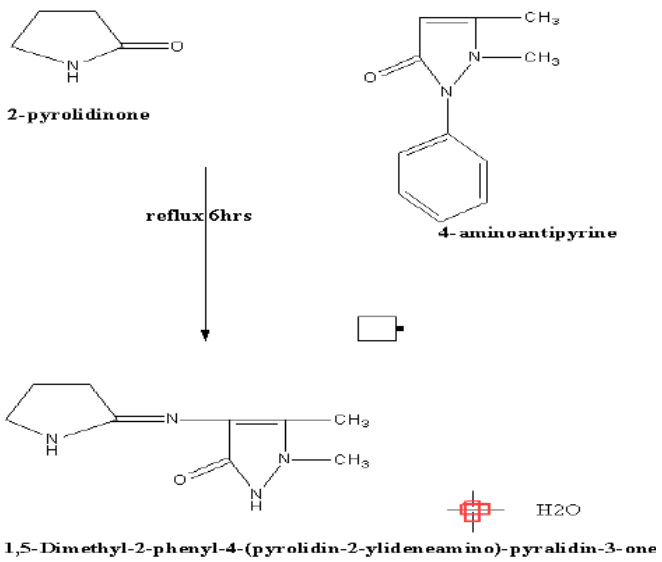
INTRODUCTION

Synthesis of a wide range derivatives of pyrrolidone and their metal complexes is of great interest due to the presence of donor sites viz, oxygen and nitrogen atoms. This can act as ligands and form complexes with metal ions through coordinate bond (Anasuya et al., 2015). Owing to their wide range of biological activities and pharmacological properties, the synthesis of substituted pyrrolidone has become a field of increasing interest in organic synthesis during the last few decades (Eleonora et al., 2012). Transition metals show many remarkable pharmaceutical as well as industrial applications and so Coordination compounds of transition metals find their use in almost every field of human life. Reviewed work has shown that Interesting pharmacological properties have been associated with pyrrolidone and their derivatives. These compounds have shown antimicrobial, antimalarial, anti-inflammatory, antitumor, and anti-parasitic activities (Arun et al., 2013; Bakr et al., 2012; Daferner et al., 2002; Haddad et al., 2015; Ignatova et al., 2007). In view of these, this work is aimed at synthesizing a novel derivative of this ligand, characterized the ligand and the complex and tests their antimicrobial potency.

MATERIAL AND METHODS

Chemical and reagents

All reagents used were of analytical grades and were employed without further purification. 4-aminoantipyrine



Scheme 1: 1, 5-dimethyl-2-phenyl-4-(pyrolidin-2-ylideneamino)-pyrazolidin-3-one synthesis route

98% and 2-pyrrolidinone 98% were obtained from Sigma Aldrich. Ethanol, Iron(II)sulphateheptahydrate ($Fe.SO_4.7H_2O$) ,methanol, chlrorform, n-hexane, THF, and Diethylether were used without further purification.

Synthesis of 1,5-Dimethyl-2-Phenyl-4-(pyrolidin-2-ylideneamino)-Pyrazolidin-3-one

Equimolar amount of 4-aminoantipyrine (4.878g,) and 2-pyrrolidinone (1.8ml) were dissolved in 25ml of ethanol in a round bottom flask. The mixture was refluxed for 6hr at 75 ^{0}C and a yellow solution was obtained. The solution was left to stand for three weeks and pale yellow crystals were obtained by filtration.

Synthesis of the Fe(II) complex

The metal complex was prepared by adding Iron(II)sulphate heptahydrate ($FeSO_4.7H_2O$) (0.139 g, 0.5 mmol) to a solution of the ligand (1,5-Dimethyl-2-phenyl-4-(pyrollidin-2-ylidenamino)-pyrazolidin-3-one (0.284 mg, 1.0 mmol) in 10mls of ethanol. The yellow solution obtained was refluxed for two hours and allowed to stay overnight. The solution was then poured into an evaporating dish, the solvent evaporated and the brown amorphous complex crystals were obtained.

UV and IR analysis

The ligand and the complex were characterized using UV-Visible and IR spectral analysis.

Antimicrobial activity evaluation

The antimicrobial activities of the ligand and the Fe(II) complex were determined using diffusion method. 0.01 g of the samples were weighed and dissolved in 10 ml of DMSO to obtain the initial concentrations of 1mg/ml which were used to test for the antimicrobial of the samples. Muller Hinton agar which was prepare according to manufacturer's instructions, sterilized at 121^{0}C for 15 minutes, poured into sterile petri dishes and was allowed to cool and solidify.

The sterilized medium was seeded with 0.1 ml of the standard inoculum of the test microbes, the inoculum was spread evenly over the surface of the medium by the used of sterile swab. By the use of a sterile cork borer of 6 mm, a weel was cut at the center of each inoculated medium. 0.1 ml of the solutions of the compounds at 1µg/ml was then introduced into each well on the inoculated medium. The inoculated mediums were then incubated at 37 ^{0}C for 24 hrs, after which each of the mediums was observed for the zone of inhibition of growth. The zones were measured with a transparent ruler and the results recorded in millimeters. The results are presented in Table 2.

Minimum inhibitory concentration (MIC) of the compounds was also determined using the Broth dilution method. Mueller Hinton broth was prepared, 10mls was dispensed into the test tubes and was sterilized at 121 ^{0}C for 15minutes, the broth was allowed to cool. Mc-farlands turbidity standard scale number 0.5 was prepared to give turbid solution. Normal saline was prepared, 10 ml was dispensed into sterile test tube and the test microbes were inoculated at 37 ^{0}C for 6 h. Dilution of the test microbes was made in the normal saline until the turbidity reached that of the Mc-farland scale by visual comparison, at this point, the test microbes had a concentration of about 1.5×10^6 CUF/ml. Two fold serial dilutions of the compounds were made in the sterile broth to obtain the concentrations at 1mg/ml, 0.5 mg/ml, 0.25 mg/ml, 0.125 mg/ml and 0.06 mg/ml. The initial concentration was obtained by dissolving 0.01g of the compound in 10mls of the sterile broth. From the various concentrations obtained, 0.1ml of the test microbes in the normal saline was then inoculated into the different concentrations, incubated at 37 ^{0}C for 24 hours after which the test tubes of the broth were observed for turbidity (growth). The lowest concentrations of the compounds in the sterile broth which shows no turbidity was recorded as the minimum inhibitory concentration.

The minimum bactericidal concentrations (MBC) were also carried out to determine if the tested microbes were killed or only their growth was inhibited. The content of the MIC in the serial dilution were then sub cultured onto the prepared medium, incubated at 37 ^{0}C for 24 hours, after which the plates of the medium were observed for colony growth. The MBC were the plates with lowest concentration of the compounds without colony growth.

RESULTS AND DISCUSSION

The color and solubility of the ligand and the complex (Table 1) shows pale yellow crystals and brown respectively with both insoluble in H_2O and CH_3OH but soluble in EtOH, THF, Et_2O, CCl_4 and n-hexane.

Table 1: Physiochemical properties of the ligand and the metal complex

Compounds	colour	Texture	M. P. (^{0}C)	λ_{max} (nm)	Solubility
Ligand	Pale yellow	Crystal	87-103	328	Insoluble in CH_3OH, and H_2O but soluble in EtOH, Et_2O,THF n-hexane and CCl_4
Iron complex	brown	Amorphous crystal	89-99	386	Insoluble in H_2O,partially soluble in CH_3OH but readily soluble in EtOH,n-hexane, CCl_4 and THF

Table 2: Antimicrobial screening of 1,5-Dimethyl-2-Phenyl-4-(pyrolidin-2-ylideneamino)-Pyrazolidin-3-one and its Fe(II) complex

Organisms	ligand	Complex	Ciprofloxacin	Fluconazole
Staphylococcus aureus	S	S	S	R
Streptococcus pyogenes	S	R	S	R
Corynebacterium ulcerans	R	S	S	R
Escherichia coli	R	S	S	R
Klebsiela pneumoniae	S	R	R	R
Salmonella typhi	S	S	S	R
Pseudomonas aerieginosa	S	S	R	R
Candida albicans	R	S	R	S
Candida tropycalis	S	S	R	S
Candida stellaftodea	R	R	R	S

S = active, R = resistant

Table 3: Zones of inhibition of 1,5-dimethyl-2-phenyl-4-(pyrolidin-2-ylideneamino)-pyrazolidin-3-one and its complex and the drugs against the tested microbes

Organisms	ligand	Complex	Ciprofloxacin	Fluconazole
Staphylococcus aureus	25	22	32	0
Streptococcus pyogenes	24	0	30	0
Corynebacterium ulcerans	0	20	34	0
Escherichia coli	0	24	37	0
Klebsiela pneumoniae	27	0	0	0
Salmonella typhi	22	21	40	0
Pseudomonas aerieginosa	20	23	0	0
Candida albicans	0	21	0	32
Candida tropycalis	21	24	0	35
Candida stellaftodea	0	0	0	37

S = active, R = resistant

From Table 1, the ligand λ_{max} (nm) was 328 nm, while that of the iron(II) complex was 386 nm. The shift in λ_{max} (nm) of Fe(II) complex is within the range at which the metal absorbs the UV-visible radiation, which confirms the ligand to metal coordination.

In order to study the binding mode of the ligand to the Iron in the complex, the IR spectrum of the ligand was compared with the spectra of the complex. The IR spectra of the free ligand shows the characteristic > C=N band in the 1540 cm^{-1} region which is shifted to 1494.7 cm^{-1} a lower frequencies in the spectra of the metal complex which is an indication of

Table 4: The MIC for the ligand and the complex (µg/ml)

Test organisms	Ligand					Complex				
	1	0.5	0.25	0.125	0.062	1	0.5	0.25	0.125	0.062
	(µg/ml)									
Staphylococcus aureus	-	-	*	+	++	-	-	*	+	++
Streptococcus pyogenes	-	-	*	+	++	-	*	+	+	++
Corynebacterium ulcerans	-	-	*	+	++	-	-	*	+	++
Escherichia coli	-	-	*	+	++	-	-	*	+	++
Klebsiela pneumoniae	-	-	-	+	++	-	*	+	+	++
Salmonella typhi	-	-	*	+	++	-	-	*	+	++
Pseudomonas aerieginosa	-	-	*	+	++	-	-	*	+	++
Candida albicans	-	-	-	+	++	-	-	*	+	++
Candida tropycalis	-	-	*	+	++	-	-	*	+	++

Key: -no growth, *MIC, +low growth, ++moderate growth

Table 5: MBC/MFC for the ligand and complex (µg/ml)

Test Organisms	Ligand					Complex				
	1	0.5	0.25	0.125	0.062	1	0.5	0.25	0.125	0.062
	(µg/ml)									
Staphylococcus aureus	-	*	+	++	+++	*	+	++	+++	+++
Streptococcus pyogenes	-	*	+	++	+++	*	+	++	+++	+++
Corynebacterium ulcerans	-	*	+	+	++	*	+	++	+++	+++
Escherichia coli	-	*	+	+	++	-	*	+	+++	+++
Klebsiela pneumoniae	-	*	+	++	+++	-	+	++	+++	+++
Salmonella typhi	*	+	++	+++	+++	*	+	++	+++	+++
Pseudomonas aerieginosa	*	+	++	+++	+++	-	*	+	++	+++
Candida albicans	*	+	++	+++	+++	*	+	++	+++	+++
Candida tropycalis	*	+	++	+++	+++	-	*	+	++	+++

Key: -no growth, * MBC/MFC, +scanty colony, ++moderate growth, +++heavy colonies growth

ligation taken place (El-Saied et al., 2001; Mahmoud et al., 2004; Ocheni et al., 2016). The ligand and complex also displayed bands at 1587-1640 cm^{-1} which is due to C=O stretch implying the C=O bond does not participate in complex formation. Similarly N-H bond in ligand and complex is assigned to the double peaks at 3224 and 3422 cm^{-1} while the band at 3067-2914 cm^{-1} is due to C-H stretch aromatic.

The antimicrobial properties of this ligand and its complex as indicated in Tables 2, 3, 4, and 5 proofs that both ligand and complex were active against the tested organisms. Table 3 shows that the ligand was active against six organisms out of ten. The complex was active against seven of the organisms out of ten. The activity of the complex is more than the ligand as earlier reported (Ocheni et al., 2016ab). Table 3 indicates the zones of inhibition of the ligand and complex as well as the control drugs. The complex was more active and show zones of inhibition against candida species which are resistant to the control drug ciprofloxacin. Table 4 indicates that the minimum inhibitory concentration that give moderate and active growth for the ligand and complex were 0.25, 0.125 and 0.062. Table 5 indicates that these organisms that show activities were actually killed by this ligand and complex at high concentration. So far, this method is proved effiecntt for the synthesis of iron(II) complexes for possible applications as an bioactive agent (Easmon et al., 2001; Hegg and Jr, 1997; Kuwabara et al., 1994; Lee et al., 2010; Langer et al., 2011; Mukherjee et al., 2005; Mülsch et al., 1991; Sugiura and Kikuchi, 1978).

CONCLUSIONS

The derivative of pyrrolidone was synthesized by condensation reaction between 4-aminoantipyrine and 2-pyrrolidinone. The ligand and Iron(II) complex were tested for their antimicrobial activities against selected panel of microorganisms and the results show that both the ligand and complex were active against various organisms microbes.

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