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Toxicological and Biochemical Investigations in Rats Administered Co(II) Chelate Of 1-(-5-Hydroxy-3-Methyl-1-Phenyl-*1H*-Pyrazol-4-yl)Ethan-1-one

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Abstract
Cobalt(II) chelate of 1-(-5-hydroxyl-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)ethan-1-one was synthesized by reacting 1mmol (189 g) previously dissolved in water (50 cm^3) was 2 mmol (163 g) of HPMAP) dissolved in ethanol (50 cm^3). The resulting pinkish clear solution mixture was poured, with constant stirring to 250 cm^3 distilled water. This work was done to evaluate synthesized Co(II) chelate of 1-(-5-hydroxyl-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)ethan-1-one, acute toxicity, hematological parameters, and biochemical effects on vital organs such as the liver and kidney. Consequently, graded doses of 10, 100, 1000, 1600, 2900, and 5000 mg Cobalt(II) chelate of 1-(-5-hydroxyl-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)ethan-1-one per kg body weight were administered to determine their effects on acute toxicity, haematological parameters, liver and renal function indices of rats. Acute toxicity tests recorded no mortality and no visible sign of toxicity. However there were significant increase in (PCV, RBC and Hb) while (WBC) there were significantly reduced. There were significant increases in AST, ALT, and ALP activities at all dose levels except at the 100 mg/kg dose level. No significant differences were observed in the (Creatinine and Urea) kidney of rats administered with these compounds. These results show that Cobalt(II) chelate of 1-(-5-hydroxyl-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)ethan-1-one may elicit toxic effects on the liver on prolonged administration, however no toxic effect was observed on the kidney within the duration of this study.

Keywords: Cobalt(II) chelate of 1-(-5-hydroxyl-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)ethan-1-one acylpyrazol-5-ones, Acute toxicity, Liver, Kidney

1. Introduction

Significant interest has been observed in the medicinal and pharmacological properties Jensen (1959) of 4-acylpyrazol-5-ones and their transition metal complexes since they were synthesized. The 4-acylpyrazol-5-one is heterocyclic β-diketone composed of *β-lactam* nucleus bearing two nitrogen atoms and two carbonyl functionalities The extensive interest in these biological compounds is based on their uses and potential applications as antimicrobial (Okereke, *et al* 2016), antitrypanosomal (Okereke *et al* 2016), antimalarial (Ujam *et al* 2019), antimycobacterial (Castagnolo *et al* 2009), antipyretic (Gunasekaran *et al*, 2011), anti-inflammatory agents (Caruso *et al* 2013). Their biological activity is based on the pyrazolone/pyrazole nucleus which is an important pharmacophoric scaffold similar to antipyrine and phenazone (de Pascali *et al*, 2014).

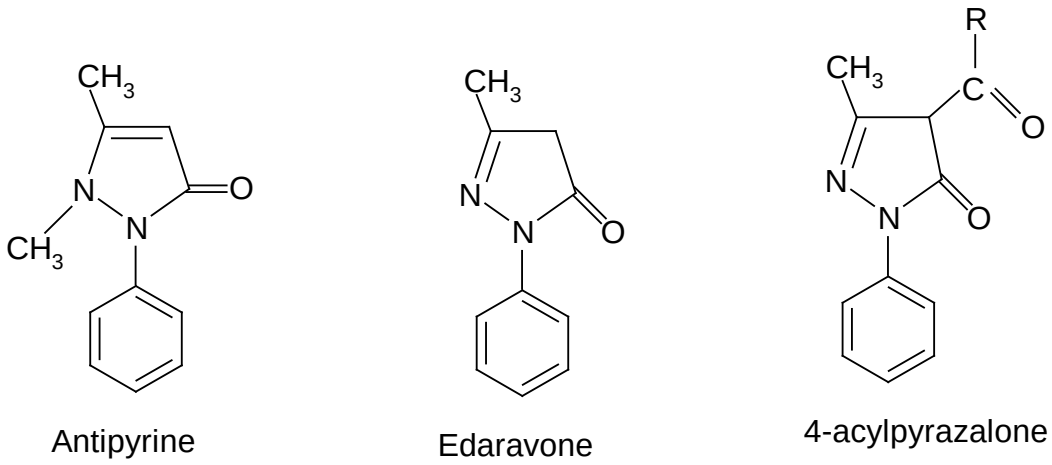

Fig 1: Structure of antipyrine, Edaravone, and 4-acylpyrazol-5-ones

These pyrazol-5-ones and their derivatives are synthesized by functionalization of 1-phenyl-3-methylpyrazol-5-one at the C-4 of PMP in dioxane at a refluxe (Jensen, B.S., 1959, Okafor, 1981), Uzoukwu *et al*, 1990, Ashegbeloyin *et al*, 2015, Okereke *et al*, 2016 and Okparaeke, *et al* 2012.

It is still uncertain whether $Ca(OH)_2$ acted as a catalyst, a calcium-pyrazolonate stability, 4-Acylpyrazolonates are used as spectator donors for intermediate species in organic reactions (Pettinari *et al* 2004). Investigation of coordination compounds of lanthanide ions has been done by several workers owing to their fluorescent broad applications in biochemistry (Jadeja *et al* 2014), materials science (Yang 2000), and medicine (Richardson *et al* 1979). Because of its promising antipyretic and analgesic activity these drugs are used for treating fever and flu-like infections, edaravone (3-methyl-1-phenyl-2-pyrazoline-5-one) which has close resemblance to 4-acyl-pyrazol-5-one is used in the treatment of brain ischemia (Watanabe *et al* 1994) and myocardial ischemia (Fung *et al*, 2002). Also, because of pyrazole functionality, 4-acyl pyrazolone exhibit cytoxic activity against bacterial (Dong *et al* 2013) and fungal pathogens (Thaker *et al*, 2008). To the best of our knowledge, no work has been done on the acute and sub-acute toxicity of these compounds. This work was done to bridge this gap in knowledge.

2. Materials and methods

2.1. Source of materials

The 3-methyl-1-phenyl-IH-pyrazol-5(4H)-one (PMP), Methanol, DMSO, DMF, CCl_3, Ethanol was obtained from Fluka. Dioxane was obtained from Aldrich.

2.2. Characterization Techniques and description of equipment

The synthesized compounds were characterized using different techniques. Elemental analyzer (C, H, N, F) of the synthesized compounds were performed on a model Perkin Elmer elemental analyzer.

2.3. Synthesis of 1-phenyl-3-methyl-4-acetylpyrazol-5-one (HPMAP)

1-phenyl-3- methyl-pyrazol-5-one (HPMP) 8.5 g (2 mmol) previously dissolved in dioxane (100 cm^3) as dissolved in 100 cm^3 in a 1-litre, 3-necked quick flask, fitted with electromechanical stirrer, a condenser by warming. The anhy. of $Ca(OH)_2$ (10g) was added and the mixture stirred. Acetyl chloride (3.5cm^3) from a quick fit dropping funnel was added drop-wise within 3 minutes. The reaction was exothermic, and was stirred for 1 hr and the flask intermittently cooled under tap water, orange mixture was then poured into a chilled HCl 3 M 500 cm^3 solution with vigorous stirring. The reaction mixture was later kept in a refrigerator until pinkish crystals separated. They were filtered off, washed with copious water and recrystallized from aqueous ethanol to give white crystals. The crystals were dried in air and stored in a desiccator.

2.4. Synthesis of 1-phenyl-3-methyl-4-acetyl-5-pyrazolonato Cobalt (II) complex

189g (5 mmol) of cobalt(II) chloride was accurately weighed and dissolved in 75 cm^3 95 % aqueous ethanol with warming and slowly added, with stirring, to a hot ethanolic solution of the ligand containing 163g (10 mmol) of PMP previously dissolved 75 cm^3 (CH_3CH_2OH) ethanol. The pinkish precipitates which formed were filtered with a Buchner, washed with aqueous ethanol-water mixture (1:1) and, air-dried. The precipitates were stored a dessiccator over fused $CaCl_2$.

2.5. Animals

Male and female albino rats of wistar strain were obtained from the Animal House of the Department of Pharmacology and Toxicology, University of Nigeria, Nsukka, Enugu State. These animals were acclimatized for two weeks; they were fed chow and

water ad libitum. The use and care of laboratory animals in the study were in accordance with ethical guideline as contained in the University of Nigeria Ethical Provisions for the use of Laboratory animals.

2.6. Chemicals

All chemicals used were of the analytical grade. Kits used for Alanine Transaminase, Aspartate Transaminase, Alkaline Phosphatase, total protein, albumin, total bilirubin, urea and creatinine tests were obtained from Randox Laboratories (Crumlin, Co Anthrim, Spain). Reagents of BDH Laboratories (BDH Chemicals Limited, Poole, England) were also used.

2.7. Acute Toxicity Tests

The Lorke's method (1983) was used. The procedure was conducted in two phases. In the first phase, nine rats were divided into three groups of three rats each. The groups were administered at 10 mg/kg, 100 mg/kg and 1000 mg/kg of the ligand and complex per kg body weight of rats. All the rats were kept under the same conditions and monitored for toxicity signs or mortality for 24 h. In the second phase, a total of three rats were used. The rats were divided into three groups of one rat each and were administered 1600, 2900 and 5000 mg/kg. They were also observed for toxicity signs and mortality after 24 h.

2.8. Sub-acute toxicity studies

A total of twenty five albino rats were divided into five groups of five rats each. The first group serves as the control (5 cm kg^{-1} of distilled water) while the remaining four groups were administered 100, 200 mg/kg ligand and complex per kg body weight of rats each for 14 days.

2.8.1. Blood sample collection

At the end of the treatment, blood samples were collected through the retro-orbital plexus puncture into sterile containers with or without anticoagulant.

2.8.2. Biochemical analysis

Packed cell volume (PCV), haemoglobin (Hb) red blood cells (RBC), white blood cell (WBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), urea and creatinine were determined colorimetrically by using the standard ready-to-use kits and methods of Randox laboratories. The manufacturer's instructions for each biochemical parameter were strictly followed in the course of the investigation.

2.9. Statistical analysis

All data were expressed as mean ± SD (n = 5). ANOVA was used to test for difference among all the groups. Dennett multiple range test was used to test for significant differences among the means, A $P<0.05$ was considered statistically significant.

3. Results

Table 1 shows the physical data for the HPMAP and its Co(II) complex.

Table 2 shows the effect of graded doses of Co(II) ligand (HPMAP) and Co(II) complex $[Co(PMAP)_2.2H_2O]$ on toxicity of rats. No significant toxic effects were observed. Administration of the compounds to rats, up to 5000 mg/kg per body weight resulted in no mortality of the test rats after 24 h. Hence the LD_{50} of Co(II) ligand (HPMAP) and its Co(II) complex $[Co(PMAP)_2.2H_2O]$ is estimated to be greater than 5000 mg/kg.

Table 3 shows that there were significant difference in the concentrations of PCV, RBC, WBC, lymphocytes and neutrophils between the control and the test groups. It also shows no significant difference in the blood composition of Hb.

AST activity were significantly increased at the 100, 200 mg/kg does levels; ALP shows a reduction in the activity except at 200 mg/kg dose of the complex; ALT show a significant reduction **(Table 4)**.

Table 5 shows the effect of graded doses of Co(II) ligand (HPMAP) and Co(II) complex $[Co(PMAP)_2.2H_2O]$ on renal function indices; there were non-dose dependent increase, Creatinine and Urea levels were not significantly affected.

4. Discussion

The Cobalt(II) chelate of bis(1-(5-hydroxyl-3-methyl-1-phenyl-1H-pyrazol-4-yl) ethan-one dehydrate, $[Co(PMAP)_2.H_2O]$ was successfully synthesized in good yield (70 %); revealed the physical data of the compounds of having good percentage yield and melting points.

Table 1

Physical Data for the 4-Acetylpyrazolones and Co(II) complex of 1-phenyl-3-methyl-4-acylpyrazolones

Molecular formula	Molar Mass	Colour	Yield %	Melting Point ^{0}C
$C_{12}H_{12}N_2$ (HPMAP)	216.23	White	52	57-58
$CoC_{24}H_{28}O_6N_4$	527.39	Pink	70	165-166

[$Co(PMAP)_2.2H_2O$]				

Table 2
Results of acute toxicity test on rats with HPMAP and [$Co(PMAP)_2.2H_2O$] showed nil toxicity, and pertinent indication that both ligand and complex are non-toxic even a very high dose of 5000 mg/kg body weight.

Treatment	No. of rats	Mortality recorded	Observations
First phase			
10 mg/kg	3	Nil	No visible sign of toxicity
100 mg/kg	3	Nil	-
1000mg/kg	3	Nil	-
Second phase			
1600 mg/kg	1	Nil	No visible sign of toxicity
2900 mg/kg	1	Nil	-
5000 mg/kg	1	Nil	-

Table 3
Effects of administration of (HPMAP) and [$Co(PMAP)_2.2H_2O$] on some haematological indices

Parameters	**Normal Control**	**Co(II) Ligand** (HPMAP)		**Co(II) Complex** ($Co(PMAP)_2.2H_2O$)	
		100mg/kg	**200mg/kg**	**100mg/kg**	**200mg/kg**
PCV (%)	45.80 ± 2.11^a	45.80 ± 1.39^a	47.25 ± 1.75^b	45.67 ± 1.05^a	48.00 ± 1.64^b
Hb (g/dl)	$14.66\pm.19^a$	$14.68\pm.16^a$	$14.63\pm.25^a$	$14.60\pm.17^a$	$14.94\pm.14^a$
RBC (x 10^{12}/L)	$4.54\pm.17^a$	$4.78\pm.12^b$	$4.77\pm.19^b$	$4.77\pm.10^b$	$4.78\pm.19^b$
WBC (x 10^9/L)	$4.85\pm.30^a$	$4.73\pm.31^a$	$4.84\pm.12^a$	$4.39\pm.21^b$	$5.19\pm.22^c$
Lymphocytes (%)	33.40 ± 1.96^a	34.20 ± 1.07^a	34.25 ± 1.43^a	$34.83\pm.79^a$	36.40 ± 1.81^b
Neutrophils (%)	66.60 ± 1.96^a	65.80 ± 1.07^a	65.75 ± 1.43^a	$65.17\pm.79^a$	63.40 ± 1.63^b

Results are expressed as mean ± SD (n = 5). Values with different superscripts are significant at $p < 0.05$.

Table 4
Effects of administration of (HPMAP) and [$Co(PMAP)_2.2H_2O$] on some Liver function indices

Parameters	**Normal Control**	**Co(II) Ligand** (HPMAP)		**Co(II) Complex** ($Co(PMAP)_2.2H_2O$)	
		100mg/kg	**200mg/kg**	**100mg/kg**	**200mg/kg**
AST (IU/L)	173.20 ± 2.5^a	179.20 ± 3.93^b	176.60 ± 3.68^b	177.40 ± 6.80^b	178.40 ± 3.69^b
ALP (IU/L)	64.00 ± 3.96^a	59.20 ± 5.43^b	57.80 ± 7.76^b	58.80 ± 5.11^b	65.00 ± 4.97^a
ALT (IU/L)	44.00 ± 3.15^a	40.20 ± 2.63^b	41.00 ± 3.41^b	45.60 ± 1.99^a	40.00 ± 2.09^b

Results are expressed as mean ± SD (n = 5). Values with different superscripts are significant at $p < 0.05$.

Table 5
Effects of administration of (HPMAP) and [$Co(PMAP)_2.2H_2O$] on Renal function indices

Parameters	**Normal Control**	**Co(II) Ligand** (HPMAP)		**Co(II) Complex** ($Co(PMAP)_2.2H_2O$)	
		100mg/kg	**200mg/kg**	**100mg/kg**	**200mg/kg**
Creatinine (mg/dl)	44.60 ± 3.33^a	47.00 ± 3.30^b	36.40 ± 2.71^c	42.00 ± 2.70^a	39.80 ± 2.76^c
Urea (mg/dl)	0.85 ± 0.03^a	0.81 ± 0.08^a	0.92 ± 0.04^b	0.84 ± 0.06^a	0.89 ± 0.04^b

Results are expressed as mean ± SD (n = 5). Values with different superscripts are significant at $p < 0.05$.

The extensive interest in these biological compounds is based on their uses and potential applications as antimicrobial (Okereke, *et al* 2016), antitrypanosomal (Okereke *et al* 2016), antimalarial (Ujam *et al* 2019), antimycobacterial (Castagnolo *et al* 2009), antipyretic (Gunasekaran *et al*, 2011), anti-inflammatory agents (Caruso *et al* 2013). Their biological activity is based on the pyrazolone/pyrazole nucleus which is an important pharmacophoric scaffold similar to antipyrine and phenazone (de Pascali *et al*, 2014). Toxicological assessment of rats administered graded doses of Cobalt(II) chelate of 1-(-5-hydroxyl-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)ethan-1-one revealed significant reduction in weight gain of rats administered. This indicates that at these doses, this compounds may be toxic especially when administered on long term basis. Acute toxicity studies **(Table 2)** revealed no mortality and no visible sign of toxicity. Acute toxicity is toxicity elicited as a result of short term exposure to a toxicant. The LD_{50} was not calculated because there was no mortality at 5000 mg/kg dose level indicating that it is relatively safe under short term exposure. However, acute toxicity data are of limited clinical application since cumulative toxic effects do occur even at low doses. Sub-acute and chronic toxicity are useful in evaluating the safety profile of compounds. PCV, RBC, WBC, Hb, Lymphocytes and Neutrophils were studied to evaluate haematological parameters and its concentrations (blood composition) **(Table 3)**. AST, ALP, and ALT were also studied to evaluate liver malfunctions **(Table 4)**. Significant increases in AST activity at the 100, 200 mg/kg does levels, ALP shows a reduction in the activity except at 200 mg/kg dose of the complex; ALT show a significant reduction. . This indicates that at these dose levels, there is a possibility of liver damage on long term exposure. The effect of compounds as most markers of renal function were not significantly affected.

5. Conclusion

No short term toxic effect was observed on administration of Cobalt(II) chelate of 1-(-5-hydroxyl-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)ethan-1-one, (Co(II) ligand (HPMAP) and Co(II) complex $[Co(PMAP)_2.2H_2O]$ there was also no toxic effect on renal function within the duration of this study. Results on liver function indicate the potential hepatotoxic effect of Cobalt(II) chelate of 1-(-5-hydroxyl-3-methyl-1-phenyl-*1H*-pyrazol-4-yl)ethan-1-one.

Conflict of interest statement

Authors declare no conflict of interest.

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