THE INTERNATIONAL JOURNAL OF SCIENCE & TECHNOLEDGE

Synthesis, Characterization and Biological Studies of Schiff Base Ligand (2Z)–2–[(1, 5–Dimethyl-3-Oxo-2-Phenyl-2, 3-Dihydro-4-Pyrazol-Yl) Imino]-1, 2-Dihydro-3h-Indole-3-One and Its Al (III), In (III) and Tl (I) Complexes

Ocheni Adejoh
Lecturer, Department of Chemistry, Kogi State University, Anyigba, Nigeria
Ukoha P.O.
Professor, Department of Chemistry, University of Nigeria, Nsukka, Nigeria
Dr. Aaron Baba
Senior Lecturer, Department of Chemistry, Kogi State University, Anyigba, Nigeria

Abstract:
A trifunctionalize Schiff base ligand (2z)–2–[(1,5–dimethyl-3-oxo-2-phenyl-2,3-dihydro-4-pyrazol-yl) imino]-1,2-dihydro-3H-indole-3-one and its Al(III) In(III) and Tl(I), complexes have been synthesized and characterized by physical methods and spectral studies. The geometry around the metals have been deduced based on solution studies and spectral information. The ligand and its complexes were also tested against different bacteria and fungi to determine their activities.

Keyword:*Synthesis, characterization, spectral studies and antimicrobial activities.*

1. Introduction

When an aldehyde or a ketone is condensed with primary amine, a Schiff base is produced[1,2], which is a compound containing azomethine group R-C=N-. Schiff base complexes comprise an important class of compounds due to their viability and potency in chelation. These compounds are reported to exhibit analgesic, anti-in-flamatory effects, antiviral, antibacterial, and herbicidal activities[3-5]. Certain derivatives have industrial applications, for example, as homogeneous catalysis. Other uses relate to their application as dyes and pigments. Transition metal Schiff base complexes have been found to play a vital role in medicine, biological systems and industries[2].

Isatin is a versatile molecule for designing potential bioactive agents, and its derivatives were reported to possess broad spectrum antiviral activity. Interest in complexes of these ligand system now covers several areas ranging from general consideration of the effect of oxygen, nitrogen and other chelating agent and electron delocalization in the metal complexes to potential biological activity and practical application[6]. More recently, the pharmaceutical properties of organoaluminum and its congeners have been reported[7]. Simulation based on formation constant indicated that no particular risk is to be expected in normal condition of ingestion and in Al-based therapy[7]. In this paper, we report the synthesis, characterization and antimicrobial studies of Schiff base ligand (2Z)-2-[(1,5-dimethyl-3-oxo-2-Phenyl-2,3-dihydro-4-pyrazol-yl-) imino]-1,2-dihydro-3H-indole-3-one and its Al(III), In(III) and Tl(I) complexes.

2. Experimental

All reagents used were of analytical grade, and these were all used without further purification.

Aluminum (III) chloride indium(III) chloride and thallium(I) acetate were purchased from corresponding authors (MERCK), Isatin (99%) and 4-amino antipyrine (98%) were obtained from EELLEE-HANNOVER and aldrich respectively. Melting points were determined using 4017 model of John-fisher melting point apparatus. The stoichiometry was determined using Jobs continous variation method. The electronic spectra were recorded with ultraviolet visible spectrophotometer of serial number 2500pc equipped with a printer. Infrared spectral analyses were recorded using Fourier transformed IR SHIMADZU 8400S model in Nujol within 400-4000cm^{-1}. Electrical conductivity measurements were carried out using conductivity meter model Jenway 4010. ^{1}H and ^{13}C NMR spectra were recorded on 1995 YH 200 MHz model of NMR spectrophotometer using DMSO and $CDCl_3$ as an internal reference while mass spectra were recorded on QP 2010 plus Shimadzu, Japan model of GC-mass spectrophotometer at 70 ev.

2.1. Preparation of Schiff base Ligand

Schiff base ligand (2z)–2–[(1,5–dimethyl-3-oxo-2-phenyl-2,3-dihydro-4-pyrazol-yl) imino]-1,2-dihydro-3H-indole-3-one (HL) was prepared by reacting equimolar amount of isatin (0.294g; 2mmol) and 4-amino antipyrine (0.406g, 2mmol) in 50ml of ethanol under reflux for 5h and cooled with ice to room temperature. The reddish crystal formed was filtered using a filter funnel and dried in the air. This was further recrystallized using methanol, dried in air and stored in the desiccators containing $CaCl_2$[7].

2.2. Preparation of the Complexes

Ethanolic solution of metal chloride that is aluminum(III) chloride (0.130g, Immol), indium(III) chloride (0.221g Immol) and thallium (1) acetate (0.263g, I mmol) were mixed separately with (0.660g,2mmol) of the Schiff base (HL)at 60^0C under reflux for 6h. The resulting crystals were filtered, washed with benzene and dried in the air. These were further recrystallized and stored in the desiccators containing $Cacl_2$ for characterization. The obtained complexes were found to be crystalline colored compounds, stable at room temperature and soluble in ethanol, methanol, THF, DMF and DMSO. The chemical reactions for both ligand and complexes are given below:

$C_8H_5NO_2$ + $C_{11}H_{13}N_3O$ ⟶ $C_{19}H_{16}N_4O_2$ + H_2O

Isatin 4-aminoantipyrine Schiff base (HL) Water.

$AlCl_3$ + HL $\xrightarrow{60^0C./\ ethanol/\ reflux}$ $[Al(HL)Cl_3]$

$InCl_3$ + HL $\xrightarrow{60^0C./\ ethanol/\ reflux}$ $[In(HL)_2]^{3+}$

$Tl(O_2C_2H_3)$ + HL $\xrightarrow{60^0C./\ ethanol/\ reflux}$ $[Tl_2(HL)_2(O_2C_2H_3)]$

3. Results and Discussion

All the physical data for the investigated compounds are given in table 1. All complexes are non-hygroscopic and are stable in air and light.

Compound	Mole ratio	M.W	Color	M.P (^{0}C)	Conductivity $Ohm^{-1}Cm^2\ mol^{-1}$	% yield
HL	1:1	332	Pale-red	150-154	1.0	59
$[Al(HL)cl_3]$	1:1	465.5	Black	130-134	27.0	58
$[In(HL)2]^{3+}$	1:2	779	Black	245-247	56.0	56
$[Tl_2(HL)_2(O_2C_2H_3)_2$	2:2	1,190	Ash	155-158	13.0	45

Table 1: Physical data of (2z)–2–[(1,5–dimethyl-3-oxo-2-phenyl-2,3-dihydro-4-pyrazol-yl) imino]-1,2-dihydro-3H-indole-3-one and the metal complexes.

Generally, ligand and complexes were found to be colored (Table 1) with significant percentage yield. This ligand and complexes have high melting point and non electrolytic in molting state with the exception of the indium complex which was found to be charged. The stoichiometric analysis of the complexes revealed 1:1, 1:2 and 2:2 for Al, In and Tl complexes respectively (Table 1).

The electronic spectra of the free ligand HL (Table 2) and its metal complexes in the region of 740-767nm revealed n ⟶ π transition of non-bonding electron in the ligand and complexes, while the band within 382- 447nm were observed to be due to π ⟶ π transition in the ligand and complexes.

Compound	nm(cm^{-1})	nm(cm^{-1})
HL	740.5 (13504)	447.5 (22346.37)
$[Al(HL)Cl_3]$	738.5 (13540.39)	382_{br}(26178.01)
$[In(HL)_2]^{3+}$	767 (13037.81)	417 (23980.82)
$[Tl_2(HL)_2(O_2C_2H_3)_2]$	740 (13504)	435 (22988.51)

Table 2: electronic spectra data of (2z)–2–[(1,5–dimethyl-3-oxo-2-phenyl-2,3-dihydro-4-pyrazol-yl)imino]-1,2-dihydro-3H-indole-3-one and its A1(III) In(III) and Tl(I), complexes.

3.1. Infrared Spectra

Table 3 record the IR data for the ligand and its Al(III), In(III) and Tl(I) complexes. The IR spectra of the ligand show strong absorption in the region of 3474cm^{-1}, which is attributed to v(N-H) stretching vibration of the indol moiety. This band was shifted in the Al(III) and Tl(I) complexes which is an evidence of complexation via the indol-nitrogen as earlier reported[8]. The band at 1724cm^{-1} is characteristic of the carbonyl group present in the Schiff base ligand. This group was shifted in all the complexes indicating the involvement of the carbonyl oxygen in coordination[9,10,11]. The band assigned to the azomethine group in the free Schiff base ligand was observed at 1600.97cm^{-1} and shifted in all the complexes. This indicates the participation of the nitrogen atom of the azomethine group in coordination[9,10,11]. The spectra of the complexes show bands in the region of 450cm^{-1}, 460 cm^{-1} and 500 cm^{-1}, due to Al-Cl, In-Cl and Tl-O Stretching vibration respectively. The stretching frequency due to N-N in the free ligand was observed at 1017.48 cm^{-1}.

This band was slightly affected in all the metal complexes, indicating the un-sharing of this linkage in coordination to the central metal ion as reported in related system[11]. From this results, we can conclude that the Schiff base ligand behave as a tridentate ligand through the isatin nitrogen, azomethine nitrogen and the oxygen of the Schiff base ligand.

Compound	v(N-H)	v(C=O)	v(C=N)	v(M-Cl)	v(M-O)
HL	3474.95	1724.42	1600.97	-	-
$[Al(HL)Cl_3]$	3533.71	1718.63	1581.68	450	-
$[In(HL)_2]^{3+}$	3480.66	1840.00	1606.76	460	-
$[Tl_2(HL)_2(O_2C_2H_3)_2]$	3606.15	1720.56	1605.79	-	500

Table 3: Infrared spectra data of (2z)–2–[(1,5–dimethyl-3-oxo-2-phenyl-2,3-dihydro-4-pyrazol-yl) imino]-1,2-dihydro-3H-indole-3-one and its A1(III) In(III) and Tl(I), complexes.

3.2.[1]HNMR Spectra of (2z)–2–[(1,5–dimethyl-3-oxo-2-phenyl-2,3-dihydro-4-pyrazol-yl) imino]-1,2-dihydro-3H-indole-3-one

The ^{1}H NMR for this compound have been carried out in the deuterated solvent, $CDCl_3$, at room temperature. Different proton resonance was assigned on the basis of their multiplicity and intensity patterns. The integration spectra were in agreement with the number of protons proposed for each molecular fragment. A downfield singlet signal at 10.80 ppm was assigned to indole proton (H_5). At 2.350 and 3.352ppm upfield signals are due to antipyrinal methyl protons (H_6) and N-antipyrinal methyl proton (H_7) respectively with both occurring as singlet. It was observed that its phenyl protons signals appeared as multiplets and were strongly deshielded to a range of 6.825-7.567ppm. These are aromatic region and have been observed in related system[11,13]. ^{1}HNMR data for the reported compound is given in Table 4.

3.3.[13]CNMR spectra

The parameters of the ^{13}CNMR spectra are given in Table 5. The complete assignment of signals confirms the structure of the compound. This assertion was supported by the evidences from its ^{13}CNMR attached proton test (apt) spectra. The carbon of the methyl group on the antipyrinal moiety were observed as singlet and give rise to signals at 11.547 and 36.242ppm respectively. These was supported by its (apt). The carbon – 13 apt shows the tertiary and primary carbons only due to absence of secondary and quaternary carbons in the structure[14,15]. All other carbon signals are aromatic carbon appearing in the region of 110-165ppm. Carbon number 1 and 10 are highly deshielded as a result of electronic effects of the carbonyl group. Thus, C_1 and C_{10} were assigned 165.484ppm and 145.812ppm respectively. This is in agreement with other reports[13]. Similarly, carbons on the isatin moiety C_2 and C_7 were also affected and give rise to signals at 129.940. On the antypyrine moiety, the down field signals at 11.547 and 36.242 were assigned to C_{12} and C_{13} respectively (aliphatic carbons). All other signals were due to aromatic carbons in the range of 110-165ppm as can be seen on Table 5. Fig.2.

Position	H(∂)	Assignment
H_1	7.529(d,1H)	Aromatic proton
H_2	7.323 (t,1H)	Aromatic proton
H_3	7.012 (t,1H)	Aromatic proton
H_4	7.492(d,1H)	Aromatic proton
H_5	10.80(s,1H)	(N-H) proton
H_6	2.356 (s,3H	Antipyrine methyl proton
H_7	3.352(s,3H)	N-antipyrine methyl proton
$H_{8\ \&\ H12}$	7.567(d,2H)	Phenyl proton
$H_{9\ \&\ H11}$	6.975(d,2H)	Phenyl proton
H_{10}	6.825(d,1H)	Phenyl proton

Table 4:[1]HNMR Data of (2z)–2–[(1,5–dimethyl-3-oxo-2-phenyl-2,3-dihydro-4-pyrazol-yl) imino]-1,2-dihydro-3H-indole-3-one.

Legend; s = siglet t = triplet, d = doublet, m= Multiplet.

Position	^{13}C (∂)
C_1	165.484
$C_{2\&7}$	129.940
$C_{3\&6}$	110.813
$C_{4\&5}$	110.285
C_8	132.952
C_9	128.582
C_{10}	145.812
C_{11}	128.006
C_{12}	11.547
C_{13}	36.242

C_{14}	125.987
$C_{15\ \&19}$	122.285
$C_{16\&18}$	110.813
C_{17}	110.285

Table 5:[13]CNMR Data of (2z)–2–[(1,5–dimethyl-3-oxo-2-phenyl-2,3-dihydro-4-pyrazol-yl) imino]-1,2-dihydro-3H-indole-3-one.

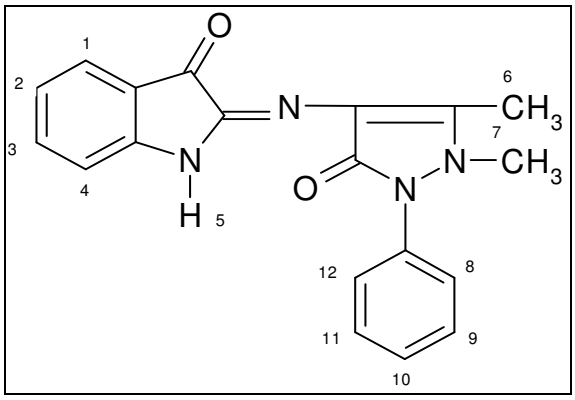

Figure 1: (2z)-2-{(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4yl) imino}-1,2-dihydro-3H-indol-3-one showing protons numbering.

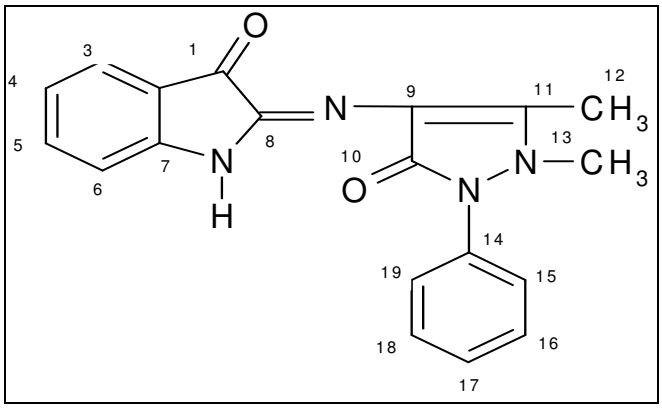

Figure 2: (2z)-2-{(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4yl) imino}-1,2-dihydro-3H-indol-3-one showing carbon numbering.

4. Mass Spectra

The mass spectral data of (2z)-2-{(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4yl) imino}-1,2-dihydro-3H-indol-3-one are given in Table 6. The molecular ion peak at m/z 131 was due to primary fragmentation of the Schiff base ligand given rise to $[C_8H_5NO]^+$. This undergoes further fragmentation to produce compound of m/z 56, 92 and104 respectively as illustrated by the scheme. A molecular ion peak at m/z 184 was due to secondary fragmentation of the antipyrinal moiety with a loss of oxygen to produce $[C_{11}H_{12}N_3]^+$. This undergoes a tertiary ionization to produce a molecular ion peaks at m/z 91 and 94 respectively. The peak at m/z 191was accounted for by the saturation of the phenyl group of the antipyrinal moiety.

Molecular weight	Ions m/z
$[C_{19}H_{16}N_4O_2]^+$	332
$[C_8H_5NO]^+$	131
$[C_2H_2NO]^+$	56
$[C_6H_6N]^+$	92
$[C_{11}H_{11}N_3O]^+$	201
$[C_7H_5O]^+$	104
$[C_{11}H_{11}N_3]^+$	184
$[C_{11}H_{18}N_3]^+$	191
$[C_6H_5N]^+$	91
$[C_5H_6N_2]^+$	94
$[C_7H_5NO]^+$	119

Table 6: Mass spectra data of (2z)-2-{(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4yl) imino}-1,2-dihydro-3H-indol-3-one.

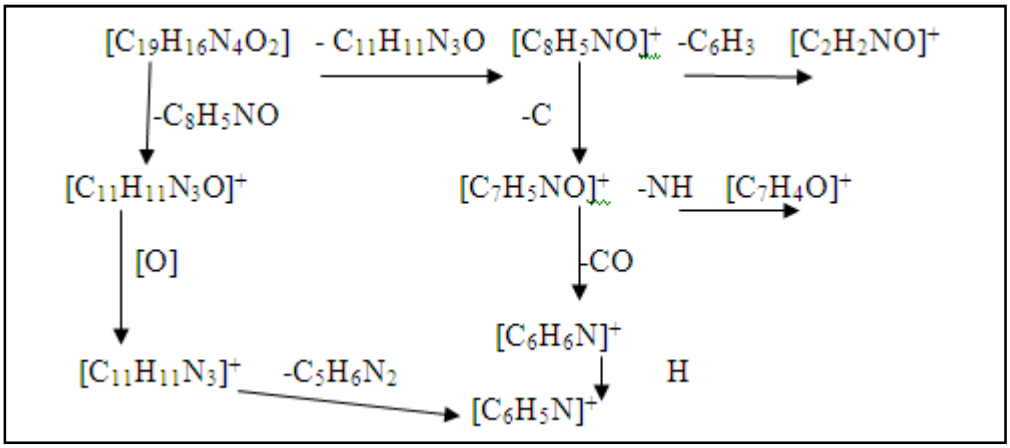

Figure 3: Fragmentation pattern of (2z)-2-{(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4yl) imino}-1,2-dihydro-3H-indol-3-one.

5. Propose Structures

The structure of the Schiff base ligand and complexes were suggested based on spectral information and physical measurements obtained on the ligand and the metal complexes.

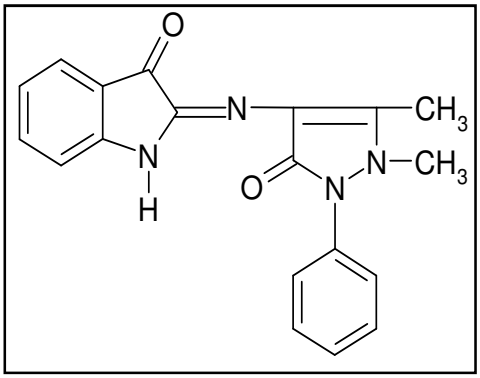

Figure 4: Suggested structure of (2z)-2-{(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4yl) imino}-1,2-dihydro-3H-indol-3-one.

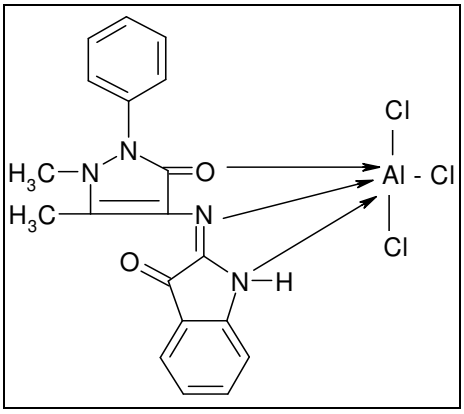

Figure 5: Suggested Structure of [Al(HL)Cl3]

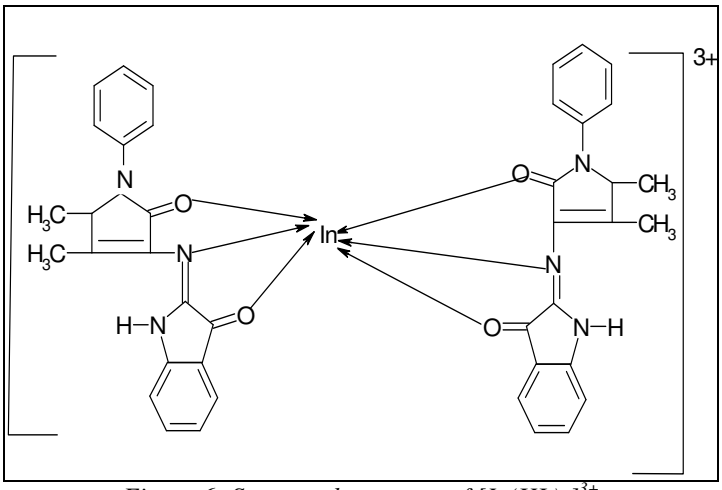

Figure 6: Suggested structure of $[In(HL)_2]^{3+}$

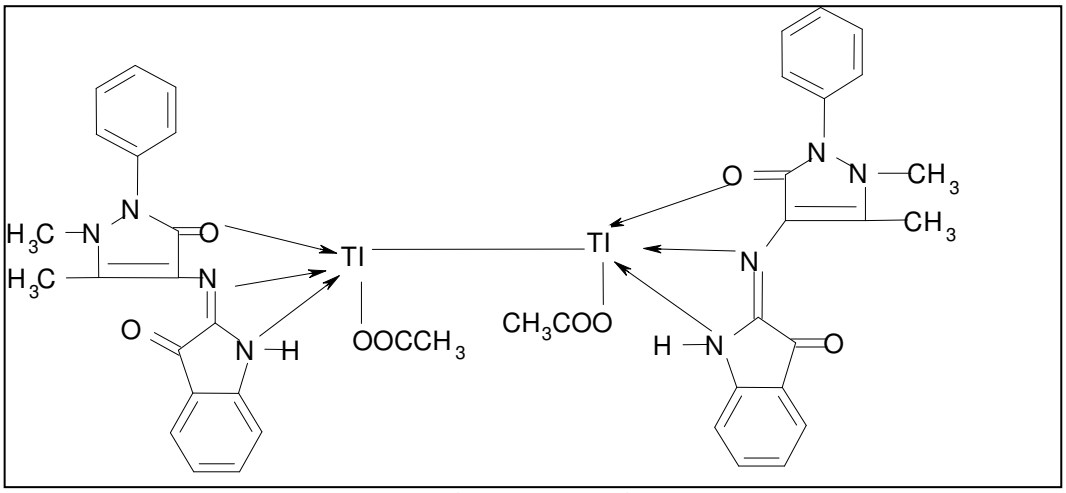

Figure 7: Suggested structure of $[Tl_2(HL)_2(O_2C_2H_3)_2]$.

6. Antimicrobial Studies

All the reported compounds were tested for their antibacterial and antifungal activities against staphylococcus aureus, pseudomonas aeruguinosa, Escherichia coli, Basillus subtilis and Candida albicans respectively. The minimum inhibitory concentration (mic) of the ligand and complexes were also determined using agar well diffusion method. The results given in Table 7 and 8 shows that the thallium and indium complexes were the most potent candidates against the tested bacteria and fungi. All of these complexes including the ligand were active against E. coli, Pseudomonas aeruguinosa, and Basillus subtilis. The broad spectrum of indium and thallium complexes in this case implies that there can be used as a chemotherapeutic agent in different bacterial infections and infections involving Candida species and antiseptic[16]. Both the Schiff base ligand and complexes showed no activity against Staphylococcus aereus and hence cannot be used as chemotherapeutic agent against infection involving the organism.

Organism	**Zone of inhibition (mm).**			
	HL	$Al(Hl)Cl_3$	$[In(HL)_2]^{3+}$	$[Tl_2(HL)_2(O_2C_2H_3)_2]$
Staphylococcus aureus	-	-	-	-
Pseudomonas aeruginosa	10	12	11	15
E. Coli	10	10	12	13
Basillus Subtilis	12	12	15	18
Candida albicans	-	-	12	30

Table 7: antibacterial and antifungal activities of (2z)-2-{(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4yl)imino}-1,2-dihydro-3H-indol-3-one and its Al(III), In(III) and Tl(I) complexes using Ampicilline as standard drug.

Organism	Compound	Conc. In µ g/ml and zone of inhibition (mm)						
		20	10	5	2.5	1.25	0.625	0.134
Pseudomonas aeruginosa	$[Tl_2(HL)_2(O_2C_2H_3)_2]$	15mm	11mm	-	-	-	-	-
E.coli		13mm	-	-	-	-	-	-
Bacillus subtilis		18mm	15mm	14mm	-	-	-	-
Staphylococcus aureus		-	-	-	-	-	-	-
Candida albicans		30mm	25mm	20mm	16mm	-	-	-
Pseudomonas aeruginosa	$[In(HL)_2]^{3+}$	11mm	11mm	10mm	-	-	-	-
E. coli		12mm	12mm	12mm	11mm	-	-	-
Bacillus subtilis		15mm	13mm	13mm	-	-	-	-
Staphylococcus aureus		-	-	-	-	-	-	-
Candida albicans		12mm	11mm	10mm	-	-	-	-
Pseudomonas aeruginosa	$Al(Hl)Cl_3$	12mm	11mm	11mm	-	-	-	-
E. coli		10mm	10mm	-	-	-	-	-
Bacillus subtilis		12mm	11mm	-	-	-	-	-
Staphylococcus aureus		-	-	-	-	-	-	-
Candida albicans		-	-	-	-	-	-	-
Pseudomonas aeruginosa	HL	12mm	11mm	11mm	-	-	-	-
E. coli		10mm	9mm	-	-	-	-	-
Bacillus subtilis		12mm	11mm	-	-	-	-	-
Staphylococcus aureus		-	-	-	-	-	-	-
Candida albicans		-	-	-	-	-	-	-

Table 8: Minimum inhibitory concentration (mic) of (2z)-2-{(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4yl) imino}-1,2-dihydro-3H-indol-3-one and its Al(III), In(III) and Tl(I) complexes.

7. References

i. Holm, R.H; Everett, J.R; & Chakravorty, R.S; (1996). "Metal complexes of Schiff bases and *B*-Ketoimines" inorganic Chemistry. 7 83-214.
ii. Aliyu, H.N and Mohammed, A.S; (2009): Synthesis and characterization of Iron(II) and Nickel(II) Schiff Base complexes. Bayero Journal of pure and applied science 2(1): 132-134.
iii. Sayed, C.H; Hamed, A.A; Meligi C. A; Shafia, M. (2003) Molecules. 8, 322
iv. Turan-Zitouni, G; Siraci, M; Kilic, F.S; Erol, K; (2001) Med. Chem., 36,685.
v. Burdulene, D; Palaima, A; Stambryarichywe, Z.(1999). Pharm. Chem. J. 33,191
vi. M.C. Roddrigue2-Arguelles, M.B. Ferrari F. Bisceglie, (2004). Synthesis characterization and biological activity of Ni, Cu and Zu complexes of Isatin hydrazone Journal of Inorganic Biochemistry, 98(2) 313-321.
vii. Mahaptra, B.B, Mahaptra, B.K. and Guru, S; (1977); "Complexes of cobalt (II) with tridentate Schiff Base", Journal of inorganic and nuclear chemistry, 39: 2291-2292.
viii. Shane G.T; Tomohiro S; Takunor, H; Reiko, K; Julie L; and Daniel, B.L.(2004), inorganic chemistry 43(20) 6168-6176.
ix. Radmakrishnan, T; Joseph, P.T.; Prabhakaran, C; (1976) inorganic Nuclear. Chemistry. 2217.
x. Shankar, G; Premkumar, R.R. Ramalingam S.K. (1986) Tetrahedron, 5,(4),991.
xi. Mahmoud, M.M.; Zinab, H.A; and Abeer. A.F.; (2004) Preparation, spectral characterization and antimicrobial activities of Schiff base complexes derived from 4-aminoantipyrine. Mixed ligand complexes with 2-aminopyrine, 8-Hydroxyquinoline and oxalic acid and their pyrolytical product. J. of Chinese Chem. Soc. 51, 901-915.
xii. Ram, K.A; and Surendra, P; (2005). Synthesis, Spectroscopic and physiochemical characterization and biological activity of Co(II) and Ni(II) coordination compounds with 4-aminoantipyrine thiosemicarbazone. J. of Bioinorganic chemistry and Applications. 3 (3-4) 271-284.
xiii. Shahid, K; Shahzadi, S; Ali, S; Bhatti, M.H.; and Khan, K.M., (2005). Organotin(IV) complexes of 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl) benzoic acid: Synthesis, spectral characterization and biological applications. J. of Iranian Chem. Soc.2(2) 140-148.
xiv. Daniel, E.; Charles, B; Nikolay, G; Paul, D; and Konstatin, D; (2004). First bivalent palladium and platinum cyanoximate: synthesis, characterization and biological activity. American chem. Soc. 43 3894-3909.
xv. Khalil, M.M.H; Al-Seif. F.A. (2008). Molybdenum and Thungsten trricarbonyl complexes of isatin with triphenyl phosphine. J. of Coordination chemistry, 60 (11) 1191-1201.
xvi. Atta-Ur-Rahaman, M.I; Thomse, W.J; (2001). Bioassay Techniques for Drug Development, Harward Academic press, Amsterdam. 14. Pp 15.